Jeffrey M. Weinberg
Mark Lebwohl *Editors*

# Advances in Psoriasis

## A Multisystemic Guide

Springer

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*I would like to dedicate this book to the memory of my father Barry M. Weinberg, DDS. He inspired me with his selflessness, and dedication to the needs and well-being of his patients, friends, and family. His influence has made me a better person and a better doctor.*

Jeffrey M. Weinberg, MD

# Foreword

Think psoriasis is just a skin disease that can be managed by one of the many treatment options? If you are saying to yourself why another book on psoriasis, then this book is a must read. Psoriasis affects 7.5 million Americans and an estimated 2–3 % of the world's population. While we at the National Psoriasis Foundation (NPF) have welcomed several therapeutic advances in the last decade, research still shows nearly 50 % of patients with the disease are under-treated. Nearly the same percentage reports dissatisfaction, for a myriad of reasons, with the treatment that they are on.

Psoriasis is a complex, autoimmune disease ranging from mild to severe – even life threatening. Despite improving research around the disease, clinically speaking, we are unfortunately facing a shortage of well-trained medical dermatologists. Individuals with psoriasis face an increased risk for cardio-metabolic comorbidities, some cancers, depression, social isolation and often a sense of hopelessness. *Advances in Psoriasis: A Multisystemic Guide*, thanks to champions like the authors Drs. Jeffrey Weinberg and Mark Lebwohl, ensures that you will walk away with a more comprehensive understanding of this disease. It is my hope that you will also walk away with a commitment to helping remove the burden of the disease from your patients.

There are chapters that cover each individual treatment option so that you best understand when to use topical therapies for a patient and when that same patient may need to be moved to a biologic or combination therapy. There are chapters such as Research Pipeline I, II and III that look at the exciting new therapies that may be coming to market soon. There are chapters that discuss phototherapy and laser therapy, treatment options the National Psoriasis Foundation fights to keep available for patients. One of the chapters is on the new advances in psoriatic arthritis and another on how to manage pediatric patients.

The NPF is proud to have this book serve as a reference for some of our patient assistance resources. There are template letters included if you need assistance in getting your patient on a specific therapy such as phototherapy or biologics. There is a handy financial assistance resources sheet that has information and contact numbers for programs to help your patients afford their treatments. We hope these resources are valuable to you and help patients get the support they need.

There are exciting treatment advances happening in psoriasis and expanding patient education. It is my hope that with *Advances in Psoriasis: A Multisystemic Guide* we will see a shift in the number of patients reaching the appropriate treatment for their disease so that they can lead happy and productive lives.

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# Preface: Evolving Perspectives on Psoriasis

Psoriasis has many different connotations to both those who are and who are not afflicted. John Updike devoted the chapter "At war with my skin" to psoriasis in his memoirs, *Self-consciousness* [1]. He observed that psoriasis keeps you thinking: "Strategies of concealment ramify, and self-examination is endless." The patient constantly invents new ways of hiding the symptoms. After an attack of measles in 1938, Updike noted that his psoriasis paraded "in all its flaming scabbiness from head to toe [2]."

Disease is too strong a word in his opinion, as psoriasis is neither contagious nor painful, nor does it weaken the body. However, the disorder does isolate the patient from the "happy herds of the healthy [2]." At the time when Updike was working on his autobiography, he had experienced psoriasis for 50 years, and he had come to understand that the war with his skin was solely a matter of self-consciousness, self-esteem, and of accepting himself. He noted, "What was my creativity, my relentless need to produce, but a parody of my skin's embarrassing overproduction?" [2]

In another vein, on January 20, 2004, the *New York Post* reported that Amy Fisher said that "her former lover Joey Buttafuoco is like a bad rash that won't go away [3]." The one-time "Long Island Lolita" vented in her *Long Island Press* column that people are still calling her about Buttafuoco's misadventures – he was arrested at about that time for insurance fraud and grand theft – and wondered "if she'll ever be able to shake her connection to the sleazy former body shop owner." She continued, "I have spent 12 years futilely attempting to distance myself from Joey Buttafuoco as one might try to get rid of psoriasis."

It is interesting to note the varying perceptions of disease from individuals of psoriasis. It is fascinating, however, when we consider how much our understanding and management of psoriasis has evolved over the last several decades:

1. A disease once considered to be a disorder of keratinocyte biology is now clearly understood to be an inflammatory condition, resulting from altered behavior of T cells and cytokines.
2. We are now in the second decade of the biologic era, in which we have available multiple therapies specifically designed to address our evolving knowledge of the pathophysiology of the disease. At the present time, we have a group of new therapies in development, which are active in even more novel pathways that have been elucidated over the past several years.

3. We now view psoriasis as not simply a disease solely of the skin, but as a systemic inflammatory condition with a myriad of potential comorbidities. Psoriasis now requires a multidisciplinary approach to successfully manage all aspects of the disease.

In designing *Advances in Psoriasis: A Multisystemic Guide*, our goal was to provide clinicians with a practical comprehensive educational tool. We hope that physicians will use this tool to update their knowledge of the science and therapy of psoriasis, and that the tool will help them to educate patients about their disease and its comorbidities, and their therapeutic options.

With an emphasis of both physician and patient education and collaboration, we hope that this book will embody the values of the National Psoriasis Foundation Patient Bill of Rights:

## Bill of Rights and Responsibilities for People with Psoriasis and Psoriatic Arthritis [4]

**People with psoriasis and/or psoriatic arthritis have the right** to receive medical care from a healthcare provider who understands that psoriasis and psoriatic arthritis are serious autoimmune diseases that require lifelong treatment.

**People with psoriasis and/or psoriatic arthritis have the responsibility** to be actively involved in managing their disease by participating in healthcare decisions, closely following treatment plans recommended by their healthcare providers, and making healthy lifestyle choices to ease their symptoms.

**People with psoriasis and/or psoriatic arthritis have the right** to a healthcare provider who is able to fully assess their disease and related conditions, is knowledgeable about the benefits and risks of all psoriasis treatments and medications, and readily coordinates psoriasis treatment plans with the individual's other providers.

**People with psoriasis and/or psoriatic arthritis have the responsibility** to be honest with their healthcare provider about their health and lifestyle decisions that may affect the success of his or her treatment plan.

**People with psoriasis have the right** to expect clear or almost clear skin with effective treatment throughout their lifetime, and to seek another healthcare provider if his or her current provider is not comfortable with prescribing and monitoring the range of psoriasis treatments.

**People with psoriasis and/or psoriatic arthritis have the responsibility** to ask for support and encouragement from their loved ones, friends, healthcare providers, clergy and others with whom they feel comfortable discussing personal and health issues.

**People with psoriasis and/or psoriatic arthritis have the right** to be treated in a courteous and nondiscriminatory manner by their healthcare providers, employers and others.

In this spirit, we hope that *Advances in Psoriasis: A Mulitsystemic Guide* is a benefit to you and your patients.

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# History of Psoriasis

1

John B. Cameron and Abby S. Van Voorhees

**Abstract**

An understanding of disease overall and, skin disease in particular, has been a unique part of modern times. Previously those with psoriasis were often mislabeled, poorly regarded, and suffered as a consequence. Symptoms were often considered the disease itself; this lack of understanding made for difficulty in establishing psoriasis as a disease entity. The subsequent struggle to understand the pathogenesis of psoriasis limited the progress in its treatment. We review the path taken to enhance our understanding of this complex skin disease as well as the discovery of the varied treatments which initially were serendipitously indentified followed over the decades by ones based on scientific knowledge. The further understanding of this disease has allowed for continued progress and specificity of these modalities as well as the identification of the associated co-morbid conditions. The history of psoriasis, therefore requires an appreciation of how the understanding of this disease has progressed over time in parallel with its evolving treatment options.

**Keywords**

Psoriasis • Intertriginous • Inverse • Inframammary • Supragluteal

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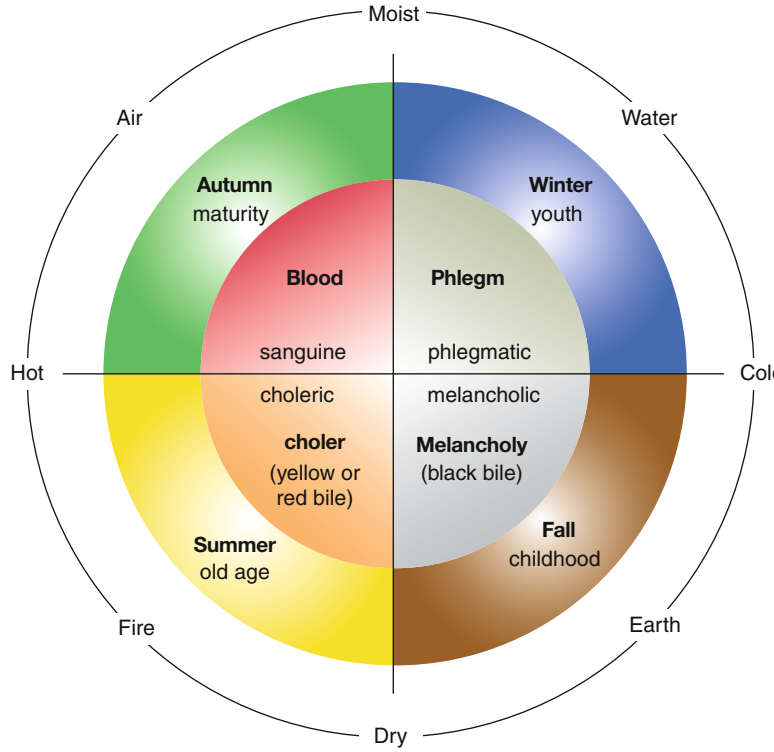


**Fig. 1.1** Diagram of humours, elements, qualities and seasons

## History of Disease

An understanding of disease overall and, skin disease in particular, has been a unique part of modern times. Previously those with psoriasis were often mislabeled, poorly regarded, and suffered as a consequence. Symptoms were often considered the disease itself, and consequent progress in treatment was limited by this lack of understanding of the disease and its cause. The history of psoriasis therefore requires an appreciation of how the understanding of disease has progressed over time and the often serendipitous findings of treatment options.

Pre-scientific societies often viewed disease as resulting from a violation of the sacred order, the malignant influence of magic or the breaking of a taboo. For example the entire thirteenth chapter of the Book of Leviticus concerns how the priests may determine if an outbreak on the skin is leprosy and the fourteenth chapter concerns which animals (lambs and birds) shall be sacrificed to purify the victim [1].

The first cultures that developed notions of rational science were China and Greece. Western medicine finds its roots in the Greek belief that disease results from natural causes, that in some way the balance or integrity of the body has been disrupted. Treatment, therefore, consisted in restoring that balance or integrity. Hippocrates may be the father of western medicine but the most influential founder was more likely Galen of Pergamon (130–200 CE) To Galen the human body was a very complex organism made up not just of the four humors but also of gradations of dry and moist and hot and cool [2]. Treatment of disease was not limited to bleedings and purges but also included the use of lotions designed to restore health. Galen's system was so completely accepted that only in the nineteenth Century would the humors and miasma disappear from medical belief to be replaced by the germ theory of disease (Fig. 1.1).

## Identification of Psoriasis as a Unique Disease

It is extremely difficult to tease out the history of psoriasis and its treatment in the ancient world because of confusion between psoriasis and many other diseases. Furthermore in the past the names assigned to diseases and symptoms were arbitrary and inconsistent. Identification of psoriasis in Egypt is especially difficult because of confusion between the disease and leprosy in later times [3]. However, since extensive examination of Egyptian mummies would indicate that leprosy was not present in Egypt before the common era, it is possible that psoriasis was mislabeled as leprosy.

We face similar problems of terminology in Greek medicine. The *Corpus Hippocraticum* contains precise descriptions and treatments for many recognizable diseases of the skin [4]. Again, it is likely that much of what was referred to as leprosy was in fact psoriasis. The appearance of true leprosy early in the common era compounded the confusion and sometimes lead to harsh treatments for those with psoriasis since lepers were often isolated and forbidden to associate with non-leprosy population.

The first indisputable reference to psoriasis comes from the fifth and sixth books of Aulus Cornelius Celsus, *De Re Medica* (circa 25 BCE-circa 50 CE) a Roman who compiled an extensive list of diseases and treatment for use by estate owners [5]. Celsus did not use the term psoriasis but rather describes it under the heading *impetigo.*

After the collapse of Roman culture, the practice of scientific medicine in the west disappeared and only returned as a part of the Renaissance. Geronimo Mercurialis penned a summary of what was known of skin diseases in 1572 [6]. Mercuralis lumped psoriasis in with other diseases as Lepra. He mentions several treatments including wolf dung rubbed in with vinegar, blood of a mountain goat as well as the rubbing of psoriasis with cantharides.

Robert Willan (1757–1812) set out clear and uniform nomenclature of skin diseases in 1809. However, his terminology unfortunately perpetuated some confusion in that he called psoriasis *lepra vulgaris* [7]. That confusion would end by mid-century when Camille Melchoir Gibert (1792–1866) dropped *lepra vulgaris* and used only psoriasis as the sole term for the disease and his work made clear important distinctions among papulosquamous diseases [8]. Gibert's successors improved the distinctions. Hebra fully distinguished the clinical practice of leprosy from psoriasis; Heinrich Auspitz (1835–1886) noted bleeding points after removing scales (Auspitz sign); Heinrich Köebner made an important contribution in 1872 when he delivered an address entitled, "The Etiology of Psoriasis" pointing out the tendency of prior trauma to produce psoriasis lesions. The "Koebner Phenomenon" is still viewed as an important indication of psoriasis [9]. In 1898 Munro described the micro abscesses of psoriasis now called Munro's abscesses. With the addition in the early twentieth century of Leo van Zumbusch of generalized pustular psoriasis and Waranoff's description of the pale halo now called "woranoff ring," accurate diagnosis of psoriasis became commonplace.

## History of the Treatment of Psoriasis

The history of the treatment of psoriasis has been largely driven by serendipitous findings until the last decade. The late 1700s and 1800s included treatments such as arsenic, chrysarobin and ammoniated mercury. Anthralin and tar came into widespread use in the first half of the twentieth century. Starting in the 1950s topical steroids were developed followed by the arrival of methotrexate, retinoids, and immunosuppressive medications in the 1970s, 1980s and 1990s respectively. An enhanced understanding of the pathogenesis of psoriasis has allowed for more targeted drug development in the twenty-first century. Our therapeutic armamentarium now includes medications known as the biologics which target various aspects of the immune system allowing for its regulation.

## Arsenic, Ammoniated Mercury and Chrysarobin

During the eighteenth and nineteenth centuries three topical agents are known to have been used in the treatment of psoriasis. While probably first developed by the ancient Greeks, arsenic solution was first utilized in dermatology in 1786 [10]. The first report of its use in psoriasis though was attributed to Girdlestone in 1806. He is credited with noting the efficacy of Fowler's solution for improving the lesions of psoriasis [11]. Ammoniated mercury, another topical agent was also used at this same time [10]. The use of this mercury in the topical treatment of psoriasis has been attributed to Dr. Fox in 1880. It was championed as well by Duhring. The use of both of these topical agents continued until the 1950s and 1960s when concerns about their possible toxicity risks and accidental poisonings caused their prohibition. The third topical agent that was identified was chrysarobin. A serendipitous finding, it was noted to be of benefit in the treatment of psoriasis by Balmonno Squire in 1876. His patient, who was using Goa powder to treat a presumed fungal infection, was noted to have improvement of his psoriasis. Kaposi in 1878 also published his experience with this topical approach to psoriasis.

## Anthralin and Tar

After the first identification of the potential benefit of chrysarobin, the 1900s were a time of its further exploration. During the early part of this century scientists learned how to convert chrysarobin to anthralin. The active agent was identified as 2-methyl dithranol. During World War 1 when natural supplies were interrupted the process of synthesizing anthralin was discovered. It was then in 1916 that Unna came to understand the potential of this compound in the treatment of psoriasis [12]. In 1953, Ingram further refined the treatment of psoriasis with anthralin [13]. He demonstrated that treatment could be enhanced by utilizing the combination of anthralin, salicylic acid, zinc oxide and ultraviolet light. For many decades this combination was the mainstay of psoriasis treatment in Europe.

Coal tar was also pioneered in the early 1900s. In 1925 Goeckerman noted the beneficial effect of the combination of coal tar with ultraviolet light B radiation in the treatment of psoriasis [14]. While the beneficial effect of sunlight on psoriasis had been long known, Goeckerman realized that this effect might be enhanced if combined with a topical photosensitizer. The success of this approach was demonstrated by its widespread use for many decades. While both the Goeckerman protocol and the Ingram protocol were often effective, the main limitation of these approaches was that they were very time-intensive, requiring patients to remain hospitalized for weeks each year to control their disease.

## Corticosteroids

The development of steroids both for systemic and topical use revolutionized the treatments of many diseases including psoriasis. First discovered in 1950, it was only 2 years later that the potential role of this agent in a topical form was demonstrated in psoriasis [15]. Known as compound F, hydrocortisone was beneficial in treating psoriasis. From this time to the present, topical steroids have continued to play a significant role in reducing the inflammation in various cutaneous conditions. Topical steroids continue to be the most frequently prescribed medication in the treatment of psoriasis today.

## Methotrexate and PUVA

Methotrexate was developed in the 1950s for the treatment of malignancies. As seen with treatments before, it was only a short while before its potential in the treatment of psoriasis was identified. In 1946 Farber developed aminopterin for the treatment of leukemia. Five years later Gubner noted its role in the treatment of psoriasis [16]. While using this agent in the treatment of Rheumatoid arthritis, he noted that his patient, who concurrently had psoriasis, also

had improvement of his skin. A more stable derivative of aminopterin with less toxicity, methotrexate, was introduced in 1958 for the treatment of psoriasis [17]. This agent was subsequently approved by the FDA for the treatment of psoriasis in 1972 after the first guidelines for its use were published [18]. It continues to be an important agent in the treatment of psoriasis today.

The efficacy of PUVA in the treatment of psoriasis was also demonstrated during the 1970s. While the combination of ultraviolet light and a photosensitizing compound had been used in the treatment of vitiligo for hundreds of years in Egypt and in India [19], the demonstration of its role in psoriasis was novel. Ancient healers had those with vitiligo ingest psoralen-rich foods such as figs and limes and then exposed their skin to natural sunlight. It took however until 1974 [20] to demonstrate the effectiveness of the combination of psoralen and artificial UVA light exposure (320–400 nm) in psoriasis. Known as PUVA, this therapeutic approach was a highly efficacious approach for many patients with chronic psoriasis. PUVA was widely utilized since it allowed patients to achieve control of their disease without incurring long inpatient hospitalizations. However, in the late 1970s the first reports surfaced of cutaneous malignancies [21]. Longitudinal studies of the original cohort of patients in subsequent years confirmed this finding [22]. Stern noted the increased risk of SCC, BCC and potentially melanoma skin cancer in those treated with high-dose exposures and long-term therapy. Concerns about the potential risk of cutaneous malignancy, particularly melanoma, has limited the utilization of this modality in recent years with the advent of newer therapies that do not appear to increase the risk of melanoma.

## Narrowband UVB, Retinoids, Vitamin D

As the potential risk of non-melanoma skin cancers associated with long-term use of PUVA became increasingly apparent, discoveries continued and additional new approaches to treat psoriasis came into prominence in the 1980s and the 1990s. Parrish and Jaenicke identified what has come to be known as narrowband UVB [23]. They identified that the most therapeutically effective wavelengths of UVB were those between 300 and 313 nm, while the remaining wavelengths of UVB light contributed primarily to the development of erythema. Subsequently, 311 nm was identified as the most efficacious wavelength for the clearance of psoriasis lesions [24]. This modality therefore allowed for clearance of the skin with more limited risk of erythema; narrowband UVB has come to replace the broad-band UVB phototherapy upon which it was based.

In the 1980s systemic retinoids previously developed for acne and hyperkeratosis were also explored for their possible benefit in the treatment of psoriasis. The second-generation retinoid etretinate, followed by the development of its metabolite acitretin, were both shown to be beneficial [25]. Etretinate was eventually removed from the market given its lipophilic nature and consequent persistence in the subcutaneous fat. Acitretin however, remains a systemic treatment of psoriasis today. A third generation retinoid, tazarotene was also developed as a topical agent which continues to be utilized in the treatment of psoriasis.

Vitamin D and its derivatives were investigated in the 1980s as well. Based on a chance observation of a patient's psoriasis skin improving with the administration of systemic Vitamin D, the development of topically applied Vitamin D derivatives began. While still not fully understood, these topical agents remain important in the armamentarium of dermatologists when treating patients with psoriasis [26].

## Systemic Immunosuppressive Medications

Understanding the importance of immunosuppression in the treatment of psoriasis was another example of gains achieved by serendipitous findings. When cyclosporine was initially developed

in the 1970s the critical role of the immune system in the pathogenesis of psoriasis was not yet appreciated. When transplant patients who coincidentally had psoriasis were placed on cyclosporine to prevent graft rejection they were noted to have improvement of their skin lesions [27]. The efficacy of this treatment on psoriasis helped to identify the importance of T cells, and the immune system more generally, in this disease. Despite its demonstrated effectiveness FDA approval was delayed until the 1990s because of concerns of possible risks associated with this medication [28].

The knowledge gained from cyclosporine in the understanding of psoriasis opened the door for the development of medications that targeted the immune system in the twenty first century. A number of biologic agents have since been developed including those targeting T cells as well as those targeting tumor necrosis factor and IL 12/23. While heralded in with great promise, the T cell targeting compounds alefacept [29] and efulizumab [30] have subsequently been removed from the market because of potential side effects and/or lack of efficacy. However the TNF inhibitors – adalimumab [31], etanercept [32], and infliximab [33] and the IL-12/23 compound ustekinumab [34] have revolutionized the care of patients with psoriasis. Additionally, with each new class of medication developed, the importance of the immune system in psoriasis has become increasingly apparent. New agents targeting different sites of the inflammatory cascade are currently under development and may further add to both our understanding of psoriasis and our therapeutic armamentarium.

Thus, our understanding of psoriasis as well as the knowledge of how to treat this disease has become inextricably linked over time. With each step forward therapeutically, more and more is learned so that we enhance our understanding this disease process. This new knowledge has facilitated the development of medications with which to treat psoriasis, thereby allowing patients to achieve control of their disease. The expectation for treatment response has increased to levels unimaginable only 20–30 years ago. Each step in the understanding of the disease as well as its possible treatments has been built upon the lessons learned previously. We may soon be entering an era where "the heartbreak of psoriasis" reigns no more.

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# The Pathophysiology of Psoriasis

2

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**Abstract**

Psoriasis is a genetically programmed pathologic interaction between skin cells, immunocytes, and numerous biologic signaling molecules triggered by environmental stimuli. The immune response is a cellular one; $T_H1$ and $T_H17$ cells are activated by IL-12 and IL-23 secreted by antigen presenting cells in the skin. Through various cytokines such as TNF alpha these cells cause a chronic inflammatory state and alter epidermal hyperproliferation, differentiation, apoptosis, and neoangiogenesis that produce the findings seen in this disease. The newer biologic therapies target the immunologic signaling pathways and cytokines identified in the pathogenesis of psoriasis and have proved to provide significant clinical improvement. Further study in the pathogenesis of psoriasis can help identify targets for future therapies.

**Keywords**

Psoriasis • Pathophysiology • Immunology • Cytokines • Biologics • TH17 • TNF

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## Introduction

The past 25 years of research and clinical practice have revolutionized our understanding of the pathogenesis of psoriasis as the dysregulation of immunity triggered by environmental and genetic stimuli. Psoriasis was originally regarded as a primary disorder of epidermal hyperproliferation. However, experimental models and clinical results from immunomodulating therapies have refined this perspective in conceptualizing psoriasis as a genetically programmed pathologic interaction between resident skin cells, infiltrating immunocytes and a host of proinflammatory

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cytokines, chemokines and growth factors produced by these immunocytes. Two populations of immunocytes and their respective signaling molecules collaborate in the pathogenesis: innate immunocytes, mediated by antigen presenting cells (including natural killer T lymphocytes, Langerhans cells and neutrophils) and acquired or adaptive immunocytes, mediated by mature CD4+ and CD8+ T lymphocytes in the skin. Such dysregulation of immunity and subsequent inflammation is responsible for the development and perpetuation of the clinical plaques and histological inflammatory infiltrate characteristic of psoriasis.

Although psoriasis is considered to be an immune mediated disease in which intralesional T lymphocytes and their proinflammatory signals trigger primed basal layer keratinocytes to rapidly proliferate, debate and research focus on the stimulus that incites this inflammatory process. While psoriasis may represent an autoimmune reaction, researchers have not isolated self-antigens or defined the specificity of the auto-reactive skin lymphocytes. Our current understanding considers psoriasis to be triggered by exogenous or endogenous environmental stimuli in genetically susceptible individuals. Such stimuli include Group A streptococcal pharyngitis, viremia, allergic drug reactions, antimalarial drugs, lithium, beta blockers, interferon alpha, withdrawal of systemic corticosteroids, local trauma (Koebner's phenomenon) and emotional stress, as these correlate with the onset or flares of psoriatic lesions. Psoriasis genetics centers on susceptibility loci and corresponding candidate genes, particularly the psoriasis susceptibility (PSORS) 1 locus on the major histocompatibility (MHC) class I region. Current research on the pathogenesis of psoriasis examines the complex interactions between immunologic mechanisms, environmental stimuli and genetic susceptibility. After discussing the clinical presentation and histopathologic features of psoriasis, we will review the pathophysiology of psoriasis through noteworthy developments including serendipitous observations, reactions to therapies, clinical trials and animal model systems that have shaped our view of the disease process.

## Clinical Presentations

There are multiple patterns of psoriasis including plaque, guttate, pustular, inverse, and erythrodermic. Approximately 80 % of patients present with plaque psoriasis which is clinically characterized by well demarcated erythematous plaques with overlying scales. These lesions are distributed symmetrically and frequently occur on the elbows, knees, lower back and scalp. These plaques can be intensely pruritic and bleed when manipulated, referred to as the Auspitz sign.

In addition to the classic skin lesions, approximately 23 % of psoriasis patients develop psoriatic arthritis with a 10 year latency after diagnosis of psoriasis [1]. The distal interphalangeal (DIP), wrist, sacroiliac (SI) and knee joints are most commonly affected with swelling, stiffness and loss of function. With longstanding disease, bone changes can be demonstrated on radiographs and bone scans. Psoriatic arthritis patients are rheumatoid factor negative which differentiates them from patients with rheumatoid arthritis. Additionally, nail involvement occurs in 30–50 % of patients and may clinically resemble a fungal oil spots infection, with pitting, onycholysis, thickening, with hyperkeratotic debris under the nail plate [1].

## Histopathology

The histology of psoriatic plaques is distinguished by excessive epidermal growth termed psoriasiform hyperplasia. This pattern includes a markedly thickened skin or acanthosis, elongated downward extensions of the epidermis into the dermis and aberrant keratinocyte differentiation. Mitotic figures are visible in the basal layer of keratinocytes demonstrating rapid proliferation and maturation responsible for incomplete terminal differentiation. Thus, keratinocytes retain their nuclei as visualized in the parakeratotic stratum corneum. The granular layer of the epidermis is also depleted. Additionally, the rapidly proliferating keratinocytes fail to secrete lipids that normally adhere the corneocytes to each other, thereby producing the classic scale of a psoriatic

plaque. The tortuous and dilated dermal blood vessels are responsible for the erythema exhibited by psoriatic plaques.

In addition to epidermal hyperproliferation, an inflammatory infiltrate distinguishes psoriatic skin. Collections of neutrophils termed Munro's abscesses are found within the stratum corneum. Furthermore, an influx of T cells is found in both the epidermis and dermis along with increased numbers of dermal dendritic cells, macrophages and mast cells. These unique histologic features of the psoriatic plaque represent the starting line for researchers determining the mechanisms that underlie the pathophysiology of psoriasis.

## Principles of Immunity

The immune system, intended to protect its host from foreign invaders and unregulated cell growth, employs two main effector pathways. These are the innate and acquired (or adaptive) immune responses, both of which contribute to the pathophysiology of psoriasis [2]. Innate immunity responses occur within minutes to hours, but fail to develop memory for when the antigen is encountered again. However, adaptive immunity responses take days to weeks to respond after challenged with an antigen. The adaptive immune cells have the capacity to respond to a greater range of antigens and develop immunologic memory via rearrangement of antigen receptors on B and T cells. These specialized B and T cells can then be promptly mobilized and differentiated into mature effector cells that protect the host from a foreign pathogen.

Innate and adaptive immune responses are highly intertwined; they can initiate, perpetuate and terminate the immune mechanisms responsible for inflammation. They can modify the nature of the immune response by altering the relative proportions of type 1 ($T_H1$), type 2 ($T_H2$), and the more recently discovered $T_H17$ subset of helper T cells and their respective signaling molecules. A $T_H1$ response is essential for a cellular immunologic reaction to intracellular bacteria and viruses or cellular immunity; a $T_H2$ response promotes IgE synthesis, eosinophilia, and mast cell maturation for extracellular parasites and helminthes as well as humoral immunity; while a $T_H17$ response is important for cell-mediated immunity to extracellular bacteria and plays a role in autoimmunity [3]. The innate and adaptive immune responses employ common effector molecules such as chemokines and cytokines that are essential in mediating an immune response.

## Implicating Dysregulation of Immunity

Our present appreciation of the pathogenesis of psoriasis is based on the history of trial and error therapies, serendipitous discoveries and the current immune targeting drugs used in a variety of chronic inflammatory conditions including rheumatoid arthritis, ankylosing spondylitis and inflammatory bowel disease. Before the mid 1980s, research focused on the hyperproliferative epidermal cells as the primary pathology as a markedly thickened epidermis was indeed demonstrated on histological specimens. Altered cell cycle kinetics were thought to be the culprit behind the hyperkeratotic plaques. Thus, initial treatments centered on oncologic and antimitotic therapies used to arrest keratinocyte proliferation with agents such as arsenic, ammoniated mercury and methotrexate [4].

However, a paradigm shift from targeting epidermal keratinocytes to immunocyte populations occurred when a patient receiving cyclosporine to prevent transplant rejection noted clearing of psoriatic lesions in the 1980s [5]. Cyclosporine was observed to inhibit mRNA transcription of T cell cytokines thereby implicating immunologic dysregulation, specifically T cell hyperactivity, in the pathogenesis of psoriasis [6]. However, the concentrations of oral cyclosporine reached in the epidermis exerted direct effects on keratinocyte proliferation and lymphocyte function in such patients [7]. Thus it begged the question as to whether the keratinocytes or the lymphocytes drove the psoriatic plaques. The use of an interleukin (IL)-2 diptheria toxin-fusion protein, denileukin diftitox, specific for activated T cells with

high affinity IL-2 receptors and nonreactive with keratinocytes distinguished which cell type was responsible. Using a single agent, the targeted T cell toxin provided clinical and histological clearing of psoriatic plaques. Thus, T lymphocytes rather than keratinocytes were recognized as the definitive driver behind the psoriatic plaques [8].

Additional studies have demonstrated that treatments that induce prolonged clearing of psoriatic lesions without continuous therapy such as psoralens plus ultraviolet A irradiation (PUVA) decreased the numbers of T cells in plaques by at least 90 % [9]. However, treatments that require continual therapy for satisfactory clinical results such as cyclosporine and etretinate, simply suppress T cell activity and proliferation [10, 11].

Further evidence has linked cellular immunity with the pathogenesis of psoriasis, defining it as a $T_H1$-type disease. Natural killer T (NKT) cells were shown to be involved through the use of a severe combined immunodeficient (SCID) mouse model. NKT cells were injected into prepsoriatic skin grafted on immunodeficient mice creating a psoriatic plaque with an immune response showing cytokines from type 1 helper T cells ($T_H1$) rather than type 2 helper cells ($T_H2$) [12]. When psoriatic plaques were treated topically with the toll-like receptor (TLR) 7 agonist imiquimod, aggravation and spreading of the plaques were noted. The exacerbation of psoriasis was accompanied by an induction of lesional $T_H1$ type interferon produced by plasmacytoid dendritic cell (DC) precursors. Plasmacytoid DCs were observed to compose up to 16 % of the total dermal infiltrate in psoriatic skin lesions based on their coexpression of BDCA2 and CD123 [13]. Additionally, cancer patients being treated with interferon (IFN)-alpha experienced induction of psoriasis [14]. Moreover, patients being treated for warts with intralesional IFN-alpha developed psoriatic plaques in neighboring prior asymptomatic skin [15]. Patients with psoriasis treated with IFN-gamma, a $T_H1$ cytokine type, also experienced the development of new plaques correlating with the sites of injection [16]. Thus, while epidermal hyperproliferation is the major phenotypic abnormality of psoriatic skin, these studies and growing evidence have shifted our focus of research to the immunologic and inflammatory mechanisms that promote these ultimate cutaneous manifestations of psoriasis.

## Intralesional T Lymphocytes

Psoriatic lesions contain a host of innate immunocytes such as antigen presenting cells (APCs), natural killer (NK) cells and neutrophils as well as adaptive T cells and an inflammatory infiltrate. These cells include CD4+ and CD8+ subtypes in which the CD8+ cells predominate in the epidermis while CD4+ cells show preference for the dermis [17]. There are two groups of CD8+ cells: one group migrates to the epidermis expressing the integrin CD103 while the other group is found in the dermis, but may be headed to or from the epidermis. The CD8+ cells residing in the epidermis that express the integrin CD103 are capable of interacting with E-cadherin which enables these cells to travel to the epidermis and bind resident cells. Immunophenotyping reveals that these mature T cells represent chiefly activated memory cells including CD2+, CD3+, CD5+, CLA, CD28 and CD45RO+ [18]. Many of these cells express the activation markers such as HLA-DR, CD 25 and CD27 in addition to the T cell receptor (TCR).

## T Lymphocyte Stimulation

Both mature CD4+ and CD8+ T cells can respond to the peptides presented by APCs. While the specific antigen that these T cells are reacting to has not yet been elucidated, several antigenic stimuli have been proposed. These include self proteins, microbial pathogens and microbial superantigens. The premise that self-reactive T lymphocytes may contribute to the disease process is derived from the molecular mimicry theory in which an exuberant immune response to a pathogen produces cross-reactivity with self antigens. Considering that infections have been associated with the onset of psoriasis, this theory merits consideration. However, it has also been observed that T cells can be activated without

antigens or superantigens, but rather with direct contact with accessory cells [19]. No single theory has clearly emerged, and thus researchers continue to search for the inciting stimulus that triggers the T lymphocyte and whether T cells are reacting to a self or non-self derived antigen.

## T Lymphocyte Signaling

T cell signaling is a highly coordinated process in which T lymphocytes recognize antigens via presentation by mature APCs in the skin rather than the lymphoid tissues. Such APCs expose antigenic peptides via MHC I or II molecules for which receptors are present on the T cell surface. The antigen recognition complex at the T cell and APC interface, in concert with a host of antigen independent costimulatory signals (described below), regulates T cell signaling and is referred to as the immunologic synapse. The antigen presentation and network of costimulatory and adhesion molecules optimize T cell activation, and dermal dendritic cells release IL-12 and IL-23 to promote a $T_H1$ and $T_H17$ response, respectively [3]. The growth factors released by these helper T cells sustain neoangiogenesis, stimulate epidermal hyperproliferation, alter epidermal differentiation and decrease susceptibility to apoptosis that characterize the erythematous hypertrophic scaling lesions of psoriasis [20]. Furthermore, the cytokines produced from the immunologic response, such as tumor necrosis factor (TNF)-alpha, interferon (IFN)-gamma and IL-2, correspond to cytokines that are upregulated in psoriatic plaques [21].

Integral components of the immunologic synapse complex include costimulatory signals including CD28, CD40, CD80 and CD86, and adhesion molecules such as cytotoxic T lymphocyte antigen 4 and lymphocyte function associated antigen (LFA)-1 that possess corresponding receptors on the T cell. These molecules play a key role in T cell signaling as their disruption has been shown to decrease T cell responsiveness and associated inflammation. The B7 family of molecules routinely interacts with CD28 T cells in order to costimulate T cell activation. Cytotoxic T lymphocyte antigen 4 immunoglobulin, an antibody on the T cell surface, targets B7 and interferes with signaling between B7 and CD28. In psoriatic patients, this blockade was demonstrated to attenuate the T cell response and correlated with a clinical and histologic decrease in psoriasiform hyperplasia [22]. Biological therapies that disrupt the LFA-1 component of the immunologic synapse have also demonstrated efficacy in the treatment of psoriasis. Alefacept is a human LFA-3 fusion protein that binds CD2 on T cells and blocks the interaction between LFA-3 on APCs and CD2 on memory CD45RO+ T cells and induces apoptosis of such T cells. Efalizumab is a human monoclonal antibody to the CD11 chain of LFA-1 that blocks the interaction between LFA-1 on the T cell and intercellular adhesion molecule (ICAM)-1 on an APC or endothelial cell. Both alefacept and efalizumab have demonstrated significant clinical reduction of psoriatic lesions, and alefacept has been shown to produce disease remission for up to 18 months after discontinuation of therapy [23–25]. Initially, alefacept and efalizumab were approved in the United States and the European Union for the treatment of moderate to severe psoriasis, although efalizumab was pulled from the US market and its marketing suspended in Europe due to reports of progressive multifocal leukoencephalopathy and alefacept was discontinued due to a lack of significant efficacy.

## Natural Killer T Cells

Natural killer (NK) T cells represent a subset of CD3+ T cells present in psoriatic plaques. While NKT cells possess a TCR, they differ from T cells by displaying NK receptors comprised of lectin and immunoglobulin families. These cells exhibit remarkable specificity and are activated upon recognition of glycolipids presented by CD1d molecules. This process occurs in contrast to CD4+ and CD8+ T cells, which due to their TCR diversity, respond to peptides processed by APCs and displayed on MHC molecules. NKT cells can be classified into two subsets: one group that expresses CD4 and preferentially produces

$T_H1$ versus $T_H2$ type cytokines and another group that lacks CD4 and CD8 that only produces $T_H1$ type cytokines. The innate immune system employs NKT cells early in the immune response because of their direct cytotoxicity and rapid production of cytokines such as IFN-gamma and IL-4. IFN-gamma promotes a $T_H1$ inflammatory response, while IL-4 promotes the development $T_H2$ cells. Excessive or dysfunctional NKT cells have been associated with autoimmune diseases such as multiple sclerosis and inflammatory bowel disease as well as allergic contact dermatitis [26–28].

In psoriasis, NKT cells are located in the epidermis, closely situated to epidermal keratinocytes, which suggests a role for direct antigen presentation. Furthermore, CD1d is overexpressed throughout the epidermis of psoriatic plaques whereas normally, CD1d expression is confined to terminally differentiated keratinocytes. An in vitro study examining cytokine-based inflammation demonstrative of psoriasis treated cultured CD1d-positive keratinocytes with IFN-gamma in the presence of alpha-galactosylceramide of the lectin family [29]. IFN-gamma was observed to enhance keratinocyte CD1d expression, and subsequently CD1d-positive keratinocytes were found to activate NK-T cells to produce high levels of IFN-gamma while levels of IL-4 remained undetectable. The preferential production of IFN-gamma supports a $T_H1$ mediated mechanism regulated by NKT cells in the immunopathogenesis of psoriasis.

## Dendritic Cells

Dendritic cells are professional APCs that process antigens in the tissues in which they reside after which they migrate to local lymph nodes where they present their native antigens to T cells. This process allows the T cell response to be tailored to the appropriate antigens in the corresponding tissues. Immature dendritic cells that capture antigens mature via migrating to the T cell center of the lymph node where they present their antigens to either MHC molecules or the CD1 family. This presentation results in T cell proliferation and differentiation that correlates with the required type of T cell response. Multiple subsets of APCs including myeloid and plasmacytoid DCs are highly represented in the epidermis and dermis of psoriatic plaques as compared with normal skin [30]. Dermal dendritic cells are thought to be responsible for activating both the $T_H1$ and $T_H17$ (discussed below) infiltrate by secreting IL-12 and IL-23, respectively. This mixed cellular response secretes cytokines and leads to a cascade of events involving keratinocytes, fibroblasts, endothelial cells, and neutrophils that create the cutaneous lesions seen in psoriasis [3].

While DCs play a pivotal role in eliciting an immune response against a foreign invader, they also contribute to the establishment of tolerance. Throughout their maturation, DCs are continuously sensing their environment, which shapes their production of $T_H1$ versus $T_H2$ type cytokines and subsequently the nature of the T cell response. When challenged with a virus, bacteria or unchecked cell growth, DCs mature into APCs. However, in the absence of a strong stimulus, DCs fail to mature into APCs, but rather present self peptides with MHC molecules thereby creating regulatory T cells involved in peripheral tolerance [31]. If this balance between immunogenic APCs and housekeeping T cells is upset, inflammatory conditions such as psoriasis can result.

## Cytokines

Cytokines are low molecular weight glycoproteins that function as signals to produce inflammation, defense, tissue repair and remodeling, fibrosis, angiogenesis and restriction of neoplastic growth [32]. Cytokines are produced by immunocytes such as lymphocytes and macrophages as well as non-immunocytes such as endothelial cells and keratinocytes. Proinflammatory cytokines include IL-1, IL-2, the IL-17 family, IFN-gamma and TNF-alpha while anti-inflammatory cytokines include IL-4 and IL-10. A relative preponderance of $T_H1$ proinflammatory cytokines or an insufficiency of $T_H2$ anti-inflammatory cytokines induces local inflammation and recruitment

of additional immunocyte populations which produce added cytokines [33]. A vicious cycle of inflammation occurs that results in cutaneous manifestations such as a plaque. Psoriatic lesions are characterized by a relative increase of $T_H1$ (IL-2, IFN-gamma TNF-alpha and TNF-beta) to $T_H2$ (IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13) type cytokines, and an increase in $T_H17$ type cytokines (discussed below). As discussed previously, NKT cells stimulated by CD1d-overexpressing keratinocytes increase production of proinflammatory IFN-gamma without effect on the anti-inflammatory IL-4. In addition to the cytokines produced by T cells, APCs produce IL-18, IL-23 and TNF-alpha found in the inflammatory infiltrate of psoriatic plaques. Both IL-18 and IL-23 stimulate $T_H1$ cells to produce IFN-gamma, and IL-23 stimulates $T_H17$ cells. Clearly, a $T_H1/T_H17$ type pattern governs the immune effector cells and their respective cytokines present in psoriatic skin.

## TNF-Alpha

Although a network of cytokines is responsible for the inflammation of psoriasis, TNF-alpha has been implicated as a master proinflammatory cytokine of the innate immune response due to its widespread targets and sources. TNF-alpha is produced by activated T cells, keratinocytes, NK cells, macrophages, monocytes, Langerhans APCs and endothelial cells. TNF-alpha was originally observed to induce septic shock and tumor cell necrosis at higher concentrations as well as function as an immune mediator of local tissue insults at lower concentrations. Psoriatic lesions demonstrate high concentrations of TNF-alpha, while the synovial fluid of psoriatic arthritis patients demonstrates elevated concentrations of TNF-alpha, IL-1, IL-6 and IL-8 [33]. In psoriasis, TNF-alpha supports the expression of adhesion molecules (intercellular adhesion molecule (ICAM)-1 and P-and E-selectin), angiogenesis via vascular endothelial growth factor (VEGF), the synthesis of proinflammatory molecules (IL-1, IL-6, IL-8 and nuclear factor (NF)-kappaB) and keratinocyte hyperproliferation via vasoactive intestinal peptide (VIP) [34].

A role for TNF-alpha in psoriasis treatment was serendipitously discovered in a trial for Crohn's disease in which infliximab, a mouse human IgG1 anti-TNF-alpha monoclonal antibody, was observed to clear psoriatic plaques in a patient with both Crohn's disease and psoriasis [35]. Immunotherapies that target TNF-alpha including infliximab, etanercept, and adalimumab show significant efficacy in the treatment of psoriasis [36–38]. TNF-alpha is regarded as the driver the inflammatory cycle of psoriasis due to its numerous modes of production, capability to amplify other proinflammatory signals and efficacy and rapidity with which it produces clinical improvements in psoriasis.

## The IL-23/$T_H17$ Axis

A new distinct population of helper T cells has been shown to play an important role in psoriasis. They develop with the help of IL-23 (secreted by dermal dendritic cells) and subsequently secrete cytokines such as IL-17, and are therefore named $T_H17$ cells. CD161 is considered a surface marker for these cells [39]. Strong evidence for this IL-23/$T_H17$ axis has been shown in mouse and human models, as well as in genetic studies.

IL-23 is a cytokine that shares the p40 subunit with IL-12 and has been linked to autoimmune diseases in both mice and humans [3]. IL-23 is required for optimal development of $T_H17$ cells [40] from a committed CD4+ T cell population after exposure to TGF-β1 in combination with other proinflammatory cytokines [41, 42]. IL-23 mRNA is produced at higher levels in inflammatory psoriatic skin lesions versus uninvolved skin [43], and intradermal IL-23 injections in mice produced lesions resembling psoriasis macro- and microscopically [44]. Furthermore, several systemic therapies have shown to modulate IL-23 levels and correlate with clinical benefit [3]. Alterations in the gene for the IL-23 receptor have shown to be protective for psoriasis [45–47] and the gene coding for the p40 subunit is associated with psoriasis [45, 46].

$T_H17$ cells produce a number of cytokines such as IL-22, IL-17A, IL-17F, and IL-26; the

latter three are considered to be specific to this lineage [41]. IL-22 acts on outer body barrier tissues such as the skin and has anti-microbial activity. Blocking the activity of IL-22 in mice prevented the development of skin lesions [48], and psoriasis patients have elevated levels of IL-22 in the skin and blood [49, 50]. The IL-17 cytokines induce the expression of proinflammatory cytokines, colony-stimulating factors, and chemokines and recruit, mobilize, and activate neutrophils [51]. IL-17 mRNA was found in lesional psoriatic skin but not unaffected skin [52], and cells isolated from the dermis of psoriatic skin have been shown to produce IL-17 [53]. IL-17A is not elevated in the serum of psoriatic patients (unlike other autoimmune diseases) [54], and it is therefore though that $T_H17$ cells and IL-17A production are localized to the affected psoriatic skin. Consistent with this is the finding that treatments such as cyclosporin A and anti-TNF agents decrease proinflammatory cytokines in lesional skin but not in the periphery [55–57]. These cytokines released by $T_H17$ cells, in addition to those released by $T_H1$ cells, act on keratinocytes and produce epidermal hyperproliferation, acanthosis, and hyperparakeratosis characteristic of psoriasis [3].

New therapies have been developed to target the IL-23/$T_H17$ axis. Ustekinumab targets the p40 subunit of IL-12 and IL-23 and prevent it from binding with its receptor. Ustekinumab is approved for moderate-to-severe plaque psoriasis; it is a very effective treatment whose effect may be sustained for up to 3 years, is generally well tolerated, and may be useful for those refractory to anti-TNF therapy like etanercept [58]. Briakinumab, another blocker of IL-12 and IL-23 is currently under investigation.

## Genetic Basis of Psoriasis

Psoriasis is a disease of overactive immunity in genetically susceptible individuals. Because patients exhibit varying skin phenotypes, extracutaneous manifestations and disease courses, multiple genes resulting from linkage disequilibrium are believed to be involved in the pathogenesis of psoriasis. A decade of genome-wide linkage scans have established that PSORS1 is the strongest susceptibility locus demonstrable through family linkage studies; PSORS1 is responsible for up to 50 % of the genetic component of psoriasis [60]. More recently, human leucocyte antigen (HLA)-Cw6 has received the most attention as a candidate gene of the PSORS1 susceptibility locus on the MCH I region on chromosome 6p21.3 [61]. This gene may function in antigen presentation via MHC I, which aids in the activation of the overactive T cells characteristic of psoriatic inflammation.

As previously mentioned, studies involving the IL-23/$T_H17$ axis have shown genetics to play a role. Individuals may be protected from psoriasis with a non-synonymous nucleotide substitution in the IL23R gene [46–48], and certain haplotypes of the IL23R gene are associated with the disease [46, 48] in addition to other autoimmune conditions.

Genomic scans have shown additional susceptibility loci for psoriasis on chromosomes 1q21, 3q21, 4q32-35, 16q12, 17q25. Two regions on chromosome 17q were recently localized via mapping which demonstrated a 6 Mb separation thereby indicating independent linkage factors. Genes SLC9A3R1 and NAT9 are present in the first region while RAPTOR is demonstrated in the second region [62]. SLC9A3R1 and NAT9 are players that regulate signal transduction, the immunologic synapse and T cell growth. RAPTOR is involved in T cell function and growth pathways. Using these genes as an example, we can predict that the alterations of regulatory genes, even those yet undetermined, can enhance T cell proliferation and inflammation manifested in psoriasis.

### Conclusion

Psoriasis is a complex disease whereby multiple exogenous and endogenous stimuli incite already heightened innate immune responses in genetically predetermined individuals. The disease process is a result of a network of cell types including T cells, dendritic cells and keratinocytes that, with the production of

cytokines, generate a chronic inflammatory state. Our understanding of these cellular interactions and cytokines originates from developments, some meticulously planned, others serendipitous, in the fields of immunology, cell and molecular biology and genetics. Such progress has fostered the creation of targeted immune therapy that has demonstrated significant efficacy in psoriasis treatment. Further study of underlying the pathophysiology of psoriasis may provide additional targets for therapy.

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# Psoriasis: Clinical Review and Update

3

Ivan Grozdev and Neil J. Korman

**Abstract**

Several types of psoriasis have been classified based upon a combination of morphology, distribution, and pattern. Plaque psoriasis is the most common and well-recognized form of psoriasis, also known as psoriasis vulgaris. It affects more than 80 % of patients. Guttate psoriasis is common in children and young adults with a family history of psoriasis and follows streptococcal infection of the upper respiratory tract or acute stressful life events. Characteristic acute generalized small, usually less than 1 cm in diameter, erythematous scaly papules develop over the whole body surface. The pustular variants of psoriasis can be divided into generalized and localized forms. Erythrodermic psoriasis is an acute, severe form of psoriasis characterized by generalized inflamed erythema and widespread scaling which affects more than 90 % of the body surface area. Additionally, psoriasis commonly presents at specific locations such as the scalp, nails, and body folds.

**Keywords**

Psoriasis • Plaque psoriasis • Guttate psoriasis • Sebopsoriasis • Pustular psoriasis • Erythrodermic psoriasis • Scalp psoriasis • Nail psoriasis • Inverse psoriasis

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Psoriasis can present in various patterns and forms. No complete agreement on the classification of the clinical variants exists [1]. However, the diagnosis is typically made by the recognition of the classic and distinctive lesions – well-demarcated erythematous plaques with adherent silvery scales. These correlate to the inflammation, vascular dilatation, and altered epidermal proliferation and differentiation seen histopathologically. The most common sites of involvement

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include elbows, knees, lower back, and buttocks, but the disease can involve any cutaneous surface. The disease varies widely in severity and extent of involvement. There are multiple types of psoriasis that have been classified based upon a combination of morphology, distribution, and pattern. This section will review the clinical forms of the disease along with some updates on its various subtypes.

## Plaque Psoriasis

This is the most common and well-recognized form of psoriasis, also known as psoriasis vulgaris. It affects more than 80 % of the patients. It is characterized by sharply defined erythematosquamous plaques, usually distributed symmetrically over the extensor surfaces of the upper and lower extremities, lower back and scalp [2]. There can be variation in the intensity of erythema and amount of scale. The size of the lesions varies from coin-sized to palm-sized and larger. The term nummular psoriasis is used if coin-sized lesions predominate [3]. If larger than palm-sized lesions predominate, the term of choice is geographical psoriasis. Additional features of psoriatic plaques include the Auspitz sign as the presence of pinpoint bleeding when the tightly adherent scales are removed from the surface of the plaque, and Woronoff's ring as the presence of a white ring around erythematous plaques undergoing topical treatment or phototherapy [4]. Psoriasis is well known to develop at sites of physical trauma (scratching, sunburn or surgery), which is the isomorphic or Koebner's phenomenon [5]. The term sebopsoriasis is used if lesions predominate on seborrhoeic areas, occasionally causing difficulties separating the disease from seborrhoeic dermatitis [6]. Lesions of plaque psoriasis are quite stable over time. The term annular or polycyclic psoriasis is used if central clearing of the lesions with an active border appear as they regress. Post-lesional hypopigmentation may also be associated with clearing (psoriatic leukoderma). Although patients may be asymptomatic, pruritus, which is quite distressing, is often present [7, 8].

## Guttate Psoriasis

Guttate psoriasis is characterized by an acute generalized eruption of small, usually less than 1 cm in diameter, erythematous scaly papules, distributed as "droplets" over the whole body surface. Lesions usually occur over the trunk and the palms and soles are usually spared. Guttate psoriasis is common in children and young adults with a family history of psoriasis and follows streptococcal infection of the upper respiratory tract or acute stressful life events [9]. It can appear either de novo or as an acute exacerbation of pre-existing psoriasis. This form of psoriasis may resemble other cutaneous conditions like pityriasis rosea or secondary syphilis. The prognosis of this manifestation is excellent in children with spontaneous remissions often occurring in the course of weeks or months. Prognosis is worse in adults [3]. The risk of developing a more chronic form of psoriasis after a first episode of guttate psoriasis has been estimated at 40 % [10]. Guttate psoriasis and chronic plaque psoriasis are genetically similar conditions with a strong association to the PSORS1 genetic locus [11]. Although guttate psoriasis is highly associated with streptococcal infections, there is little evidence-based data to support treatment of these patients with antibiotics or tonsillectomy [12].

## Pustular Psoriasis

The pustular variants of psoriasis include the most confusing nosology and difficult problems for the clinicians. The pustuloses can be divided into generalized and localized forms (Table 3.1).

## Generalized Pustular Psoriasis

This form of psoriasis is also known as von Zumbusch psoriasis. It is a severe form of psoriasis and can be life-threatening. It may be preceded either by plaque psoriasis or arise de novo. Withdrawal of systemic steroids may trigger the disease. This form of psoriasis is characterized by sterile pustules arising from the surface of

**Table 3.1** Generalized and localized pustuloses

| Generalized variants | Localized variants |
|---|---|
| Von Zumbusch-type | One or more plaques with pustules |
| Impetigo herpetiformis | Palmoplantar pustulosis |
| Acute generalized exanthematous pustulosis | Annular (Subcorneal pustular dermatosis of Sneddon and Wilkinson) |
| | Acrodermatitis continua of Hallopeau |
| | Keratoderma blenorrhagicum (Reiter's syndrome) |
| | SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis) |

Adapted with permission from Camisa C. [11]
Some of these variants are currently considered as separate entities

large erythematous patches of skin distributed over the trunk and extremities. The pustules eventually dry and peel. In some cases, these pustules may form confluent large lakes of pus. Oral lesions may be present with pustules or acute geographic tongue. The eruption is usually accompanied by systemic symptoms including fever, chills, diarrhea, and arthralgias. Leukocytosis and an elevated erythrocyte sedimentation rate are commonly encountered. Generalized pustular psoriasis may be associated with polyarthritis and cholestasis from neutrophilic cholangitis [14]. It has been reported that pustular psoriasis occurs in 9 % of psoriasis patients with no articular involvement and in 41 % of patients with arthropathic psoriasis [15].

## Impetigo Herpetiformis

As originally described, impetigo herpetiformis refers to generalized pustular psoriasis in a pregnant woman without prior history of psoriasis [16]. Onset is usually before the 6th month of pregnancy and resolution occurs with delivery. There have been reports of recurrences following pregnancy but associated with monthly menses and oral contraceptives [17].

Acute generalized exanthematous pustulosis is a self-limiting febrile drug reaction usually resolving in 2 weeks after withdrawal of suspected agent. It is a separate entity that should be distinguished from generalized pustular psoriasis, even in patient with pre-existing psoriasis, by the following features: recent drug intake; higher fever; greater leukocytosis and eosinophilia along with a lack of arthritis [13].

## Localized Pustular Forms

A pustular form of psoriasis may occur anywhere pre-existing or new plaques are developing. Pustules appear within established psoriasis plaques or alone. Palmoplantar pustulosis is the most common pustular variant of psoriasis. It is characterized by pruritic or burning erythematous patches on the palms and soles, within which multiple pustules develop. Initially the pustules are yellow. Later they turn dark brown and crust over creating a tender and diffusely eroded surface. Those patients experience great impairment of their quality of life with difficulty in walking and using their hands. Some authors consider palmoplantar pustulosis to be a separate dermatologic disorder as it affects predominantly female patients, has a higher age of onset, is associated with cigarette smoking (up to 100 % of cases at onset), and consistently responds poorly to topical therapy. Palmoplantar pustulosis does not share the association of PSORS1 gene locus with plaque psoriasis, supporting the concept that these are distinct entities [11]. A specific form of palmoplantar pustulosis is acrodermatitis continua of Hallopeau. The pustules are located on the fingertips or toes and are very painful and disabling. Nail dystrophy and paronychial erythema are often seen.

## Erythrodermic Psoriasis

Erythrodermic psoriasis is an acute, severe form of psoriasis characterized by generalized inflamed erythema and widespread scaling which affects more than 90 % of the body surface area. It may develop gradually or acutely during the course of chronic psoriasis, but it may also be the initial

manifestation of psoriasis. Erythrodermic psoriasis is more common in patients suffering simultaneously from psoriatic arthropathy then in psoriatic patients with no articular involvement [13, 15]. Important precipitating factors for erythrodermic psoriasis include inappropriate use of potent topical and systemic corticosteroids. Psoriatic erythroderma is not substantially different from erythroderma caused by eczematous dermatitis, seborrhoeic dermatitis, pityriasis rubra pilaris, drugs, lymphoma, or leukemia. Associated findings may include lymphadenopathy, hypothermia, tachycardia, peripheral edema, elevated erythrocute sedimentation rate (ESR), hypoalbuminemia, anemia, leukocytosis or leucopenia, elevations of lactate dehydrogenase, liver transsaminases, uric acid, and calcium [18]. Severe medical complications can develop due to dehydration from extensive fluid and electrolyte disturbances, protein losses, high-output cardiac failure, and infection.

## Manifestations of Psoriasis in Specific Locations

Although psoriasis predominates at certain areas, there are several other locations that should be examined in patients in whom the diagnosis of psoriasis is suspected.

### Scalp Psoriasis

The scalp is the most common location of psoriasis [3]. Plaques typically form on the scalp and along the hair margin. Many patients discover they have psoriasis because of a dandruff-like desquamation. When the scalp is the only location of psoriasis, it is difficult to distinguish it from seborrheic dermatitis. The term sebopsoriasis is sometimes used in such cases [6]. The scales sometimes are firmly attached to the scalp hair. This particular variety is called pseudotinea amiantacea and is more frequent in children [19]. Cicatricial alopecia may develop in some patients [20].

### Nail Psoriasis

Nail involvement is characteristic of psoriasis and helps in diagnosis when characteristic skin changes are equivocal or absent. Nail abnormalities as a major clinical feature is found in about 20 % of psoriasis patients [21]. Nail changes are frequently associated with arthritis. The most common stigma of nail psoriasis is pitting – small depressions within the surface of the nail plate resulting from psoriatic involvement of the nail matrix producing nail plate growth. Other signs of nail psoriasis include the salmon patch or oil drop sign indicating nail bed involvement, subungual hyperkeratosis, red spots in the lunula, leukonychia [4]. Psoriasis of the nail bed can also cause onycholysis, which is separation of the nail from the nail matrix. Nail psoriasis may have a significant impact of patient's quality of life [22].

### Inverse (Flexural, Intertiginous) Psoriasis

This form of psoriasis affects skin folds, also known as intertriginous regions, such as axillae, submammary regions, gluteal cleft, retroauricular folds, and inguinal folds. It is estimated at 2–6 % in psoriatic patients [3]. Obese patients are likely to have this form of psoriasis. Thin well-demarcated erythematous patches without desquamation are the typical skin lesions [23]. Usually the patches are superficially eroded with fissuring in the body fold. Inverse psoriasis may occur alone but is more frequently accompanied by plaque psoriasis elsewhere. In cases in which it is the only location of psoriasis, inverse psoriasis may be confused for bacterial, fungal, or candidal intertrigo. Scrapings or cultures are then needed to exclude infection. Napkin psoriasis is difficult to be differentiated from napkin dermatitis or seborrhoeic dermatitis. Sharp demarcation of patches and silvery scaling might be helpful, but often this diagnosis remains uncertain [3].

## Rare Forms and Some Specific Locations

Geographic tongue also known as benign migratory glossitis is often seen in psoriatic patients, especially in patients with generalized pustular psoriasis. It is characterized by erythematous patches surrounded by a white line and loss of filiform papillae on the dorsum of the tongue [4]. The lips can be affected in psoriasis but this should be differentiated from discoid lupus erythematosus and desquamative cheilitis [24]. Location at the genitalia has been reported in 2 % of the patients with psoriasis [3]. If psoriasis only affects the glans, the most common site of involvement is the proximal part [19]. It should be differentiated from erythroplasia of Queyrat. Patients with Reiter's syndrome can develop psoriasiform skin lesions 1–2 months after the onset of arthritis. The presentation is known as keratoderma blenorragicum and affects soles, toes, legs, scalp, and hands [25]. The psoriasiform patch has distinctive circular scaly borders that develop from fusion of papulovesicular plaques with thickened yellow scale. Ocular involvement has been reported in up to 10 % of psoriatic patients. Blepharitis and keratitis are the established features of ocular psoriasis [3].

## Differential Diagnosis of Psoriasis

The clinical features of psoriasis are usually sufficient to make the diagnosis. However, differential diagnosis of some of the different clinical variants of psoriasis should be mentioned (Table 3.2).

The presentation and clinical course of psoriasis show wide variations, from subtle minimal signs to generalized skin involvement [27]. Classification of the clinical features of the disease has been a controversial subject among investigators. In the future, a classification based on more specific phenotypic features such as psoriasis plaque thickness might be more helpful in understanding the genetics and the underlying pathomechanism of psoriasis [28].

**Table 3.2** Differential diagnosis of variants of psoriasis

| Clinical variant | Differential diagnosis |
|---|---|
| Guttate psoriasis | Pityriasis versicolor, Pityriasis rosea, Secondary syphilis |
| Palmoplantar plaques psoriasis | Hand eczema, Contact dermatitis, Dermatophytosis |
| Palmoplantar pustulosis | Pompholyx, Dermatophytosis |
| Generalized pustular psoriasis | Acute generalized exanthematous pustulosis |
| Erythrodermic psoriasis | Atopic dermatitis, Drug reactions, Cutaneous T-cell lymphoma, Ichthyoses |
| Nail psoriasis | Dermatophytosis, Drug reactions, Phototoxic reactions |
| Inverse psoriasis | Candida infection, Erythrasma, Seborrhoeic dermatitis, Contact allergic dermatitis, Benign familial pemphigus (Hailey-Hailey disease) |
| Scalp psoriasis | Seborroeic dermatitis, Contact allergy, Ringworm |

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# Psoriasis: Epidemiology, Potential Triggers, Disease Course

4

Ivan Grozdev and Neil J. Korman

**Abstract**

Worldwide prevalence rates of psoriasis range from 0.6 to 4.8 %. The disease tends to have a bimodal distribution of onset with the major peak occurring at age of 20–30, and a later smaller peak occurring at age of 50–60. While there are many potential triggers of psoriasis, infections are an important trigger and up to half of children with psoriasis have an exacerbation within 2 weeks following an upper respiratory infection. Psychological distress is a causative or maintaining factor in disease expression for many patients with psoriasis. Other well-documented triggers for flares include trauma, alcohol and smoking, as well as obesity. Plaque psoriasis is usually chronic with intermittent remissions. Plaques may persist for months to years at the same locations; however, periods of complete remission may occur.

**Keywords**

Psoriasis • Epidemiology • Trauma • Koebner phenomenon • Drug-induced psoriasis • Stress • Infections • Psoriasis remission

## Epidemiology

Worldwide prevalence rates of psoriasis range from 0.6 to 4.8 % [1, 2]. Women and men are equally affected. The prevalence of the disease varies depending on the climate and ethnicity, although these relationships are complicated. The Caucasian population of Europe and the US are affected equally by psoriasis [3, 4]. The disease is uncommon in the Mongoloid race. Asian Americans have a prevalence of between 0.4 % [5] and 0.7 % [6]. African-Americans have a prevalence of 1.3 % [7], while American-Indians have prevalence of 0.2 % or less [6]. Psoriasis is

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absent in certain populations such as South American Indians and Australian Aborigines [8], while in the Arctic Kasah'ye its prevalence is 11.8 % [9]. A positive correlation between latitude and psoriasis prevalence would be expected given the efficacy of ultraviolet light as a treatment [10]. However, Jacobson et al. identified 22 population-based surveys, case-control studies, and reviews on psoriasis prevalence rates from numerous regions around the globe and found no correlation between absolute latitude and psoriasis prevalence [11]. These findings suggest that other factors or a combination of factors may play a role in the frequency of psoriasis rather than latitude alone. Differences in the prevalence rates of psoriasis between two areas of the same continent (West Africa prevalence rates of 0.05–0.9 % compared to South Africa prevalence rates of 2.8–3.5 % [12]) suggest that genetic factors play an important role [13].

Although new onset psoriasis occurs in all age groups from newborns to age 108 [14], the disease tends to have a bimodal distribution of onset with the major peak occurring at age of 20–30, and a later smaller peak occurring at age of 50–60. Patients with early age onset of psoriasis are more likely to have a family history of psoriasis, the course of the disease tends to be more unstable with frequent remissions and relapses, the disease tends to be more resistant to treatment and more severe disease tends to be more common. Late age onset psoriasis tends to have a more stable chronic clinical course, and is more likely to be associated with psoriatic arthritis, nail involvement and palmoplantar pustular involvement [15, 16]. The mean age of onset of psoriasis varies from study to study, but nearly 75 % percent of patients with psoriasis have an onset before the age of 40, and 12 % of patients have the onset of psoriasis at age of 50–60 [17]. More recent studies have indicated an increasing prevalence of childhood psoriasis [18]. The known familial concentration of psoriasis indicates an important role of hereditary factors; however a 67 %-concordance in monozygotic twins suggests that environmental factors may also be an important component of psoriasis [19].

## Potential Triggers

### Trauma

Trauma can trigger the exacerbation of psoriatic lesions or the development of new lesions (this is known as the Koebner phenomenon, originally described by Heinrich Koebner in 1872). Trauma as a trigger is more commonly seen in patients who develop psoriasis at an early age and those who require multiple therapies to control their disease [20]. In clinical studies the prevalence of the Koebner phenomenon may range from 24–51 % of patients while in experimental studies among selected patients with severe psoriasis and a history of the Koebner phenomenon, it was observed in up to 92 % of patients [21]. Factors that may lead to the Koebner phenomenon include acupuncture, vaccinations, scratches, removal of adhesive bandages, insect and animal bites, burns (thermal, chemical, electrosurgical), radiation, incisions, cuttings, abrasions, tattoos, irritant and allergic contact dermatitis, phototoxic dermatitis, as well as skin diseases including acne, furuncles, herpes zoster, and lichen planus. The "reverse" Koebner phenomenon which occurs when trauma within a psoriatic lesion causes clearing of that psoriatic lesion has also been observed [22]. Some treatment modalities for psoriasis are based on the reverse Koebner phenomenon such as electrodissecation, dermabrasion, cryotherapy, and CO2-laser therapy.

### Infections

Infections have long been recognized as important triggers for psoriasis exacerbations. Up to half of children with psoriasis have an exacerbation of their disease within 2 weeks following an upper respiratory infection [23, 24]. Infection with streptococcus pyogenes has a well-known association with guttate psoriasis [25]. Up to 85 % of patients with an episode of acute guttate psoriasis show evidence of a preceding streptococcal infection as demonstrated by positive anti-streptolysin-O titers [24]. In another study,

84 % of patients with guttate psoriasis had a history of infection prior to occurrence of skin lesions, and the majority of these patients (63 %) had a verified streptococcal pharyngitis [26]. Although pharyngeal origin of the infection is most common, skin infection with streptococcus pyogenes can also lead to guttate psoriasis. Streptococcal infections can elicit exacerbations of other types of psoriasis and psoriatic arthritis as well. Patients with psoriasis develop sore throats much more frequently than non-psoriatic individuals and it is well documented that streptococcal throat infections can trigger the onset of psoriasis, and such infections cause exacerbation of chronic psoriasis [27]. The study of 111 patients isolated streptococcus pyogenes in 13 % of patients with a guttate flare of chronic plaque psoriasis, in 14 % of patients with chronic plaque psoriasis, and in 26 % of patients with acute guttate psoriasis, while 7 % of the patients in the control group had streptococcus pyogenes isolated [28]. Although many reports suggest a possible role for antibiotics or tonsillectomy in the treatment of guttate psoriasis [27, 29–33], the data is controversial about the beneficial effect of either intervention [34].

Superantigens such as streptococcal pyogenic exotoxin [35–38] as well as peptidoglycan derived from various different bacterial sources [39, 40] can lead to the development of psoriasis due to an abnormal response of the innate immune system towards the super antigen. Development and use of experimental vaccines to treat psoriasis are based on this hypothesis [41, 42]. Other microorganisms reported to be potential triggers for psoriasis include Staphylococci, Candida, H pylori and Malassezia spp [25, 43] while infections with Yersinia spp have been reported to induce psoriatic arthritis [25].

Another important potential triggering factor for psoriasis is infection with the human immunodeficiency virus (HIV). The link between HIV infection and psoriasis onset seems paradoxical as the immunosuppression should lead to psoriasis improvement [44]. It is suggested that either HIV could function as a super antigen or other microorganisms, including opportunistic ones, could develop in the host because of the immune dysregulation [44]. The prevalence of psoriasis in patients with HIV infection is nearly 5 %, about twice that seen in the general population. The clinical manifestations of psoriasis in HIV-infected patients are similar to those in non-HIV-infected patients. However, lesions of more than one subset of psoriasis are often found in the same HIV patient [45]. For example, a patient with chronic plaque psoriasis may go on to develop guttate or pustular lesions. Psoriasis may occur at any time in the course of an HIV infection and exacerbations tend to be longer and more frequent than those in otherwise healthy psoriasis patients [46]. There is no observed relationship between psoriasis and the CD4 count. There is one report of psoriasis remission in the terminal stages of the acquired immunodeficiency syndrome [47] and another report on complete resolution of erythrodermic psoriasis in an HIV and HCV patient, unresponsive to anti-psoriatic treatments after highly active antiretroviral therapy [48]. Rapid onset of acute eruptive psoriasis, frequent exacerbations or resistance to conventional and biologic treatments should raise the possibility of underlying HIV disease [48, 49]. It has been suggested that inflammation within psoriatic lesions develops against unknown antigens and super antigens of viral origin such as human papilloma virus 5 (HPV5), human endogenous retroviruses, Coxsackie adenoviruses, Arboviruses and others [43, 50, 51].

## Stress

Psychological distress is a causative or maintaining factor in disease expression for many patients with psoriasis. In one study, over 60 % of psoriasis patients believed that stress was the principal factor in the cause of their psoriasis [52]. Farber and colleagues surveyed over 5,000 patients with psoriasis and 40 % reported that their psoriasis occurred at times of worry and 37 % experienced worsening of psoriasis with worry [5]. In a more recent study of 400 patients with newly developed psoriasis, 46 % of the patients with plaque

psoriasis and 12 % of the patients with guttate psoriasis linked the onset of their disease with a life crisis, including divorce, severe or life-threatening disease of the patient or a family member, death in the family, financial burden, dismissal, or harassment in school [53]. In another study among 50 psoriasis patients, stressful life events were seen in 26 % of the patients within 1 year preceding onset or exacerbation of psoriasis, suggesting the potential value of relaxation therapies and stress management programs in the management of patients with psoriasis [54]. Stress-induced relapse rates of up to 90 % have been reported in children [23]. In an epidemiological study of 784 Greek psoriasis patients, stress was self-reported as the main cause for psoriasis exacerbations by 60 % of patients [55]. It was demonstrated that "low level worriers" achieved clearing of their skin with PUVA (psoralen plus ultraviolet-A) a median of 19 days earlier than "high level worriers" undergoing the same treatment [56]. Other studies reveal that cognitive-behavioral therapy in conjunction with medical therapy can lead to a significantly greater reduction in the severity of psoriasis than medical therapy alone [57, 58]. The role that acute psychosocial stressors play in altering hypothalamic-pituitary-adrenal (HPA) responses in patients with psoriasis is an area of controversy. Some data shows that stress-exacerbated psoriasis flares lead to decreased levels of cortisol [59], while other fails to show such a correlation [60, 61]. The epidemiologic data linking psychological stress and onset or exacerbation of psoriasis is also controversial with some studies supporting this association [62], while others do not [63, 64].

## Medications

Various medications used for concomitant diseases may influence psoriasis in terms of precipitating or worsening it. Drug-induced psoriasis is defined as the development of psoriasis after treatment with a medication that remits when that medication is withdrawn, while drug-triggered or drug-exacerbated psoriasis is defined as the development of psoriasis after treatment with a medication whose withdrawal does not influence the clinical course [65]. The time between the start of the drug intake and the outbreak of psoriatic eruption may vary and depends on the drug and is classified as follows: short (<4 weeks between the start of the drug and the onset of psoriatic eruption), medium (>4 and <12 weeks), and long (>12 weeks) [66]. Several medications may trigger or worsen psoriasis. The most common medications that have been reported to trigger psoriasis include lithium, beta-blockers, non-steroidal anti-inflammatory drugs, tetracyclines, and antimalarials [65, 67]. Several other medications that have reported to worsen psoriasis include angiotensin converting enzyme (ACE) inhibitors, terbinafine, clonidine, iodine, amiodarone, penicillin, digoxin, interferon-alpha, and interleukin-2. The abrupt discontinuation of systemic or superpotent topical corticosteroids can serve as triggers of psoriasis although the frequency of this association has not been studied. While these observations suggest the possibility that certain medications may trigger psoriasis worsening, no controlled trials have proven an association.

Newly developed psoriasis has been reported in patients taking TNF-alpha blockers for indications other than psoriasis, including Crohn's disease and rheumatoid arthritis [68, 69].

Interferons play an important role in the pathogenesis of psoriasis. Their use as medications such as IFN (α, β, γ) and imiquimod may induce or worsen psoriasis [43, 70]. Additionally, withdrawal of interferon use in hepatitis C commonly leads to improvement in psoriasis [71].

## Alcohol and Smoking

Alcohol and smoking have both been implicated as triggering factors for psoriasis exacerbations. It is well documented that the prevalence of psoriasis is increased among patients who abuse alcohol [72]. However, conflicting evidence exists as to whether increased alcohol intake in psoriasis patients is a factor in the pathogenesis or whether having a chronic disorder like psoriasis leads to greater intake of alcohol in an attempt

to self-medicate. A study of 144 Finnish patients with psoriasis demonstrated that alcohol consumption in the previous 12 months was linked to the onset of psoriasis. This study suggests that psoriasis may lead to sustained alcohol abuse and that this alcohol intake may perpetuate the disease [73]. Qureshi et al. prospectively evaluated the association between total alcohol consumption and risk of incident psoriasis in a cohort of 82,869 nurses [74]. Compared with women who did not drink alcohol, the multivariate relative risk of psoriasis was significantly higher for an alcohol consumption of 2.3 drinks per week or more. Moreover, examining the type of alcoholic beverage, non-light beer intake was associated with an increased risk of developing psoriasis among women, while other alcoholic beverages did not increase this risk. Recently, a meta-analysis of case-control studies showed that the overall odds ratio of psoriasis for drinking persons compared to those with non-drinking habits was 1.531 ($P=0.002$), suggesting that alcohol consumption is associated with an increased risk of psoriasis [75]. Further support of increasing alcohol abuse as a post-diagnosis condition was seen in a case-control study of 60 Australian twins who were discordant for psoriasis [76]. In this study, no difference in alcohol consumption between discordant twins, either monozygotic or dizygotic, was discovered. The influence of increasing alcohol consumption on the severity of psoriasis has also been investigated and there appears to be a tendency for heavy drinkers to develop more extensive and severe psoriasis that lighter drinkers [77].

Mortality related to alcohol use in psoriasis has also been evaluated. A population-based study of over 5,000 patients followed for 22 years demonstrated that psoriatic patients have an increased mortality rate when compared to a control group [78]. However, this study did not account for previous hepatotoxic psoriasis therapies or other medical conditions, and used the most severe psoriasis patients (those who required hospital admission for their psoriasis), suggesting that the elevated mortality rates attributed to these patients may have been overstated. In summary, alcohol consumption is more prevalent in psoriasis patients, and it may also increase the severity of psoriasis. The association of alcohol with the pathogenesis and exacerbation of psoriasis is less clear. Prolonged alcohol abuse may lead to alcoholic liver disease, and in that way may decrease treatment responsiveness and options, which may prolong exacerbations.

Patients with psoriasis are more likely than those without psoriasis to smoke. In a large cross-sectional study from Utah, 37 % of psoriatic patients acknowledged they were smokers compared to 25 % smokers in the general population [79]. Although the Finnish study of 144 psoriasis patients, mentioned above, found no association between smoking and the onset of psoriasis [73], another study of 55 women demonstrated an increased smoking rate of psoriasis patients compared to controls [80]. Naldi et al. examined 560 patients and showed that the risk for developing psoriasis was the greater in former smokers and current smokers than in those who had never smoked [81]. A hospital-based Chinese study evaluated 178 psoriasis patients and 178 controls and found a graded positive association between the risk of psoriasis and the intensity or duration of smoking [82]. Moreover, they showed that the risk of psoriasis in smokers with the HLA-Cw6 haplotype was increased by 11-fold over non-smokers without the HLA-Cw6 haplotype demonstrating an additive effect of genetics on that of smoking in inducing psoriasis. Gene-smoking interaction was found also by Yin et al. [83]. In a larger Italian study of 818 patients, those that smoked greater than 20 cigarettes per day were at a twofold increased risk for more severe psoriasis than those who smoked less than 10 cigarettes per day [84]. The largest and most definitive study investigating the association of smoking with psoriasis was the Nurses' Health Study II which prospectively followed a cohort of over 78,000 US nurses over a 14 year time period. They demonstrated a "dose-response" relationship for smoking and the risk of developing incident psoriasis [85] and that the risk of incident psoriasis decreases nearly back to that of never smokers 20 years after stopping smoking. In addition, they also found that prenatal and childhood exposure to passive smoke was associated with an increased risk of psoriasis.

## Obesity

Numerous studies demonstrate an increased prevalence of obesity, defined as a body mass index (BMI) ≥30 kg/m$^2$, among patients with psoriasis [79, 86–90]. The findings of a systematic review and meta-analysis of multiple observational studies support an increased prevalence of obesity in patients with psoriasis [90]. The pooled odds ratio [OR] for obesity for patients with psoriasis compared with a control group without psoriasis was 1.66 (95 % CI 1.46–1.89). Further support for this link between psoriasis and obesity derives from a review of over 10,000 patients with moderate to severe psoriasis enrolled in clinical trials of biologic therapies [86] where the average BMI for all patients in the trials was 30.6 kg/m$^2$. There is also a correlation between obesity and the severity of psoriasis [79, 87, 91]. In the systematic review and meta-analysis described above, the risk for obesity was more pronounced in patients with severe psoriasis (pooled OR 2.23, 95 % CI 1.63–3.05) than patients with mild psoriasis (pooled OR 1.46, 95 % CI 1.17–1.82) [91]. One study of 4,065 individuals with psoriasis and 40,650 controls that was included in the meta-analysis illustrated a progressive relationship between disease severity and obesity. Among patients with mild (≤2 % body surface area [BSA]), moderate (3–10 % BSA), and severe psoriasis (>10 % BSA), the prevalence of obesity compared to controls increased by 14, 34, and 66 %, respectively [91].

Children with psoriasis also have an increased risk for obesity. In an international cross-sectional study of 409 children with psoriasis, children with psoriasis were significantly more likely to be obese (BMI ≥95th percentile) than controls (OR 4.29, 95 % CI 1.96–9.39) [92]. Similar to the general population of patients with psoriasis, a correlation between disease severity and obesity was observed. Children with severe psoriasis had a greater increase in risk for obesity than children with mild disease (OR 4.92, 95 % CI 2.20–10.99 versus 3.60, 95 % CI 1.56–8.30).

More than one factor may contribute to the association between obesity and psoriasis. Although the negative psychosocial impact of psoriasis was initially considered the sole reason for excess weight in patients with psoriasis [79], more recent data suggest that obesity may increase risk for psoriasis. In an analysis of data collected from almost 80,000 women in the Nurses' Health Study II, increased adiposity and weight gain were identified as strong risk factors for psoriasis [93]. Compared to women with a BMI of 21.0–22.9 kg/m$^2$ at age 18, the multivariate relative risk for the development of psoriasis for subjects with a BMI ≥30 kg/m$^2$ at the same age was 1.73 (95 % CI, 1.24–2.41), and only 0.76 (95 % CI, 0.65–0.90) for women with a BMI <21 kg/m$^2$.

Data on the effects of weight loss on disease severity in psoriasis are limited. The first randomized trial designed to explore the effect of weight loss on the severity of psoriasis found a statistically non-significant trend towards greater improvement in psoriasis (as assessed by Psoriasis Area Severity Index [PASI] score) in overweight or obese psoriasis patients who were placed on a low-energy diet compared with a similar group of patients who continued to eat ordinary healthy foods [94]. The median baseline PASI score for all patients (5.4) correlated with mild to moderate psoriasis, and during the 16-week trial, patients allocated to the low-energy diet lost a mean of 15.8 kg compared with a mean loss of 0.4 kg in the control group. By study end, PASI scores were reduced by a mean of 2.3 in the low-energy diet group compared with only 0.3 in the control group. In addition, improvement in the Dermatology Quality of Life Index (a secondary outcome measure aimed at assessing the change in the impact of psoriasis on patient quality of life) was significantly greater in the low-energy diet group.

Improvement in psoriasis following gastric bypass surgery has been previously documented [95–97]. The mechanism of this is unclear, but may be related to alterations in the production of pro-inflammatory and anti-inflammatory adipokines, or weight-loss related changes in cutaneous microflora that result in the elimination of an antigenic stimulant [98]. However, worsening of psoriasis has also occurred after weight loss and weight loss surgery [99–101]. Further study is

therefore necessary to better understand the effect of weight loss on psoriasis.

Obesity may impact the efficacy of some psoriasis treatments [102]. A cohort study of approximately 2,400 patients receiving systemic therapy for psoriasis (including conventional and biologic agents) found that compared to individuals with a BMI of 20–24 kg/m$^2$, obese subjects (BMI ≥30 kg/m$^2$) were less likely to achieve 75 % improvement in disease severity (odds ratio 0.62, 95 % CI 0.49–0.79 at 16 weeks) regardless of the type of therapy [103]. In addition, in a randomized trial of 61 obese patients with moderate to severe psoriasis, weight loss improved the response to cyclosporine (2.5 mg/kg per day) [104]. The weight-based dosing regimen for ustekinumab, a newer treatment option for psoriasis, is used to mitigate the reduction in drug efficacy observed when the standard dose is utilized in obese patients [102].

### Estrogen

Elevated estrogen levels may serve as a trigger for psoriasis in some patients. Reports of new onset psoriasis at puberty, psoriasis worsened by estrogen therapy, and psoriasis that may be cyclical and related to menses, all suggest an etiologic role for elevated estrogen levels [105]. However, there have also been reports of psoriasis occurring or being exacerbated at the onset of menopause, which supports the opposite interpretation. These findings demonstrate that the potential role of estrogen as a triggering factor for psoriasis is not entirely clear. Additionally, while some patients report a worsening of psoriasis during pregnancy, nearly twice as many report improvement of their psoriasis during pregnancy [106–108]. Relapse during the early postpartum period is common. The mechanism by which psoriasis tends to improve during pregnancy is not well understood. However, there is now data to suggest that the up regulation of Th2 cytokines during pregnancy counteracts the effects of pro-inflammatory Th1 cytokines which are key players in the pathogenesis of psoriasis [77].

## Disease Course

Psoriasis encompasses a spectrum of cutaneous manifestations that varies from patient to patient and even in the same patient over time. While the majority of patients have chronic plaque psoriasis throughout the typically lifelong course of their disease, some patients may develop other variants including guttate, pustular, inverse or erythrodermic variants.

Plaque psoriasis is usually chronic with intermittent remissions. Plaques may persist for months to years at the same locations; however, periods of complete remission do occur. Psoriatic plaques usually develop slowly over time. During exacerbations, however, plaques tend to enlarge more rapidly with an active peripheral edge of increasingly intense erythema and scale along with increases in plaque thickness. New psoriatic papules may arise in areas of normal skin surrounding the established plaques and coalesce with these to form increasingly larger plaques. Resolution of a plaque typically begins at its center. The end result of plaque clearance may be post-inflammatory hypo- or hyper-pigmentation that gradually fades giving way to normal-appearing skin. Complete remission of psoriasis for several years followed by reoccurrence of disease can occur.

Traditionally, chronic plaque psoriasis has been considered a single entity; however, recent evidence demonstrates that patients with thin and thick plaque psoriasis have differing clinical features [109]. In addition to cutaneous involvement, plaque psoriasis may be associated with internal involvement, including joints and extra-articular sites such as the eyes. Concomitant psoriatic arthritis occurs in up to 30 % of patients with cutaneous psoriasis [110]. In a minority of patients, the symptoms of psoriatic arthritis appear before skin involvement. The prevalence of ophthalmic involvement in patients with cutaneous disease is not known; however, it is thought to occur in approximately 10 % of patients [111]. Psoriasis may affect almost any part of the eye, leading to blepharitis, peripheral keratopathy, acute anterior uveitis, posterior synechiae, conjunctivitis, and cataract formation.

Guttate psoriasis may clear spontaneously over weeks to months. There is a tendency toward younger age of onset with elevated antistreptolysin O (ASO) titer in patients with involuting course. Guttate psoriasis may become chronic and progress to plaque psoriasis, particularly in patients with a family history of psoriasis [112].

Palmoplantar pustulosis, which is now considered a single entity distinct from pustular psoriasis, is a chronic disease which tends to remain localized to the palms and soles. It is significantly aggravated by extrinsic factors, such as stress, smoking, and infections. It is less responsive to standard treatment and is commonly associated with sterile inflammatory bone lesions, such as the SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis).

Localized palmoplantar psoriasis presents with sterile pustules found only on the palms and soles that may be also seen with or without evidence of classic plaque type disease. Generalized pustular psoriasis (von Zumbusch) is a severe acute form of psoriasisin which small, monomorphic sterile pustules develop in painful inflamed skin which is triggered by pregnancy, rapid withdrawal of corticosteroids, infections, and hypocalcemia. It is complicated by systemic symptoms of fever, chills, and fatigue, as well as electrolyte derangements and liver abnormalities. This variant requires aggressive treatment with systemic immunosuppressive therapy. The mortality rate of generalized pustular psoriasis due to sepsis is high without appropriately aggressive treatment [77].

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# Psoriatic Arthritis: Clinical Review and Update

5

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**Abstract**

Psoriatic arthritis (PsA) a debilitating, seronegative spondyloarthropathy associated with psoriasis. The prevalence of PsA among psoriatic patients is estimated to be between 7 and 42 %. Skin lesions of psoriasis most often precede arthritic symptoms, however up to 20 % of patients with PsA manifest joint disease prior to skin involvement. Potential benefits of treatment include better quality of life and radiologic improvement of joint damage. Currently no universally accepted gold standard exists for diagnosing PsA, although the ClASsification criteria for Psoriatic Arthritis (CASPAR) criteria may gain widespread acceptance. While there is no universal agreement on the most accurate methods to evaluate PsA treatment, the Outcome Measures in Rheumatology (OMERACT) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommend using tools to assess of joint, skin, function, pain, patient's global assessment and quality of life. Treatment guidelines vary between GRAPPA and AAD, but generally recommend that mild PsA should be managed with NSAIDs and intralesional corticosteroid injections, and moderate to severe PsA should be managed with methotrexate or biologics. Biologic therapies, including TNF-α inhibitors, are recommended in the treatment of moderate to severe PsA, especially those patients with poor prognostic factors. With the potential benefits of early

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treatment, dermatologists and rheumatologists are strongly encouraged to assess patients for the signs and symptoms of PsA at each visit.

**Keywords**
Psoriatic Arthritis • Psoriasis • DMARD • Disease Modifying Anti-Rheumatic Drug • TNF • TNF blocker • Therapeutic recommendations • Comorbidities • Ustekinumab • Systemic therapies

## Introduction

Psoriatic arthritis (PsA) a debilitating, seronegative spondyloarthropathy associated with psoriasis. PsA was first described in 1818 by Baron Jean Louis Alibert [1], but has only been considered a distinct disease from rheumatoid arthritis since the 1960s [2, 3]. While clinical, radiological and genetic evidence supports PsA as a distinct disease entity, some authors describe PsA as a variant of RA that is modified by psoriasis [4].

Skin lesions of psoriasis most often precede arthritic symptoms, however up to 20 % of patients with PsA manifest joint disease prior to skin involvement [5]. The prevalence of PsA among psoriatic patients is estimated to be between 7 and 42 % although most experienced clinicians estimate a rate of approximately 25 % [6–9]. Although rates of PsA have been shown to correlate with psoriasis severity, 6 % of patients with minimal psoriasis compared to 56 % of patients with psoriasis affecting >10 % body surface area [6, 10], the extent of skin disease has not been found to correlate with the severity of joint disease [11]. The presence of nail dystrophy, scalp lesions, and intergluteal or perianal psoriatic lesions are associated with an increased likelihood of PsA [7]. Nail lesions in particular, are more common in patients suffering from PsA compared to patients who have psoriasis alone or RA [12].

PsA most commonly presents as an asymmetric oligoarthritis or polyarthritis with pain and stiffness [13]. PsA may affect the peripheral joints, axial skeleton, entheses and tenosynovial sheaths, but most commonly targets the joints of the hands and wrists as well as the feet, ankles, knees, shoulders [14]. Joint damage is present in 40–60 % of patients within the first year of disease onset [15–17]. See Fig. 5.1 for images of patients afflicted with PsA.

## Diagnosis and Classification

No universally accepted gold standard exists for diagnosing PsA [19], yet the criteria first proposed by Moll and Wright [20] are currently the most frequently used, and include:

1. an inflammatory arthritis (peripheral arthritis and/or sacroiliitis or spondylitis)
2. the presence of psoriasis
3. the (usual) absence of serological tests for rheumatoid factor.

Using these criteria, PsA has been subdivided into five types, including oligoarticular, spondylitic, asymmetric polyarticular, distal interphalangeal, and arthritis mutilans. Other authors, however, have suggested alternative criteria [21], or proposed minor changes to the Moll and Wright criteria [22–27].

PsA is a difficult disease to classify as it covers a large spectrum clinically, tends to relapse and remit, and requires evaluation of arthritic and psoriatic involvement [1]. Patients who have seronegative polyarthritis and psoriasis are particularly difficult to diagnose, as 5–30 % of RA patients may be seronegative, and those patients may also have psoriasis [19, 28].

In response to this need for clarity in PsA diagnosis, ClASsification criteria for Psoriatic

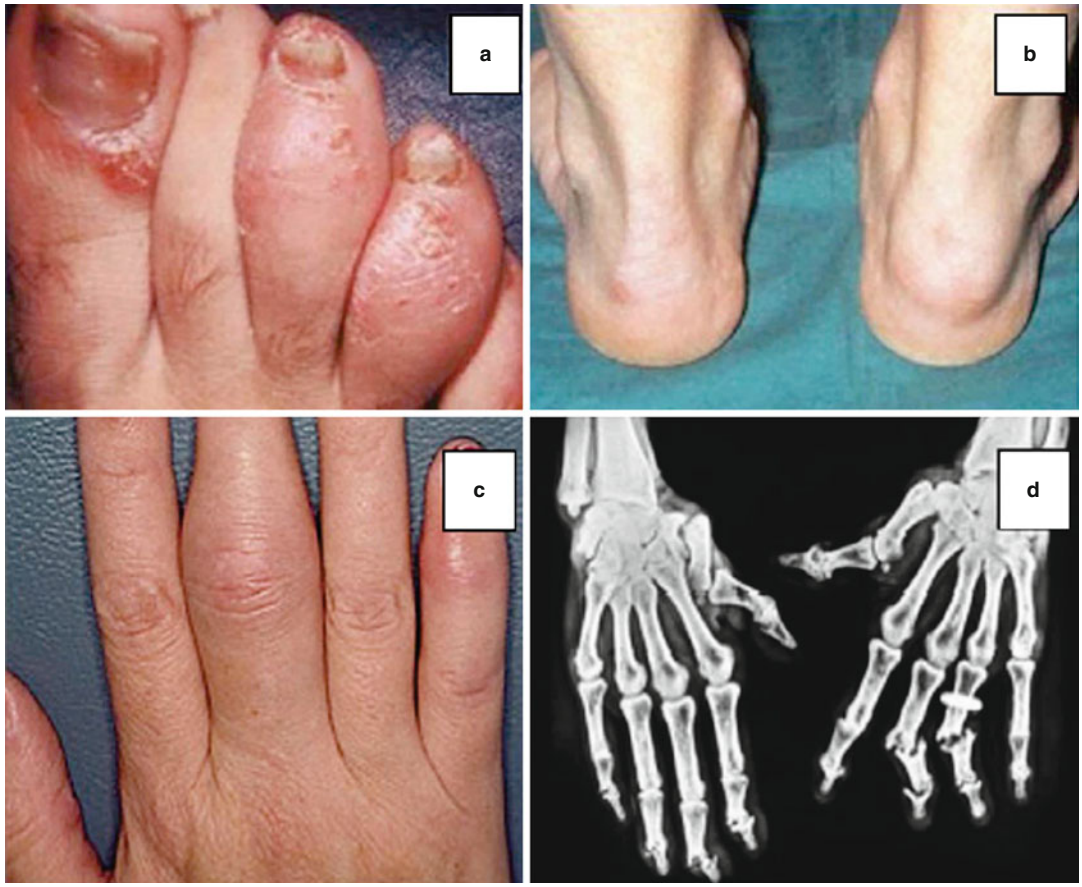


**Fig. 5.1** Photographs of patients with psoriatic arthritis. (**a**) Dactylitis of third and fourth toes. (**b**) Enthesitis of right Achilles' tendon. (**c**) Dactylitis of middle finger. (**d**) Radiograph of hands (Reprinted with permission from Gottlieb et al. [18])

Arthritis developed the CASPAR [29], a clinical research-oriented diagnostic tool developed for rheumatologists and based opon results from 600 PsA patients and 600 non-psoriatic arthropathy patients from 30 rheumatology clinics in 13 different countries since 2002. The tool is based on the presence of three or more clinical criteria, radiologic and laboratory tests, a diagnostic result that is 98.7–99.7 % sensitive and 91.4–99.1 % specific [29–33]. Although developed for patients with longstanding PsA, the tool has also been useful in identifying new onset disease [32], and establishing diagnoses in a retrospective cohort [30]. CASPAR has also been validated in multiple settings and against other proposed and existing standards, and has proven to be robust [31, 34]. Despite the efficacy of this tool, some diagnoses remain difficult, such as diagnosing early onset or RA versus symmetric PsA [35, 36].

An important problem in distinguishing PsA from other arthropathies, and RA in particular (see Table 5.2 for a comparison between arthropathies), is that most classifications require the presence of psoriatic skin disease, a diagnostic standard that results in several difficulties for rheumatologists [19], notably:

1. Psoriasis is relatively common, occurring in approximately 2 % of the Northern European population, and there may be patients with RA who also have psoriasis by chance.
2. Psoriasis may precede (68 %), occur simultaneously (15 %), or follow the onset of arthritis (17 %) [26]. Thus, family history may be a necessary adjunct for accurate diagnosis.
3. The presence of a positive family history in a first degree relative may be as strong as presence of psoriasis from a diagnostic point of view [37].
4. Psoriasis may be present but misdiagnosed or hidden, in areas such as under the breasts or gluteal cleft, or only in the nails [38].

Radiologic studies, in particular ultrasound, may aid in diagnosis. Ultrasound may be capable of distinguishing PsA and RA, with one study showing peritenon extensor inflammation (PTI) in 20 patients with PsA (65.8 %) compared to none in 18 RA patients [39]. MRI and ultrasound studies have demonstrated that enthesitis can show inflammatory changes distant from the insertion sites [40, 41], and in particular, inflammation at the MCP join which is seen in PsA and not RA [42].

## Evaluation

Significant heterogeneity exists in the tools and methods used to evaluate PsA. Current recommendations by the Outcome Measures in Rheumatology (OMERACT) initiative and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) have recommended that for clinical trials of PsA, the following areas should be assessed: joint, skin, function, pain, patient's global assessment and quality of life [43]. Although the OMERACT recommendations were published in 2007, a review of publications from 2006 to 2010 showed only 10.3 % of studies reporting all six core domains, with no consistency in the number of joints to assess or in the evaluation instruments used for dactylitis and enthesitis [44].

Joint assessment tools, quality of life tools, radiographic tools will be discussed below. Although cutaneous lesions are an important finding in PsA, they will not be specifically discussed in this chapter.

### Joint Assessment Tools

The majority of tools for evaluating PsA have been adapted from the field of rheumatoid arthritis [45], and until recently, there were few tools that evaluated all aspects of PsA, from peripheral joints to skin and nail disease, dactylitis, enthesseal involvement or axial disease [46]. For these reasons, there are currently numerous tools to evaluate joints in PsA, some of which will be discussed below. Many have not been validated, although a comparison ACR20, EULAR and PsARC showed that all were able to find statistically significant differences between outcomes in patients treated with active drug compared to placebo in data from clinical trials, with a $p<0.0001$ for each [47, 48] (See Table 5.1 for a comparison of ACR20, EULAR and PsARC).

#### ACR20, ACR50, ACR70

According to the American College of Rheumatology criteria (ACR20), an improvement of at least 20 % in swollen and tender joint count and in three of five other measures (erythrocyte sedimentation rate or C-reactive protein level; physician global assessment of disease activity; patient global assessment of disease activity; patient pain assessment; and disability) is indicative of treatment efficacy in patients with PsA [50]. Other measures, such as ACR50 or ACR70 criteria were found to be less discriminative than the ACR20 for RA [51], although similar studies have not been performed for PsA [45].

#### DAS28

The Disease Activity Score (DAS28) was originally developed to evaluate RA treatment [52], DAS28 evaluates 28 joints with the following criteria: number of tender joints; number of swollen joints; patient assessment of pain; patient and physician global assessments of disease activity; patient assessment of physical function; and laboratory evaluation of an acute-phase reactant. The DAS tracks disease activity and response to

**Table 5.1** Overview of selected response criteria

| PsARC | ACR 20 criteria | EULAR criteria |
|---|---|---|
| Response is defined by improvement in two of four measures, one of which must be joint swelling or tenderness. No worsening of any four measures: | Improvement defined by at least 20 % improvement in | Good response defined as reaching DAS ≤2.4 or DAS28 ≤3.2 in combination with an improvement >1.2 in DAS or DAS28 |
| 1. PtGA of articular disease (1–5) | Total Joint Count, and | Non-response defined as improvement ≤0.6, and also as an improvement ≤1.2 with a DAS 3.7 or DAS28 >5.1 |
| 2. PhGA of articular disease (1–5) | Swollen Joint Count | All other responses are moderate response |
| 3. Joint pain/tenderness score | And at least 20 % improvement in 3 of 5 measures: | |
| 4. Joint swelling score | 1. ESR or CRP | |
| | 2. PtGA of disease activity | |
| | 3. PhGA of disease activity | |
| | 4. Patient assessment of pain | |
| | 5. Disability | |

Modified with permission from Fransen et al. [49]
*PsARC* psoriatic arthritis response criteria, *ACR* American College of Rheumatology, *EULAR* European League Against Rheumatism, *PtGA* patient global assessment, *PhGA* Physician global assessment, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

**Table 5.2** Comparison of psoriatic arthritis with rheumatoid arthritis, osteoarthritis, ankylosing spondylitis

| | Psoriatic arthritis | Rheumatic arthritis | Osteoarthritis | Ankylosing spondylitis |
|---|---|---|---|---|
| Peripheral disease | Asymmetric | Symmetric | Asymmetric | No |
| Sacroiliitis | Asymmetric | No | No | Symmetric |
| Stiffness | In morning and/or with immobility | In morning and/or with immobility | With activity | Yes |
| Female:male ratio | 1:1 | 3:1 | Hand/foot more common in female patients | 1:3 |
| Enthesitis | Yes | No | No | No |
| High titer rheumatoid factor | No | Yes | No | No |
| Nail lesions | Yes | No | No | No |
| Psoriasis | Yes | Uncommon | Uncommon | Uncommon |

Modified with permission from Gottlieb et al. [18]

change [53]. However, joints that are often involved in PsA, such as the distal interphalangeal joints of the hands, are not included in the DAS28 assessment, and therefore evaluations may overlook key joint changes.

## PsARC

The Psoriatic Arthritis Response Criteria (PsARC) is a composite instrument created for a study of sulfasalazine in patients with PsA [54]. PsARC response is defined by improvement in joint swelling or tenderness in association with improvement in any of four other measures (patient global assessment of articular disease; physician global assessment of articular disease; joint pain or tenderness; and joint swelling) [47, 54]. However, PsARC has not been formally validated, and may overestimate response rates [55].

## EULAR

The European League Against Rheumatism (EULAR) criteria defines a good response to treatment based on DAS or DAS28 score. One study found that the EULAR criteria were better

than ACR20 or PsARC for distinguishing the effects of a TNF inhibitor from placebo in patients with PsA [49].

### Other Tools

Others include the Ritchie articular index [56], DAPSA [57], PsAJAI [58]. Also, the following tools combine multiple domains, including skin, joint function, and quality of life, into a single score.

### PASDAS

A combination of three VAS scores, patient global, patient skin and physician global has been proposed as the Psoriatic Arthritis Disease Assessment Scale (PASDAS) [46]. Although this tool has not been validated, the basis for this simplified tool was the observation that over 90 % of the variability in a set of 457 PsA patients was due to those three VAS scales [46].

### CPDAI

The Composite Psoriatic Disease Activity Index (CPDAI) assesses five domains, including peripheral joints, skin, enthesitis, dactylitis and spine involvement. Each domain is scored individually on a scale of mild, moderate or severe, and contribute to the composite score for both skin and joint disease [59]. However, while controversy exists over precise the definitions of mild, moderate and severe disease, CPDAI has been shown to distinguish between patients who require a change in treatment regimen and those who do not [59].

## Quality of Life Tools

Patients with PsA possess significantly diminished ability to carry out daily activities, when compared to general population. These patients may suffer from psychological burden that can result in embarrassment, self-consciousness and also depression [60, 61]. Patients with PsA have more bodily pain, decreased mental health, social functioning, and poorer quality of life compared to those with psoriasis alone [62–65], or those with rheumatoid arthritis [64, 66]. The reduced quality of life observed with PsA has been shown to be similar to that seen with other chronic and life-threatening diseases, including cancer, diabetes mellitus and depression [67], and 5–20 % of patients with psoriasis have contemplated suicide [68, 69]. The financial burden of PsA, from one US study, estimated the direct annual cost for PsA per patient to be $3,638, or about 1.9 billion US dollars, not counting indirect costs and decreased productivity [65].

The most widely used questionnaire assessing quality of life for rheumatic disease is the Stanford Health Assessment Questionnaire (HAQ), which measures productivity, healthcare utilization and cost, and morbidity [70]. However, because the HAQ does not assess skin disease, the HAQ-SK, an alternate version for PsA, was developed to measure skin involvement and addresses the functional, instead of psychological or social impact of psoriasis [71].

Clinically, psoriatic disease activity and function are also assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Disease Function Index BASFI [72, 73], which focus on overall function and activities of daily living. Recent studies focusing on radiologic evaluations suggest that BASFI [74] correlate well with measures of functional capabilities when disease activity is minimal, one of the recommendations by OMERACT [75]. Some studies support Ankylosing Spondylitis Disease Activity Score (ASDAS) as an effective, but more complex tool which may discriminate between PsA and RA. However, this approach was not found to be superior to the BASDAI in differentiating between low and high PsA disease states [76].

Other tools have been developed specifically for psoriasis, such as the Psoriatic Arthritis Quality of Life (PsAQoL) tool, developed to determine the impact of PsA on functional, social, psychological and vocational issues [43, 61]. However, the correlation of the PsAQoL with treatment effect has not yet been validated [61].

## Radiology

PsA is characterized by numerous radiographic features, including erosions such as pencil-in-cup changes, bone resorption in the form of large eccentric erosions, and bone formation such as periostitis or ankylosis. A typical pattern in PsA involves erosion with accompanying bone production. Until recently these changes were considered irreversible, but studies on anti-tumor necrosis factor have shown to support joint repair in both PsA [77, 78] and RA [79, 80].

PsA affects both peripheral and axial joints, and thus, the tools for evaluation of PsA radiographically spring initially from those used in RA and AS, and may be broadly categorized into two broad groups: tools primarily to evaluate peripheral joints, specifically hands and feet, and those used to conduct axial or complete skeletal assessments.

### Hands and Feet

#### Steinbrocker Method

The original Steinbrocker method [81] evaluated only the patient's worst joint, while the modified technique evaluates multiple joints on the basis of degree of lysis or ankylosis [82]. This method reflects the biological changes in the joint, from soft tissues swelling to total joint destruction. This method has been validated in PsA [82, 83].

#### The van der Heijde (vdH) Modification of the Sharp Methods

The van der Heijde modification [84] of the Sharp methods [85] was developed to evaluate erosions and joint space narrowing of hand and foot joints in RA. For PsA, finger joints, many hand joints, and most foot joints are evaluated.

#### Psoriatic Arthritis Ratingen Scoring System

The Psoriatic Arthritis Ratingen Score (PARS) [14] was developed specifically for the radiographic assessment of patients with PsA. PARS includes 40 joints of the hands and feet, each evaluated separately for destruction and proliferation. The method has been validated using complete sets of X-rays of 20 patients with PsA, taken 3 years apart [86].

### Axial Assessment

The frequency of spinal involvement in PsA varies between 20–70 % [52]. Anklyosing Spondylitis (AS) is frequently evaluated radiographically, and some overlap exists between the tools used for the spondyloarthropathies, including AS and PsA. However, these diseases are very different [87]. Radiographically, certain features are more often seen in psoriasis compared to AS, such as [87, 88]:

- less severe and asymmetrical sacroiliitis
- non-marginal syndesmophytes
- asymmetrical syndesmophytes
- paravertebral ossification
- more frequent involvement of cervical spine
- high frequency of posterior element fusion in the cervical spine [89, 90]

There are three validated scoring tools for AS: Bath AS Radiology Index (BASRI) [91], Stoke AS Spine Score (SASSS), and a modification of SASSS (m-SASSS) [92]. The tools have not yet been validated for use in PsA. The Psoriatic Arthritis Spondylitis Radiology Index (PASRI) [93] was developed to evaluate radiologic axial involvement specifically in PsA. As compared to the m-SASSS, the PASRI encompasses a greater range of spinal radiologic features of PsA, while correlating well with patient reported outcomes. The m-SASSS is more time consuming than BASRI, but is more sensitive to detecting disease change [94]. While PASRI and BASRI had similar correlations to clinical measures, and appear to be valid for radiologic assessments, PASRI has been shown to offer a greater degree of measuring change [93].

## PsA Comorbidities

### Cardiovascular and Metabolic Risk

Just as patients with psoriasis, an association between PsA and risk of the metabolic syndrome has been demonstrated, with one study showing a prevalence rate of 58.1 % compared to 35.2 % in the general population [95]. Additionally, a study of 611 patients with PsA and 449 patients with psoriasis without arthritis revealed higher rates of hypertension, obesity, hyperlipidemia, type 2 diabetes mellitus, and at least 1 cardiovascular event in the group of PsA patients [96].

### Mortality

Numerous studies have illustrated an increased risk of mortality for patients with psoriasis [97], with an estimated 6 year reduction in lifespan most frequently related to with cardiovascular events [98]. Similarly, PsA confers an increased mortality risk, with a study in 1998 showing a 1.36-fold increased risk of mortality [99]. Also, PsA has been associated with increased arterial stiffness in the absence of other known cardiovascular risk factors [100].

Overall, major causes of death among patients with psoriasis include myocardial infarction, respiratory causes, pneumonia, chronic obstructive pulmonary disease and cancer [101]. Patients with PsA have a fivefold greater risk of death from respiratory disease, compared with a 1.3-fold increased risk of death from cardiovascular disease [102]. The pathophysiologic factors connecting pulmonary disease and PsA remain unknown. Data suggest that patients with psoriasis and psoriatic arthritis are more likely to smoke [103–106], and smokers are more than twice as likely to develop psoriasis than non-smokers [107].

In terms of disease management and reduction of risk, there is currently some evidence to suggest that successful treatment may reduce cardiovascular disease risk or mortality. Some authors theorize that cardiovascular disease risk will be reduced with systemic anti-inflammatory treatment [108], while there are others who believe the risk will increase [109–111]. Although treatment of RA with biologics has been shown to reduce cardiovascular risk [112–116], a similar effect has not yet been demonstrated in PsA. A 4 year retrospective database analysis of psoriasis patients treated with systemic anti-inflammatories versus light therapy showed that systemic therapy did not cause statistically significant difference in rates of myocardial infarction, except in patients under 50 [117].

In evaluating surrogate markers for cardiovascular disease, some studies have shown promising results, such as one study showing treatment of PsA patients with etanercept showing improvements in Lp(a), homocysteine, Apo A-I and SHBG, with concurrent increases in the concentrations of triglyceride and Apo B levels [118]. C-reactive protein levels in psoriasis and PsA patients decreased with treatment [119], insulin sensitivity improved [120]. The development of serological biomarkers of psoriatic arthritis may aid in monitoring treatment response, and importantly, detect joint disease at an early stage before the overt clinical manifestations.

Although there is insufficient evidence to suggest methotrexate reduces cardiovascular disease in PsA, one study has shown that methotrexate use, regardless of disease being treated, reduced overall cardiovascular disease risk by 21 % [121]. Another trial demonstrated a decrease in the incidence of cardiovascular disease in veterans with psoriasis or RA treated with methotrexate [122].

Large prospective, long-term, controlled studies are needed to evaluate whether control of inflammation decreases cardiovascular events and mortality in patients with PsA.

### Psychological Impairment

The link between psychological impairment and PsA is well documented, with PsA patients displaying poor mental and emotional health, and social functioning [66, 123, 124]. In particular, the degree of peripheral and axial involvement in PsA correlates with poor mental functioning especially in severe cases [125]. In a study by Khraishi et al., patients with PsA for longer than 2 years had rates of depression that were two to five times higher than those of age-matched controls who had no history of PsA or psoriasis [126].

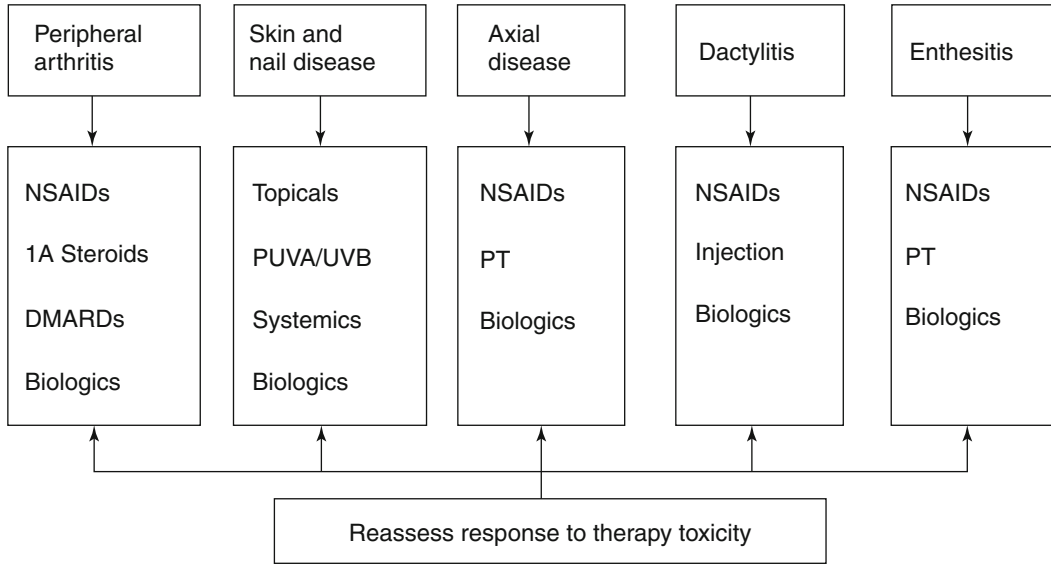


**Fig. 5.2** GRAPPA treatment guidelines for psoriatic arthritis, categorized by disease characteristics. *NSAIDSs* non-Steroidal Anti-Inflammatory Drugs, *PT* physiotherapy, *DMARDs* disease-modifying antirheumatic drugs (i.e. leflunomide, methotrexate, cyclosporine, sulfasalazine), *PUVA* psoralen-ultraviolet light A, *UVB* ultraviolet light B (Modified with permission from Kavanaugh and Ritchlin [131])

Overall, 45 % of patients with any form of arthritis had a concomitant mental disorder at a rate that is double that of patients without arthritis [127]. Psychiatric medication use, alcohol consumption and smoking are all increased in patients with high rates of psoriasis-related disability, further exacerbating the risk of significant psychological impairment and decreasing the quality of life [128].

## Joint Progression

PsA may follow different courses, with some patients experiencing long-term, mild disease, while others suffering rapid, progressive joint destruction [129].

Prospective studies of PsA patient cohorts have demonstrated that some patients experience deteriorating functional status and progression assessed both radiographically and clinically [6, 15, 17, 24, 130]. One 5-year study showed the proportion of patients with >5 damaged joints increased from 19 to 40 % [15]. One prospective study of 100 PsA patients followed for 5 years showed 11 patients showing increased numbers of joints involved and six showing decreased joint involvement [17]. Together, these studies suggest that PsA should not be considered as a mild arthropathy, but instead a slowly progressive, structurally damaging disease that should be treated aggressively.

## Treatment

Given the many long-term consequences of untreated PsA, early intervention is imperative.

GRAPPA has devised guidelines to categorize treatments according to type of evidence and strength of recommendations [131], also see Fig. 5.2 and Table 5.3. A general pathway for the treatment of patients with PsA on the basis of current GRAPPA guidelines is as follows [132]:

- Peripheral arthritis
  - Mild: NSAIDs, intra-articular glucocorticoid injections (but not in plaques). DMARDs if non-responder
  - Moderate to severe: DMARDs. TNF inhibitors if non-responder or if poor prognosis. Etanercept, infliximab and adalimumab all considered equally effective

**Table 5.3** Psoriatic arthritis disease severity

| | Mild | Moderate | Severe |
|---|---|---|---|
| Peripheral arthritis | <5 points swollen or tender | >5 joints swollen or tender | >5 joints swollen or tender |
| | No damage on X-ray | Damage on X-ray | Severe damage on X-ray |
| | Minimal impact QoL | Inadequate response to mild Rx | Inadequate response to mild-moderate Rx |
| | Patient evaluation mild | Moderate Loss of Function | Severe Loss of Function |
| | | Moderate impact QoL | Severe impact QoL |
| | | Patient evaluation moderate | Patient evaluation severe |
| Skin disease | BSA <5, PASI <5, asymptomatic | Non-response to topical, DLQI <10, PASI <10 | BSA >10, DLQI >10, PASI >10 |
| Spinal disease | Mild pain | Loss of function or BASDAI >4 | Failure of response |
| Enthesitis | No loss of function 1–2 sites | >2 sites or loss of function | Loss of function or <2 sites and failure of response |
| Dactylitis | No loss of function | Erosive disease or functional loss | Failure of response |
| | Pain absent to mild | | |
| | Normal function | | |

Modified with permission from Ritchlin et al. [132]
*QoL* quality of life, *DLQI* dermatology life quality index, *PASI* psoriasis activity disease score, *BSA* body surface area

- Spinal Involvement
  - Mild to moderate: NSAIDs, physiotherapy, education, analgesia and injection of sacroiliac joint
  - Moderate to severe: TNF inhibitors
- Enthesitis
  - Mild: NSAIDs, physical therapy, corticosteroids
  - Moderate: DMARDs
  - Severe: TNF inhibitors
- Dactylitis
  - Initial treatment: NSAIDs, progress to injected corticosteroids
  - Resistant: DMARDs
  - Limited evidence for infliximab

There was limited evidence and only some agreement on the treatment of nail disease, which included retinoids, oral PUVA, cyclosporine and TNF inhibitors [132].

The American Academy of Dermatology (AAD) guidelines for PsA differ from GRAPPA [18, 133]. The current AAD guidelines recommend that mild PsA should be managed first with NSAIDs and intralesional corticosteroid injections. For patients who do not show response after 2–3 months, methotrexate should be considered. Patients with moderate to severe PsA and concurrent psoriasis should be treated with methotrexate and/or TNF blockade. Ustekinumab with or without methotrexate can be considered as a second-line treatment [18, 133].

Despite the potentially aggressive course of the disease, it is not known if use of biological agents for psoriasis before arthritis develops will delay or prevent the appearance of PsA [134].

## NSAIDs

### Mechanism

NSAIDs reduce inflammation via nonselective inhibition of the cyclooxygenase 1 and 2 enzymes, thereby preventing the formation of prostaglandins and leukotrienes. NSAIDs do not alter the course of the disease, but may aid with pain management.

### Safety

NSAIDs are approved by the FDA for the treatment of the symptoms of PsA [135]. NSAIDs are generally well tolerated, however NSAIDs do have related side-effects, such as gastrointestinal bleeding, with over 100,000 hospitalizations and 16,500 deaths each year in the USA attributable to NSAID use [136]. Some studies have shown an increased association between NSAID use and

cardiovascular events, and NSAIDs may attenuate the efficacy of antihypertensives [137, 138]. Patients taking NSAIDs should be evaluated with caution in those with cardiovascular risk factors.

## Prednisone

### Mechanism

Systemic corticosteroids, such as prednisone, modify gene transcription via the glucocorticoid receptor. Prednisone relies on liver conversion to its active form, prednisolone. Systemic corticosteroids reduce inflammation via multiple pathways: inhibition of cytokines, COX-2, cytokines, leukocyte infiltration, cell adhesion molecules, and nitric oxide synthetase.

### Safety and Efficacy

Prednisone is approved by the FDA for short-term treatment of the signs and symptoms of PsA [139]. Low-dose prednisone (5–10 mg daily) may be used long-term for management of PsA [18]. Short courses of prednisone are generally well tolerated; however, higher doses, especially over long-term, may produce potentially serious adverse effects. As an immunosuppressant, this agent may increase susceptibility to infections such as tuberculosis and decrease response to vaccinations. Corticosteroids also impair calcium absorption and new bone formation, increasing the risk of osteopenia and fractures. Therapies for preventing bone loss should be initiated and continued for the duration of glucocorticoid treatment [140, 141]. Systemic corticosteroids are rarely used by dermatologists secondary to the risk of psoriasis flare upon cessation, particularly in those patients who are not concurrently taking any other systemic treatments for their psoriatic arthritis.

## Nonbiologic DMARDs

### Methotrexate

#### Mechanism

Methotrexate antagonizes the activity of dihydrofolate reductase, which leads to cytotoxicity in rapidly dividing cells.

#### Safety and Efficacy

Methotrexate is currently FDA-approved for the symptomatic control of severe, recalcitrant, disabling psoriasis [142]. Methotrexate is very inexpensive, making it an attractive and accessible option as a first line therapy for PsA.

Methotrexate as monotherapy in PsA is supported by two small trials [143, 144]. Methotrexate in patients with PsA is usually dosed up to 25 mg per week, with concomitant folic acid (1 mg daily) given to reduce the risk of pancytopenia. Methotrexate may be given in combination with biologics, though it is often used alone. Early aggressive therapy with methotrexate at high doses has been associated with mild inhibition of joint damage progression [145]. Methotrexate is contraindicated in patients with renal impairment, hepatitis or cirrhosis, leukemia or thrombocytopenia, or who are pregnant or nursing [146]. Bone-marrow suppression, especially with concomitant use of trimethoprim and/or sulfamethoxazole or NSAIDs, is a particularly serious concern. Methotrexate may induce pneumonitis. Methotrexate is also a known teratogen, abortifacient, and decreases sperm count. Male patients should avoid conception until 3 months after discontinuation of methotrexate due to its possible effects on spermatogenesis [147]. Drug interactions are frequent and must be accounted for before starting therapy. In general, alcohol-abusing patients and patients unable to comply with the required frequent blood monitoring should also not be treated with methotrexate.

Methotrexate can cause hepatotoxicity through unknown mechanisms [148]. However, most rheumatology guidelines do not suggest routine liver biopsy in healthy patients [149], although this may be due to the lower doses of methotrexate used in RA [150]. Dermatology guidelines divide patients being treated with methotrexate into high-risk and low-risk [151]. In patients with pre-existing liver disease, or risk factors for liver disease, such as obesity or diabetes mellitus, dermatology guidelines recommend monitoring and a liver biopsy after a 1.5 g cumulative dose of methotrexate [151–153]. Individuals at low risk of liver injury should follow the current ACR criteria for methotrexate,

and consider a biopsy after a total cumulative dose of 3.5–4.0 g.

### Sulfasalazine

#### Mechanism

Sulfasalazine and its metabolite, 5-ASA, are poorly absorbed from the intestine. Their mechanism of action on PsA is not clearly understood.

#### Safety and Efficacy

Sulfasalazine is not currently approved by the FDA or EMA for treatment of PsA. One randomized, controlled trial, showed that 2 g sulfasalazine daily resulted in a mild improvement in terms of PsARC criteria (57.8 % versus 44.6 % with placebo) [54]. Sulfasalazine is contraindicated in patients with porphyria, intestinal and/or urinary obstruction, and hypersensitivity to sulfasalazine and its metabolites, or salicylates [154]. Sulfasalazine must be used with caution in patients with severe allergies or bronchial asthma, hepatic or renal damage or blood dyscrasias [154]. Gastrointestinal upset is a frequent occurrence and may limit dosing. Also, adequate fluid intake must be maintained to prevent crystalluria and stone formation [154].

A complete blood count with differential and liver function tests are checked prior to starting sulfasalazine and repeated monthly for the first 3 months of treatment and then every 6 months for safety monitoring [55]. Renal function and urinalysis should also be evaluated periodically during treatment [55].

Sulfasalazine is considered pregnancy category B. Female fertility does not appear to be affected by sulfasalazine use, however, men may experience reversible oligospermia and reduced sperm motility [155]. Pregnant women taking sulfasalazine require at least 800 μg of folic acid replacement, as sulfasalazine inhibits dihydrofolate reductase [156]. Also, in late-term pregnant patients, sulfapyridine, a metabolite of sulfasalazine, can cross the placenta and displace bilirubin from albumin. This may lead to neonatal jaundice [157], and thus one may consider discontinuing sulfasalazine use during lactation in preterm or jaundiced babies for 1–2 months. Except in the setting of prematurity or hyperbilirubinemia, sulfasalazine is considered safe during lactation [158].

### Leflunomide

#### Mechanism

Leflunomide inhibits dihydroorotate dehydrogenase, affecting *de novo* synthesis of uridine monophosphate.

#### Safety and Efficacy

Leflunomide is approved in Europe, but not in the USA, for treatment of PsA inpatients for whom methotrexate is contraindicated [159]. In a small study, leflunomide demonstrated a benefit in patients with PsA, with a PsARC response observed in 58.9 % of treated patients compared with 29.7 % of those who received placebo at an oral dosing regimen of 100 mg per day for 3 days followed by 20 mg per day thereafter [160].

Caution should be used in patients with hypertension, chronic renal insufficiency and those with hepatic insufficiency [161]. Rare cases of severe fatal liver injury have been reported during treatment with leflunomide [162]. This drug is not recommended in patients with severe immunodeficiency, bone marrow dysplasia or severe, uncontrolled infections [162]. Hepatotoxicity may be a limiting factor, and liver function tests should strictly monitored, although transient transaminase elevations were observed in 14–35 % of patients taking leflunomide [161, 163].

Leflunomide is a pregnancy category X drug and is absolutely contraindicated in pregnant women and in patients who plan to become pregnant within 2 years of stopping the drug unless a washout regimen of cholestyramine (8 g three times daily for 11 days) is completed and drug concentrations in the blood are below 0.02 mg/l.66 [162, 164].

## Biologic Therapies

### TNF Inhibitors

The cytokine tumor necrosis factor-α (TNF-α) has been strongly implicated in the pathogenesis of psoriasis and has been recognized as an attractive therapeutic target for the treatment of psoriasis and PsA [146]. Currently, biologic therapies including the TNF-α inhibitors, are recommended

in the treatment of moderate to severe PsA, especially those patients with poor prognostic factors. These include: polyarticular disease, elevated erythrocytes sedimentation rate, prior treatment failures, clinical and/or radiographic evidence of joint destruction, loss of function, and decreased quality of life [132]. Although there is a considerable cost associated with biologic therapies, TNF-α inhibitors have been demonstrated to be cost-effective treatments for psoriatic disease [165]. Therefore, a cost-benefit approach is taken and these treatment options are usually reserved for those who have failed other treatments options and those at high risk of progressive joint damage and destruction.

Currently, there are four FDA- and EMA-approved TNF-α inhibitors for the treatment of moderate to severe PsA: adalimumab, etanercept, infliximab, golimumab. All have been shown to achieve a significant ACR20 response, inhibit radiographic progression and improve quality of life in patients with PsA receiving these medications.

### General Efficacy of TNF-α Inhibitors

PsA is a chronic inflammatory disorder requiring long-term management and treatment, and loss of efficacy over time has been observed with biologic therapies. This potential side effect of the TNF-inhibitors has been potentially attributed to the production of autoantibodies [166, 167]. Some evidence suggests that the loss of response to a TNF-inhibitor can be overcome by switching to another in its class [168–171]. Moreover, adding concomitant methotrexate to the treatment regimen may preemptively avoid autoantibody formation, and therefore, possibly maintain treatment efficacy over time [167, 172].

### General Safety of TNF-α Inhibitors

TNF-inhibitors are all associated with an increased risk of acquiring infections, especially involving the upper respiratory tract. Although serious infections, including rare opportunistic fungal infections, are infrequent, TNF-inhibitors should be avoided or used with caution in patients with a history of recurring or serious infections [173, 174]. Importantly, TNF-α plays a role in the response against the hepatitis B infection [175] and tuberculosis (TB) [176]. Therefore, TNF-inhibitors are avoided in patients with concurrent hepatitis B, and appropriate tuberculosis screening is recommended before starting any of the TNF-inhibitors [177, 178].

Neurologic conditions such as the demyelinating disorder, multiple sclerosis (MS), have been associated with the use of TNF-inhibitors and should be avoided in patients with a personal or family history of MS in first-degree relatives [179–182]. Of note, MS signs and symptoms that occur after introduction of TNF-inhibitor therapy resolve once the treatment is discontinued [179].

There have been numerous reports of lymphomas associated with TNF-inhibitor treatment, yet most cases resolved after discontinuation of treatment [183–185]. Some evidence exists suggesting increased mortality from congestive heart failure (CHF) with infliximab, and its use is not recommended in patients with severe CHF (New York Heart Association class III or IV) [146]. There have also been reports of TNF-inhibitors causing exacerbation of psoriasis, especially of the palmoplantar pustular type [186].

## Adalimumab

### Mechanism

Adalimumab is a fully human-derived monoclonal antibody that binds specifically to TNF-α molecules and interferes with their interactions with the TNF-α receptors [187].

### Safety and Efficacy

Adalimumab is FDA approved for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with PsA [188]. The efficacy of adalimumab in the treatment of moderate to severe psoriatic arthritis was evaluated in a double-blind, randomized, placebo-controlled clinical trial. Patients with moderate to severe psoriatic arthritis, defined by at least three swollen joints and three tender or painful joints in concomitance of active psoriatic skin lesions or a documented history of psoriasis, were enrolled to receive either adalimumab 40 mg subcutaneously every other week for 24 weeks or placebo [189]. After 12 and 24 weeks of treatment patients who received adalimumab had significantly higher

ACR20, ACR50, and ACR70 response rates compared to those who received placebo [189]. Furthermore, improvements in these efficacy parameters were maintained in an open-label extension study with adalimumab through week 48 [190]. Other studies have illustrated adalimumab's efficacy with both subjective and objective metrics. In particular, improvements in the Disability Index of the Health Assessment Questionnaire, which assesses the qualitative burden of disease [190] as well as the stabilization of radiographic progression and even joint disease improvement [191], have been shown with adalimumab treatment.

## Etanercept

### Mechanism

Etanercept is a recombinant fusion protein that combines the TNF α receptor with the Fc portion of human IgG and works by binding to soluble and membrane-bound TNF α [192].

### Safety and Efficacy

Etanercept is FDA approved for reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with PsA [193]. Etanercept may be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone [193]. Etanercept was shown to contribute a significant reduction in the signs and symptoms of PsA as evaluated in a double-blind, randomized, placebo-controlled trial [194]. In this particular study, patients with psoriatic arthritis either received etanercept 25 mg subcutaneously weekly for 24 weeks or placebo, and after 12 weeks, significant ACR20 response rates were noted in the treatment group compared to those on placebo (59 % versus 15 %, $p < 0.0001$) [194]. Of note, disease stabilization by radiographic evidence was also observed and maintained in those receiving etanercept compared to those administered placebo throughout 2 years [194]. Other trials that demonstrating etanercept's efficacy with various dosing regimens include the Experience Diagnosing, Understanding Care, and Treatment with Etanercept (EDUCATE) that showed improvements in the patient global assessment of joint pain and disease at 12 and 24 weeks after treatment with etanercept 50 mg subcutaneously once weekly in patients with active PsA [195]. In the trial Psoriasis Randomized Etanerept Study in Subjects with Psoriatic Arthritis (PRESTA), there was a clear advantage of twice-weekly over once-weekly dosing of etanercept 50 mg in the skin response at 12 weeks as measured by a physician's global assessment of psoriasis (PGA) and the psoriasis area and severity index (PASI) (46 % versus 32 %, $p < 0.0001$ for PGA; 71 % versus 62 %, $p < 0.0001$ for PASI) [196]. However, no difference was noted between the two dosing regimens in the percentage of patients achieving significant joint improvements, as measured by PsARC (77 % versus 76 %) [196]. This evidence suggests that the etanercept dosing regimen may be tailored to more appropriately target skin or joint involvement, with etanercept 50 mg once weekly more suitable for PsA and twice-weekly dosing for initial skin improvement [196].

## Infliximab

### Mechanism

Infliximab is a chimeric antibody composed of a mouse variable region and a human IgG-α constant region that acts by binding to both soluble and membrane-bound TNF-α molecules [197].

### Safety and Efficacy

It is currently approved for reducing the signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with PsA [178].

It is the only intravenous medication for PsA, typically given 5 mg/kg over 2–3 h at weeks 0, 2, and 6 and then every 8 weeks thereafter [178]. The first randomized, double-blind clinical study (IMPACT) assessing the use of infliximab in patients with treatment-resistant PsA established its efficacy, with significant improvements seen in joint and skin disease as well as dactylitis and enthesitis [48]. By week 16, a significant percentage of patients treated with infliximab 5 mg/kg attained a ACR20, ACR50, and ACR70 response compared to those on placebo (65 % vs. 10; 46 %

vs. 0 %; 29 % vs. 0 %, p<0.001) [48]. The joint and skin improvements including inhibition of radiographic progression were sustained through week 50 of the IMPACT trial and continued into the 2-year open-label extension study [86, 198]. A second double-blind trial confirmed infliximab's efficacy in a larger patient cohort, with a statistically significant difference between patients treated with infliximab 5 mg/kg versus placebo, using ACR20 and PsARC (58 % vs. 11 %; 77 % vs. 27 %, p<0.001) [199]. Fewer patients were also noted to have active dactylitis and enthesitis by week 14 in the treatment group, and all improvements were sustained through week 24 [199].

## Golimumab

### Mechanism

Golimumab, the newest TNF-inhibitor, is a human monoclonal antibody that binds both soluble and transmembrane TNF-α, which initially showed its promising effects in rheumatoid arthritis trials [200]. With a terminal half-life of 2 weeks, golimumab is administered on a monthly basis, less frequent than the other FDA-approved subcutaneous injections for PsA [200].

### Safety and Efficacy

Golimumab is FDA approved for the treatment of, in combination with methotrexate or alone, the signs and symptoms in patients with PsA [201]. In a randomized, double-blind study of 405 patients, a significant percentage of patients receiving golimumab, both 50 and 100 mg every 4 weeks, achieved an ACR20 response compared to placebo by week 14 and sustained through week 24 (48 % vs. 9 %, p<0.001) [200]. In addition, improvements in the disability indices in the HAQ and SF-36 as well as PsARC and EULAR's responses and assessments of enthesitis were shown with golimumab treatment [200].

## Certolizumab Pegol

### Mechanism

Certolizumab pegol is a monoclonal antibody directed against tumor necrosis factor alpha. More precisely, it is a PEGylated Fab' fragment of a humanized TNF inhibitor monoclonal antibody.

### Safety and Efficacy

Certolizumab was approved by the FDA for use in treating the signs and symptoms of PsA on September 27, 2013. In the landmark study evaluating the efficacy and safety of certolizumab pegol (CZP) after 24 weeks in a Phase III trial in patients with psoriatic arthritis, patients were randomized 1:1:1 to placebo, 200 mg CZP every 2 weeks (Q2W) or 400 mg CZP every 4 weeks (Q4W) [201]. Primary endpoints were ACR20 response at week 12 and modified Total Sharp Score change from baseline at week 24.

Of 409 patients randomized, 368 completed 24 weeks of treatment. ACR20 response was significantly greater in CZP 200 mg Q2W and 400 mg Q4W-treated patients than placebo (58.0 % and 51.9 % vs 24.3 % (p<0.001)) at week 12, with improvements observed by week 1. Sustained improvements were observed in psoriatic skin involvement, enthesitis, dactylitis and nail disease. Higher ACR20 response with CZP was independent of prior TNF inhibitor exposure [201]. Furthermore, evidence suggests that these certolizumab treated trial patients showed inhibited radiographic progression compared with placebo [202].

# IL-12/23 Inhibitors

A new class of biologic agents, IL-12/23 inhibitors, offers an alternative option in the treatment of PsA. On September 23, 2013, ustekinumab was approved by the FDA, alone or in combination with methotrexate, for the treatment of signs and symptoms, inhibition of X-ray progress and quality of life improvements in adult patients (18 years or older) with active psoriatic arthritis.

## Ustekinumab

### Mechanism

Ustekinumab, which offers an additional biologic therapy to the TNF-α inhibitors, targets the common p40 subunit of the cytokines IL-12 and −23 [203]. These cytokines both share homology with IL-6, and interactions with their receptors activate the STAT and NF-κB transcription pathways [204]. This activation causes pathogenic changes

associated with psoriatic disease to occur, specifically, a shift toward specific T-cell lineages and release of cytokines. As a monoclonal antibody, ustekinumab coats IL-12 and IL-23, and prevents interactions with their respective receptors, IL-12β1 and IL-23Rβ1, found on T-cells and Natural Killer cells. Signaling cascades are therefore disrupted, and as a result dampens the release of pro-inflammatory cytokines.

### Safety and Efficacy

In 2009, Gottlieb et al. published a multi-center, double-blind, placebo-controlled Phase II study of the efficacy and safety of ustekinumab in 146 subjects, 18-years and greater with active PsA [205]. 76 were randomized to receive ustekinumab weekly for 4 weeks and placebo at weeks 12 and 16, and remaining 70 subjects were randomized to receive placebo weekly for 4 weeks and ustekinumab at weeks 12 and 16. Ustekinumab was administered as a 90 mg unfiltered dose (16 % of subjects) or 63 mg filtered dose (84 % of subjects). The primary endpoint of ACR20 response at week 12 was achieved by 42 % of subjects in the ustekinumab arm compared to 14 % in the placebo arm ($p=0.0002$). Statistically significant differences in ustekinumab versus placebo treated subjects were also observed for secondary endpoints at week 12, including improvements in ACR50 (25 % vs 7 %; $p=0.0038$), ACR75 (11 % vs 0 %; $p=0.0055$), HAQ (−0.25 vs 0.00; $p=0.0005$), DAS28 (59 % vs 30 %; $p=0.0009$), enthesopathy (23 % vs 42 %; $p=0.0163$), tender joint count ($p<0.0001$), pain assessment ($p=0.0002$) and doctor and patient global assessments of disease ($p<0.0001$). Differences in rates of dactylitis at week 12 were not found to be statistically significant ($p=0.54290$). After crossover from the placebo arm at week 12, evaluations of ACR 20 responses at weeks 24, 28 and 36, were 51, 45 and 42 %, respectively. Improvements in HAQ (42 % versus 47 %) and DAS28 (59 % versus 60 %) were also similar for the placebo arm at week 24 compared to the ustekinumab arm at week 12.

Data from two recent Phase III multicenter, randomized, double-blind, placebo controlled trials investigated the safety and efficacy of ustekinumab in patients with PsA. The first study published June 13, 2013, randomized 615 subjects with active PsA to receive either 45 or 90 mg of ustekinumab or placebo [206]. ACR 20 at week 24 was achieved in a statistically higher percentage of both the 45 mg group (87 of 205, 42.4 %) and 90 mg group (101 of 204, 49.5 %), than in placebo (47 of 206, 22.8 %). Subjects enrolled in this study were TNFα and IL-12/23 inhibitor naïve. Adverse event rates were not statistically different between treatment and placebo groups.

The other study's preliminary data was presented at EULAR in June 2013 by Richlin et al. [207].

In this cohort of 312 subjects, who were permitted a previous history of anti-TNFα treatment, subjects were also randomized to 45, 90 mg or placebo. Results from the presentation showed both doses of ustekinumab showed significant and sustain improvements in the signs and symptoms of PsA at both week 12 and week 52, with comparable safety profiles between placebo and treatment groups [207].

### Safety

The safety data available on ustekinumab is similar to the experience with TNF-α inhibitors. Only a limited number of studies have reported data from ustekinumab treatment for PsA. In Gottlieb et al's study, 61 % of subjects in the ustekinumab arm compared to 63 % of subjects in the placebo arm experienced an adverse event by week 12 [205]. Upper respiratory tract infections, nasopharyngitis and diarrhea were the most commonly reported events, with infections representing approximately 50 % of all reported adverse events. There is more extensive safety data available from the treatment of plaque-type psoriasis [208–210], with which a total of 3,117 patients, 6,791 patient-years of follow-up and 4 years of treatment in 20 % of cases have been reported. The most frequent adverse events were similar to those reported in Gottlieb et al's Phase II trial on PsA [205]. Rates of malignancy or serious infections were not significantly increased with ustekinumab treatment.

Additional potential risks with ustekinumab treatment include increased susceptibility to

disseminated mycobacterial, salmonella and Bacillus Calmette-Guerin infections, as patients with genetic deficiencies in IL-12/23 functions show a higher incidence of these infections [211–213]. Live vaccines are also contraindicated due to immunosuppression during treatment. There is a theoretical risk of $T_H$-2 hyperactivity, as ustekinumab interferes with $T_H$-1 differentiation, and may be associated with risk of allergic reactions [204]. One case of reversible posterior leukoencephalopathy syndrome has also occurred, but resolved with treatment and discontinuation of ustekinumab [214].

## Conclusion

Many patients with untreated PsA will develop persistent inflammation, leading to progressive joint damage, severe functional limitations and disability. With the potential benefits of early treatment, dermatologists and rheumatologists are strongly encouraged to assess patients for the signs and symptoms of PsA at each visit. Use of the CASPAR criteria is recommended for diagnosing and categorizing PsA, and although there is no universally agreed upon standard for evaluating PsA radiographically or clinically, there are continued developments from OMERACT and GRAPPA. Treatment guidelines from GRAPPA and AAD differ, but emphasize aggressive treatment, including TNF inhibitors, such as etanercept, adalimumab or infliximab, for patients with poor prognosis. Potential benefits of treatment include better quality of life and possible radiologic improvement of joint damage.

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# Topical Therapy I: Corticosteroids and Vitamin D Analogues

6

Ani L. Tajirian and Leon Kircik

**Abstract**

Psoriasis is a life-long disease that affects approximately 2 % of the population. Approximately 80 % of psoriasis patients have mild to moderate disease. Topical therapies play an important role in the treatment of patients with mild to moderate disease. Patients often start treatment with topical steroids, vitamin D3 cream or ointment or a combination of the two. This chapter will describe the pharmacokinetics and mechanism of action of topical steroids and vitamin D analogues. Long-term side effects, the importance of vehicle, potency ratings as well as combination use with other treatment modalities will be discussed.

**Keywords**

Psoriasis • Topical steroids • Vitamin D cream • Cutaneous atrophy • Topical treatment of psoriasis • Topical steroid side effects

## Introduction

Topical corticosteroids (TCS) are a mainstay in treatment of a wide range of inflammatory dermatoses and are the cornerstone of psoriasis therapy. As long-term use of topical steroids can cause side effects, vitamin D analogues have arisen as an important adjunct to therapy for mild to moderate psoriasis.

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## Topical Corticosteroids

### Pharmacokinetics/Mechanism of Action

There are seven classes of topical steroids which range from superpotent (class 1) to the very low-potency topical steroids (class 7). These classes have been developed based on vasoconstrictor assays [1]. The vasoconstrictor assay involves preparing the test corticosteroid in 95 % alcohol and then applying it to the volar surface of a normal volunteer's forearm, the alcohol is left to

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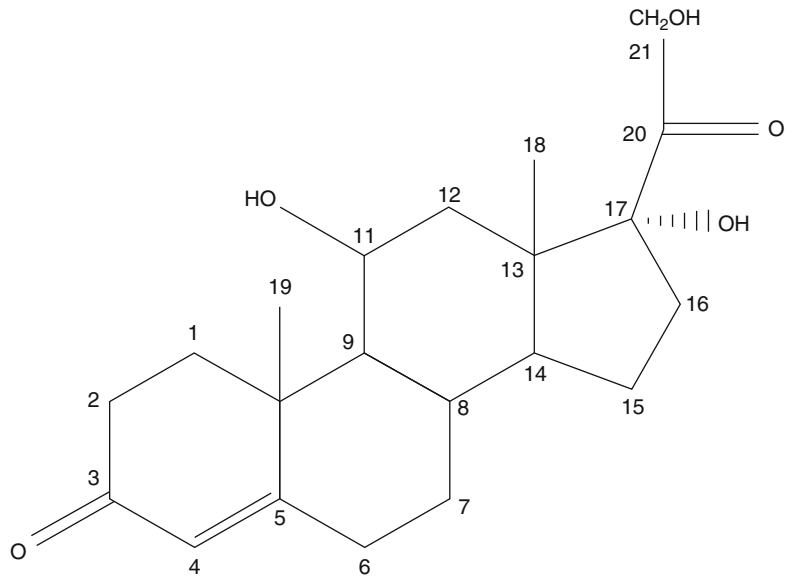


**Fig. 6.1** Topical corticosteroid

evaporate and then the test area is covered with an occlusive dressing for 16 h. The area is then washed off and vasoconstriction is assessed using a statistical analysis. The vasoconstrictive assay correlates well with clinical efficacy and is reproducible.

Three factors determine the pharmacokinetics and potency of a topical corticosteroid: the structure of the corticosteroid molecule, the vehicle and the skin onto which the corticosteroid is applied [2]. Hydrocortisone is the central structure of most topical corticosteroids. Variations are formed by placing hydroxyl groups into the 11-β, 17-α, and 21 positions. Additionally, ketone groups at the 3 and 20 positions and a double bond into the 4 position of the glucocorticoid nucleus distinguish between classes. Adding or altering functional groups such as hydroxyl, hydrocarbon, ester, fluoro, chloro, acetonide or ketone at certain positions can vastly impact the molecule's pharmacokinetics [2]. The alteration of hydroxyl groups modifies the molecule's lipophilicity, solubility, percutaneous absorption and glucocorticoid receptor binding ability [2].

Glucocorticoid potency is increased by adding a double-bond at position one, additional fluorination or chlorination [2] (Figs. 6.1 and 6.2). Additionally, halogenation at the 6-α or 9-α position increases glucocorticoid receptor binding activity [2]. Decreased mineralocorticoid activity as in dexamethasone, betamethasone and triamcinolone is accomplished by the addition of a 16-α methyl, 16-β methyl, or 16-α hydroxyl group.

Finally, epidermal enzymes cause the de-esterification of topical corticosteroids into inactive metabolites. Increased potency can be accomplished by inhibiting de-esterification through halogenation at the 21 position.

## Vehicle

The vehicle of a topical corticosteroid can influence percutaneous absorption and therapeutic efficacy. Corticosteroids in an ointment vehicle may be more potent than the same molecule in a cream, lotion or other preparation because occlusive vehicles enhance percutaneous absorption through increased hydration of the stratum corneum.

When choosing a topical steroid, one must first decide on the desired potency based on the severity and the location of the skin disease. Then, one must decide on the vehicle based on the type of lesion to be treated, need for hydration or drying effect, location and potential for irritation

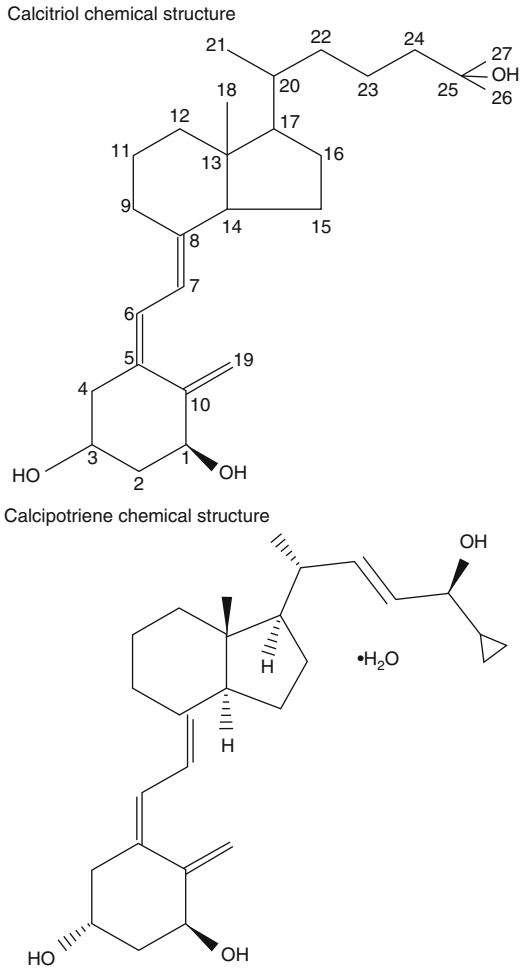


**Fig. 6.2** Diagram of steroid molecule. (*Top*) Calcitriol chemical structure, (*Bottom*) Calcipotriene chemical structure

by components of the vehicle. Lotions tend to be elegant for the face, ointments work well for dry lesions and gels are more useful in hairy areas or for a drying effect for a wet lesion. Potent and superpotent topical steroids should be avoided on the face and intertriginous areas due to the risk of atrophy.

The vehicle may alter the pharmacokinetics of a topical steroid molecule thereby affecting its potency. Propylene glycol and alcohol, common solvents, can affect percutaneous absorption by altering the topical corticosteroid molecule's solubility in the vehicle. Propylene glycol enhances potency through increasing penetration through the stratum corneum. Very occlusive agents, such as ointments, also increase the absorption of topical corticosteroids through increased hydration of the stratum corneum [3].

For some agents brand-name preparations are not always equivalent to generics and may have higher or lower potency. For example, Valisone 0.1 % cream (Schering) and Kenalog 0.1 % cream (Westwood-Squibb) have both demonstrated increased vasoconstriction over generics [2]. In addition, Synalar 0.025 % cream is also more potent than generic fluocinolone acetonide 0.025 % cream (Fougera and Company) [2]. However, Aristocort 0.025 % cream and Aristocort 0.05 % cream (Lederle Laboratories) are significantly less potent than generic triamcinolone 0.025 and 0.05 % cream (Fougera and Company) [2]. In general, generic vs. brand-name ointments tend to be closer in vasoconstrictive assays than creams. Additionally there are differences between different generic preparations as well as different brand-name preparations of the same topical corticosteroids [4].

Bioavailability and penetration of the topical corticosteroid increase with inflamed or diseased skin as well as with increased hydration of the stratum corneum. The thickness of the stratum corneum is inversely proportional to the degree of penetration of the topical corticosteroid [5].

## Immunologic Mechanisms

Topical corticosteroids are closely involved with all aspects of inflammation in the body. They affect both the adaptive and innate immunity. TCS have been shown to decrease the number and function of Langerhans' cells which are antigen presenting cells found in the skin important in initiating immune responses. Neutrophils are decreased, less adherent to vascular endothelium and have decreased phagocytic function [6–8]. Similarly, leukocytes show decreased antibody-dependent cellular toxicity and natural killer cell function [9, 10]. In addition, the production of many cytokines is decreased including interleukin (IL)-1, IL-2, interferon (IFN)-γ, tumor necrosis factor and granulocyte-monocyte-stimulating factor [2].

Topical steroids decrease the mitotic rate of the epidermis thereby causing thinning of the stratum corneum and granulosum and flattening of the basal layer [11]. TCS also cause atrophy of the dermis through inhibition of fibroblast proliferation, migration, chemotaxis and protein synthesis. They have also been shown to cause inhibition of fibroblast synthesis of both glycosaminoglycans and collagen [12–14].

## Use in Psoriasis

The antiproliferative and atrophogenic characteristics of TCS are useful in treating psoriasis. Topical corticosteroids are the mainstay of treatment and often first-line for the management of mild to moderate psoriasis as well as for intertrigous areas and genitalia as these areas can become irritated with the use of other topical agents. In general, for the treatment of localized plaque-type psoriasis high potency or superpotent TCS are prescribed twice daily. Optimal improvement with high potency TCS is often achieved after 2 weeks. Katz and colleagues in several studies indicated the efficacy of clobetasol ointment or betamethasone dipropionate ointment in clearing plaque type psoriasis and found that remission could be maintained by applying 3.5 g three times a week: on Sat am, Sat pm and Sun am [15, 16].

In a placebo-controlled trial, Katz et al. demonstrated that with maintenance therapy consisting of 12 weeks of weekend-only use of betamethasone dipropionate ointment, 74 % of patients remained in remission as compared to 21 % of the patients receiving placebo [17].

Occlusion can greatly increase penetration and efficacy of TCS. Studies have demonstrated that triamcinolone acetonide 0.1 % ointment under occlusion is more effective than clobetasol propionate 0.05 % cream twice daily or triamcinolone acetonide 0.1 % ointment alone [18, 19]. Flurandrenolide (Cordran) tape is frequently prescribed due to its occlusive nature and has been shown to be superior to twice-daily diflorasone diacetate ointment in a randomized bilateral comparison study of plaque-type psoriasis [20]. Clobetasol propionate lotion applied under occlusion with a hydrocolloid dressing (Duoderm ET) once weekly also showed faster remission of psoriasis than unoccluded clobetasol propionate ointment applied twice daily [21, 22]. Foams have been found to have increased efficacy over lotions of the same class of TCS when treating the scalp [23, 24].

In the case of more severe psoriasis, vitamin D analogues are frequently added at the onset as there is a synergistic effect with TCS.

## Combination with Other Therapies

Topical corticosteroids work synergistically with light therapy as well as many systemic agents. Psoriasis clears faster when using psoralen plus ultraviolet A (PUVA) with TCS versus PUVA alone. The addition of topical corticosteroids to cyclosporine therapy also leads to more rapid clearance of psoriasis [25]. Topical steroids may also be combined with salicylic acid, anthralin or tazarotene and which provide increased efficacy due to increased penetration. Lower dose etretinate can be prescribed when using a combination of triamcinolone 0.1 % cream compounded with 5 % salicylic acid [25].

## Adverse Effects

Systemic adverse effects from topical corticosteroids are uncommon and are increased with young age, liver disease, renal disease, the potency of the drug, amount of skin surface involvement, the use of occlusion, frequency of application and the duration of treatment [2]. The liver metabolizes corticosteroids and the kidneys excrete metabolized and unmetabolized corticosteroid [26]. A higher skin surface-to-body ratio is present in infants and young children as they are not able to rapidly metabolize corticosteroids [27]. Catch-up growth is expected when topical corticosteroids are discontinued in this population. However, caution should be exercised when

prescribing long-term topical corticosteroids near puberty as this may cause premature fusion of the epiphyseal plates and ultimate growth suppression [28]. Cushing's syndrome and hypothalamic-pituitary-adrenal (HPA) axis suppression has been noted in patients applying high quantities of topical corticosteroids for prolonged periods of time [29–31]. Screening for HPA axis suppression is done using the 8 AM plasma cortisol level and definitive diagnosis requires the cosyntropin test.

Local adverse effects are also rare but occur more frequently than systemic adverse effects. Cutaneous atrophy is the most commonly observed side effect and is characterized by telangiectasias, striae, hypopigmented, wrinkled or shiny skin [32]. Striae are typically seen after many weeks to months of topical steroid use; risk factors include the potency of corticosteroid, the location of application, the use of occlusion and the use in infancy/childhood. A 2011 pediatric study by Hong et al. demonstrated that appropriate long-term use of topical corticosteroids in children with dermatitis does not cause skin atrophy [33]. Their findings counter the commonly held "corticosteroid phobia" which describes an exaggerated and often irrational fear of using topical steroids. The primary concern often being that they will "thin the skin".

Another potential side effect is perioral dermatitis that may sometimes occur on the face after the use of topical corticosteroids. It is characterized by erythematous papules in a periorificial distribution. Perioral dermatitis is treated with oral tetracycline in addition to a long taper with a non-fluorinated topical corticosteroid such as hydrocortisone acetate cream.

Prolonged use of topical glucocorticoids on the eyelids can lead to glaucoma and cataracts and thus is not recommended [34]. Glaucoma has also been reported in a patient who used 0.1 % betamethasone-17-valerate cream at bedtime for hand eczema for seven consecutive years. Eye contact occurred inadvertently at night [35].

Allergic contact dermatitis to topical steroids may occur and can be suspected when a patient fails to respond to topical steroid therapy or flares with topical steroid therapy [36, 37]. The allergy may be to the vehicle or the actual corticosteroid molecule, this can be confirmed with patch testing. A delayed check at 96 h is required as topical corticosteroids often have a delayed reaction and persist for at least 96 h [38]. Loss of clinical effect or tolerance may occur with repeated application of topical corticosteroids and is known as tachyphylaxis. This occurs more commonly with higher strength topical corticosteroids. Recovery from tachyphylaxis usually occurs after a rest period of a few days. There is no established regimen to prevent tachyphylaxis. A commonly recommended regimen is twice daily application of TCS for 2 weeks followed by a 1 week rest period or weekend-only application [39]. Inadequate response to topical corticosteroids in the treatment of psoriasis can be mistaken for tachyphylaxis [40].

## Vitamin D Analogues

### Structure, Biosynthesis and Mechanism of Action

Vitamin D as a treatment for psoriasis was first discovered after a patient receiving oral vitamin D for osteoporosis was cured of psoriasis [41]. Calcitriol which is the active form of vitamin $D_3$ was found to inhibit the proliferation and modulate the differentiation of keratinocytes [42]. However, the therapeutic doses of oral vitamin $D_3$ produce hypercalcemia and hypercalciuria thus limiting its dermatologic usage. As a result, vitamin D analogues were developed which have a lower risk of hypercalcemia but maintain the other beneficial cellular effects. There are currently four vitamin $D_3$ analogues out in the market which include: calcipotriene, calcitriol, tacalcitol and maxacalcitol.

The skin is both a synthesizer of vitamin D (where 7-dehydrocholesterol is converted to vitamin D3 in the presence of ultraviolet (UV) radiation) and a target organ for vitamin D activity. Vitamin D receptors transduce the effects of 1,

25-dihydroxyvitamin $D_3$ and have been identified in keratinocytes, Langerhans' cells, melanocytes, fibroblasts and endothelial cells [43]. The vitamin D receptor (VDR) is activated by binding to its ligand (1,25-dihydroxyvitamin $D_3$) or a synthetic analogue such as calcipotriene or calcitriol. This vitamin D receptor complex in association with the retinoid X receptor-α (RXR-α) then binds to specific DNA binding sites called vitamin D response elements resulting in induction or repression of the gene that contains these vitamin D response elements. In addition to inhibiting the proliferation of keratinocytes and promoting epidermal differentiation, vitamin D promotes the formation of the cornified envelope by increasing gene expression and thereby increasing levels of involucrin and transglutaminase [44].

Vitamin D also possesses anti-inflammatory benefits. It has been shown to increase levels of interleukin (IL)-10 (which is an anti-inflammatory cytokine) and decrease levels of IL-8, a pro-inflammatory chemokine, in psoriatic plaques [45]. In addition, it has been shown to inhibit the production IL-2 and IL-6 by T cells, blocks transcription of interferon (IFN)-γ and inhibits cytotoxic T cell and natural killer cell activity [46].

## Calcitriol

Calcitriol is the natural active form of vitamin D3. Calcium metabolism is affected by calcitriol through release of calcium from bone, decreasing parathyroid hormone, increasing tubular resorption of calcium in the kidney and stimulating calcium transport in the intestines. Thus, if applied excessively, it may result in hypercalcemia and hypercalciuria. It is available in an ointment form as Vectical (USA) and Silkis (Europe).

## Calcipotriene (Calcipotriol)

Calcipotriene is a synthetic form of calcitriol. It was the only vitamin D analogue that was available in the U.S. for many years. Its molecular structure differs slightly from calcitriol. Calcipotriene contains a double bond and ring structure in its side chain enabling it to be metabolized much more rapidly and, as a result, is less likely to cause hypercalcemia. It is available under ointment, cream and solution forms under the trade names Dovonex (USA), Daivonex (Europe, Asia), Psorcutan (Europe) and Dermocal (South America).

## Tacalcitol

Tacalcitol's (1,24(OH) $_2D_3$) structure is slightly different from calcitriol but it has a similar affinity for vitamin D receptors and therapeutic effects. It contains a hydroxyl group at the 24-position rather than at the 25-position. It is less selective than calcipotriene in its effect on calcium metabolism and has been shown to induce hypercalcemia at equivalent doses to calcitriol. It is available in an ointment, cream, lotion and solution form in Japan and as an ointment form only in Europe as Curatoderm.

## Maxacalcitol

Maxacalcitol (1α,25-dihydroxy-22-oxacalcitriol) is available as Oxarol in Japan and has been shown to be ten times more potent than calcitriol and tacalcitol in inhibiting keratinocyte proliferation and 60 times less calcemic than calcipotriene [47]. It has shown benefit in the treatment of psoriasis and has not posed a significant risk of hypercalcemia.

## Taclonex ®

Taclonex is a two-compound ointment or solution containing calcipotriol 50 μg/g plus betamethasone dipropionate 0.5 mg/g which combines a vitamin D analog and a corticosteroid. This formulation is used bid and preserves the activity and bioavailability of the two components. It is convenient for patients, well tolerated and has been shown to aid with compliance [48].

## Indication for Psoriasis

Vitamin D analogues perform as well as midpotency steroids but less well than superpotent steroids in the treatment of psoriasis [49, 50]. Calcipotriene applied twice daily has been shown to be more effective than applied once daily, though once-daily application was more effective than placebo [51]. Ashcroft et al. found calcipotriene to be equivalent to potent topical steroids at 8 weeks of treatment [52]. Calcipotriene was associated with slightly more skin irritation than topical steroids but rarely led to withdrawal of therapy. Twice daily usage as compared to daily usage has not been associated with increased irritation [53].

In a study of 114 patients by Bruce and Colleagues, they found that calcipotriene ointment was superior to fluocinonide ointment in the treatment of plaque psoriasis and that this superior efficacy continued through week 6 [54]. A study by Camarasa et al. in 2003 randomized 258 psoriasis patients to be treated with either calcitriol or betamethasone dipropionate 0.05 % ointment and found that though betamethasone was associated with slightly higher global improvement, a statistically significantly higher proportion of patients remained in remission following calcitriol therapy (48 %) than betamethasone therapy (25 %) [55].

Calcipotriene may be used for intertriginous psoriasis though burning and irritation are commonly encountered [53]. Once daily application in these areas may be less irritating. Calcipotriene is an effective and well-tolerated modality for treating scalp psoriasis and in combination with other topical agents may lead to improved response to treatment. In long-term studies, calcipotriene has been shown to be a safe and effective therapy for the chronic management of psoriasis. Sustained disease improvement has been documented with its use twice daily for 1 year with no elevation in serum calcium levels [56].

The use of vitamin D analogues has been studied in children with psoriasis and has been found to be effective. In an uncontrolled pilot study, with long-term follow-up of 106 weeks, patients showed significant improvement in PASI scores compared with the baseline level. No serious side effects or hypercalcemia were detected. However, the mean plasma values of 1,25-dihydroxyvitamin D3 were decreased and half of the patients had levels below the normal range. Thus if using long-term calcipotriol monitoring vitamin D levels is suggested [57].

## Use with Other Treatment Modalities

Topical steroids are commonly used in conjunction with vitamin D analogues. They have a synergistic effect when used in combination. It has been clearly demonstrated that the combination improves the clinical response rate and minimizes the side effects of both treatments [53, 58]. Topical steroids reduce or eliminate the irritation associated with calcipotriene use. Additionally, a study by Lebwohl demonstrated that patients using superpotent topical steroids on weekends and calcipotriene during the week maintained a longer remission than if using superpotent topical steroids alone [59].

Formulations of a combination of calcipotriene and betamethasone valerate ointment have demonstrated greater efficacy and a more rapid onset of action compared to either medication alone [60]. The combination, which is now available in gel form, is highly effective for scalp psoriasis and is associated with significantly fewer side effects than with calcipotriol alone [61].

Combining vitamin D analogues and phototherapy has been documented in numerous studies to cause lesions to clear more rapidly than either entity alone and produces a greater reduction in Psoriasis Area and Severity Index (PASI) [62, 63]. Studies combining PUVA with calcipotriene have also demonstrated increased efficacy than when using PUVA alone [64]. Total cumulative UVA exposure required for clearance of psoriasis is reduced thus decreasing the risk of developing skin cancer.

It is recommended that vitamin D analogues be applied following phototherapy as the application of vitamin D analogues prior to UV radiation

has been shown to lead to degradation of vitamin D analogues and can alter the transmission of UV light. Lebwohl and colleagues showed that greater than 90 % of calcitriol ointment is degraded upon exposure to UVA, broadband UVB or narrowband UVB [65].

Vitamin D analogues have been combined with many systemic therapies to enhance efficacy and decrease toxicity. The combination of acitretin and calcipotriene has been shown to enhance the response of acitretin in psoriatic patients and has allowed for a reduction in dosing, leading to fewer dose-dependent side effects [66]. Similarly, the combination of calcipotriol with cyclosporine has shown increased efficacy when compared to cyclosporine and placebo and allows for lower cyclosporine dosing and less toxicity [67, 68]. Calcipotriene paired with methotrexate has also allowed for decreased dosing of methotrexate and increased time to relapse following the discontinuation of methotrexate [69]. Vitamin D analogues are now also being studied with biologics. A recent study by Kircik demonstrated that the combination topical agent of betamethasone dipropionate 0.064 % with calcipotriene 0.005 % maintains the efficacy of etanercept after a step down dose to 50 mg weekly from 50 mg twice weekly [70]. Campione et al. demonstrated the effectiveness of calcipotriol in a group of etanercept low-responders [71].

## Adverse Effects

The main side effects of vitamin D analogues are application-site burning and irritation. These symptoms are more common on the face and in intertriginous areas, with irritation developing in about 20 % of patients treating those areas [72]. Irritation is self-limited and resolves quickly once the drug is discontinued. The current recommendation is that weekly amounts of topical calcipotriene be kept under 100 g [73]. Serum parathyroid hormone levels should be checked if weekly amounts exceed 100 g. Patients with renal disease may be at higher risk of developing hypercalcemia even when applying less than 100 g per week.

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# Topical Therapy II: Retinoids, Immunomodulators, and Others

7

Lyn C. Guenther

**Abstract**

Tazarotene is the only topical retinoid approved for treatment of psoriasis. Although it is used primarily for plaque psoriasis, it may be beneficial for palmoplantar and nail psoriasis. Use in combination with a mid- to high potency topical steroid enhances efficacy and reduces irritancy and the atrophogenic potential of steroids. Thrice a week use with a twice weekly superpotent topical steroid may maintain improvement long-term. Addition of tazarotene to broadband or narrowband UVB, or PUVA phototherapy enhances efficacy and decreases the total dose of ultraviolet radiation. The calcineurin inhibitors pimecrolimus and tacrolimus are not approved for treatment of psoriasis, although they are efficacious and well tolerated in the treatment of intertriginous, facial and genital psoriasis. The use of tar and anthralin has declined with the development of cosmetically elegant, efficacious treatments that do not stain the skin or clothing. Although coal tar contains many known carcinogens, use in psoriasis has not been associated with an increase in skin cancer. Addition of tar to erythemogenic UVB does not enhance efficacy.

**Keywords**

Topical Therapy • Retinoids • Immunomodulators • Tazarotene • Calcineurin inhibitors • Pimecrolimus • Tacrolimus • Tar • Anthralin • Psoriasis

In addition to the commonly used topical corticosteroids and vitamin D analogues, there are several other topical therapies which are used in the management of psoriasis. Tazarotene, a receptor-selective topical retinoid, is the first and only topical retinoid to be approved to treat psoriasis. Topical tretinoin and isotretinoin, two other retinoids, have been abandoned due to the variable efficacy and irritancy of tretinoin [1–5], and failure to show superior efficacy of isotretinoin compared to placebo [6]. The calcineurin inhibitors pimecrolimus and tacrolimus are commonly used off-label for intertriginous, facial,

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and genital psoriasis [7]. Coal tar and anthralin were once in common use, however their use has declined with the development of more cosmetically elegant, efficacious agents [8].

## Tazarotene

Tazarotene is available as a 0.05 and 0.1 % gel and cream [9] (Fig. 7.1).

## Mechanism of Action

Tazarotene is a synthetic acetylenic retinoid which is a prodrug. Its free-acid active metabolite tazarotenic acid, binds to the nuclear retinoic acid receptor (RAR) β and γ, weakly to RARα, but not to retinoid X receptors (RXRs) [10]. RARγ is the predominant subtype in the epidermis [11]. RARs affect gene transcription after forming heterodimers with RXRs [12]. Tazarotenic acid cannot be converted to other retinoids since it does not contain isomerizable double bonds [10].

Tazarotene decreases inflammation and normalizes the abnormal keratinocyte hyperproliferation and differentiation seen in psoriasis [10]. The lymphocytic infiltrate in the dermis, number of HLA-DR and intracellular adhesion molecule (ICAM-1) positive cells in the epidermis and dermis, expression of epidermal growth-factor receptor (EGFR), the hyperproliferative keratins K16 and K6, skin-derived antileukoproteinase (SKALP) and macrophage migration inhibitory factor-related-protein-8 (MRP-8), keratinocyte transglutaminase type 1 (TGase K), and involucrin, are reduced, and filaggrin expression in the upper stratum spinosum and stratum granulosum increased [10, 13]. SKALP is an elastase inhibitor [14] in the suprabasal layers of psoriatic epidermis, which is not present in normal epidermis [15]. The enzyme TGase K and protein involucrin are involved in formation of the cross-linked envelope and are prematurely expressed in psoriasis [16]. Tazarotene can also induce expression of tazarotene-induced genes (TIG). TIG1 is a cell adhesion molecule which promotes cell-to-cell contact and reduces keratinocyte proliferation [17]. TIG2 is not anti-proliferative, but is involved in keratinocyte differentiation [18, 19]. TIG3 regulates keratinocyte terminal differentiation and cornified envelope formation through the activation of type 1 transglutaminase (TG1) [20].

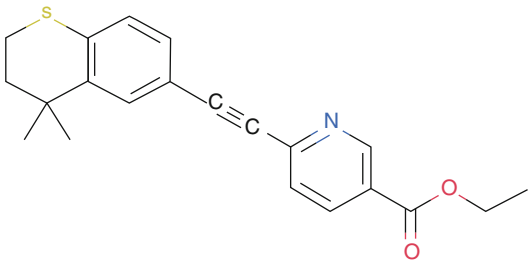


**Fig. 7.1** Also known as; Tazorac, Zorac, Avage, 118292-40-3, tazaroteno, tazarotenum, Suretin, Tazoral, AGN-190168
Molecular Formula: $C_{12}H_{21}NO_2S$
Molecular Weight: 351.46194
Tazarotene (marketed as Tazorac, Avage and Zorac) is a prescription topical retinoid sold as a cream or gel. This medication is approved for treatment of psoriasis, acne and sun damaged skin

## Pharmacokinetics

The half life of tazarotene is 2–18 min. Tazarotene is converted via esterase metabolism to its active metabolite tazarotenic acid which has linear pharmacokinetics and a 1–2 h elimination half-life [10]. Tazarotenic acid is then metabolized into inactive sulphoxide and sulphone metabolites and more polar conjugate metabolites [10]. Fecal elimination peaks approximately 2.5 days after dosing and is for all intensive purposes complete by 1 week [21]. Urinary excretion is virtually complete by 2–3 days [21]. Tazarotene and tazarotenic acid do not accumulate in tissues [10].

In a study of 6 patients with psoriasis, 4.54 % of a 2 mg dose administered at a concentration of 2.5 μg/cm$^2$ was absorbed into the stratum corneum, 1.38 % into the epidermis, and 0.97 % into the dermis; 0.43 % was recovered in the feces and 0.33 % in the urine [21]. The systemic absorption after an occluded 10 h 2 mg application (2.5 μg/cm$^2$) of tazarotene 0.1 % gel to the backs of 6 healthy males was 5.3 % and drug

half life in blood and urine, 17–18 h [22]. Application of the 0.1 % gel to 20 % body surface area (BSA) of healthy volunteers for 7 days resulted in a mean Cmax +/− SD of tazarotenic acid of 0.72 ± 0.58 ng/ml [23]. Low plasma concentrations of tazarotene (<0.15 ng/ml) and tazarotenic acid (0.05–6.1 ng/ml) were noted in 2.8 % (2/72) and 47.2 % (34/72) of patients treated with 0.05 % or 0.1 % gel [24, 25]. In a similar study, after 12 weeks of therapy only 1 psoriasis patient had a low concentration (0.069 ng/ml) of tazarotene, while 69.4 % had detectable tazarotenic acid [26]. In two phase 3 cream studies, tazarotenic acid was found in approximately ½ of the samples, with a highest concentration of 0.874 ng/ml [27].

## Toxicology

In contrast to tretinoin, tazarotene and tazarotenic acid are not cytotoxic to Chinese hamster ovary cells [28]. In addition, tazarotene is not mutagenic [10]. In a 21-month mouse study, it was not carcinogenic, however, in the hairless mouse photocarcinogenicity study, similar to other retinoids, it enhanced the photocarcinogenicity associated with ultraviolet irradiation [21]. Tazarotene 0.05 % and 0.1 % gels did not exhibit phototoxic or photoallergic potential in healthy adult Caucasians [29]. In common with other retinoids, systemic tazarotene is teratogenic [10]. Topical tazarotene should not be used in pregnant women and has been given an FDA Pregnancy Category X [30], although healthy babies were reported in all three women who became pregnant in 1 study [24].

## Clinical Studies in Psoriasis

Clinical trials of tazarotene and other topicals are summarized in Table 7.1. In the two phase 2 trials, 0.01 % tazarotene aqueous gel was not found to be efficacious, while 0.05 and 0.1 % tazarotene gels once and twice daily showed similar efficacy with significant improvement in elevation, scaling, erythema and overall clinical severity of plaques as early as 1 week [31]. Treatment-related adverse effects (primarily burning, pruritus, stinging, and erythema) occurred in 30 % in the first trial and 22.2 % in the second trial. In the second trial, up to 50 % of plaques had erythema of the surrounding skin.

In a phase 3, placebo-controlled study, once daily tazarotene 0.05 and 0.1 % gel for 12 weeks had similar efficacy and were superior to vehicle ($p<0.05$) in all efficacy measures [24]. At the end of treatment, 59 % on 0.05 % tazarotene gel and 70 % on the 0.1 % gel had at least 50 % improvement. Twelve weeks after treatment discontinuation, 52 % in the 0.05 % group and 41 % in the 0.1 % group continued to have at least 50 % improvement. Treatment related adverse effects (AEs) consisted primarily of mild to moderate local irritation. A small uncontrolled study ($n=43$) suggested that these AEs could be minimized without compromising efficacy, by short-contact application for 20 min followed by washing with water [32]. Two phase 3 placebo-controlled cream studies involving 1,303 patients showed that tazarotene 0.05 and 0.1 % creams were significantly better than vehicle with regards to overall assessment, global response to treatment, and reduction in plaque elevation and scaling [27]. One of the studies included a 12-week follow-up phase; treatment response was generally maintained after the drug was discontinued. In this study, an overall lesional score of mild or better was noted at the end of the 12 weeks treatment period and 12 weeks follow-up period in 24.4 and 21.8 % respectively on vehicle, 41.7 and 33.4 % respectively on 0.05 % tazarotene, and 39.4 and 30.3 % respectively on tazarotene 0.1 % cream. The skin-associated treatment-related AEs including pruritus, burning, erythema, skin irritation, stinging and desquamation were more common in the tazarotene arms, particularly the 0.1 % arm.

In a steroid comparison study, after 12 weeks of therapy, tazarotene 0.05 and 0.1 % gels had comparable efficacy to fluocinonide 0.05 % cream [26]. However, the psoriasis returned faster in the steroid group. In those patients who achieved an overall lesional score of mild or better at the end of treatment, relapse to a score of moderate or worse was noted at the end of the 12 weeks follow

**Table 7.1** Clinical trials of tazarotene in psoriasis

| Study | # Patients | Treatment | Efficacy | Safety |
|---|---|---|---|---|
| Krueger et al. (1998) [31] | 45 (with 90 bilateral symmetrical plaques) | 2 of: 0.01 or 0.05 % tazarotene (taz) gel, or vehicle gel BID × 6 weeks (weeks) | 0.01 % taz: minimal efficacy. 45 % on 0.05 % gel had ≥75 % improvement vs. 13 % on vehicle. ($p<0.05$) | 33 % of plaques had Rx-related adverse effects (AEs), especially erythema and pruritus |
| Krueger et al. (1998) [31] | 108 (with 216 bilateral symmetrical plaques) [31] | 2 of the following: 0.05 % taz gel OD or BID, 0.1 % taz gel OD or BID × 8 weeks then 8 weeks follow-up | No significant differences in ≥75 % improvement with Rx (range: 48 % with 0.05 % taz OD to 63 % with 0.05 % taz BID) or 8 weeks follow-up | Rx-related AEs in 22.2 % (burning, pruritus, stinging, erythema; 13 % with 0.05 % OD vs. 30 % with 0.1 % BID). Perilesional erythema in 1/2. Rx withdrawal due to AEs in 5.1 % |
| Weinstein (1997) [24] | 324 with 318 evaluable [24] | Taz 0.05, 0.1 % gel or vehicle gel OD × 12 weeks then 12 weeks follow-up | Taz 0.05 and 0.01 % similar and better than placebo in all efficacy measures ($p<0.05$). 59 % on 0.05 and 70 % on 0.1 % had ≥50 % improvement. At follow-up, 52 and 41 % respectively maintained improvement | Mild to moderate irritation: pruritus (8 % on vehicle, 17 % on 0.05 % taz, 23 % on 0.1 % taz), burning (6, 15, 19 % respectively), erythema (1, 7, 8 % respectively). Withdrawal due to AEs: 3, 10 and 12 % respectively |
| Weinstein et al. (2003) [27] | 1,303 in 2 studies | Taz 0.05 or 0.1 % cream (cr) or vehicle × 12 weeks (with 12 weeks follow-up in 1 study) | Taz 0.05 and 0.1 % more efficacious than vehicle. 12 weeks pooled data: 25.3 % on vehicle, 41.1 % on taz 0.05 and 44.9 % on 0.1 % taz had an overall lesional assessment ≤mild | In the 2 studies, pruritus on vehicle: 12.2 and 8.9 %, vs. 16.1 and 7.1 % on taz 0.05 %, and 29.4 and 15.6 % on taz 0.1 %. Taz: more burning, stinging desquamation, skin irritation, erythema |
| Lebwohl et al. (1998) [26] | 348 with 340 evaluable for efficacy | Taz 0.05, or 0.1 % gel OD OR fluocinonide 0.05 % cr BID × 12 weeks with 12 weeks follow-up period | At week 12, no significant difference between taz & fluocinonide<br>More rapid relapse with fluocinonide after treatment discontinuation | Taz: mild to moderate pruritus, burning, erythema. Fluocinonide: Minimal irritation. Withdrawal due to AEs: 12 % on taz 0.05,18 % on 0.1 % taz, 2 % on steroid |
| Tzung et al. (2005) [33] | 23, but 19 evaluable with 44 lesion pairs | Taz 0.1 % gel OD + petrolatum, or, calcipotriene 0.005 % ung BID × 12 weeks with 4 weeks follow-up | Comparable efficacy at week 12<br>Taz: Greater maintenance of improvement | Irritation in 35 % on taz and 0 % on calcipotriene |
| Kaur et al. (2008) [34] | 20 | Left side: taz 0.05 % or 0.1 % gel OD × 8 weeks Right side: calcipotriene 0.005 % BID | Comparable efficacy of OD taz 0.1 % & BID calcipotriene<br>Greater efficacy of calcipotriene than OD taz 0.05 % | No discontinuation due to AEs<br>No statistically significant difference in AEs between the 2 sides |

**Table 7.1** (continued)

| Study | # Patients | Treatment | Efficacy | Safety |
|---|---|---|---|---|
| Kumar et al. (2010) [35] | 30, with 27 evaluable for per protocol | Taz 0.1 % gel OD right side<br>5 % crude coal tar (CCT) ung OD left side × 12 weeks. 8 weeks follow-up | No significant difference between 2 sides (74.15 % ESI reduction with taz; 77.37 % with CCT, $p > 0.05$) | AEs in 48.1 % on taz, but none on CCT |
| Lebwohl et al. (1998) [36] | 300 with 284 evaluable for efficacy and 299 for safety | Taz 0.1 % gel OD + (fluocinolone acetonide 0.01 % cr or mometasone furoate 0.1 % cr or fluocinonide 0.05 % cr or placebo [Glaxal® base]) × 12 weeks + 4 weeks follow-up | Taz + mometasone furoate 0.1 % or fluocinonide 0.05 % was superior to taz 0.1 % + placebo after 2, 8 and 12 weeks. Similar efficacy of fluocinolone & placebo groups | Burning peaked at week 4 and was seen in 19 % in the taz + placebo group compared to 7–15 % in the taz + steroid groups |
| Dubertret et al. (1998) [38] | 398 | Taz 0.1 % gel alternate evenings with: 1 % hydro-cortisone, 0.05 % aclometasone dipropionate, betamethasone valerate 0.1 %, or placebo | Greater reduction in elevation, scaling and erythema with taz + betamethasone valerate. Median time to 50 % improvement was 2 weeks vs. 4 weeks in the other groups | Fewer treatment-related AEs with steroids (36 % with hydrocortisone, 32 % with aclome-tasone, 31 % with betamethasone) vs. 42 % with placebo |
| Dhawan et al. (2005) [40] | 10 | Taz 0.1 % cr OD + 0.12 % betame-thasone valerate foam OD × 12 weeks (open label) | 2 clear at week 4.<br>4 clear at week 8.<br>1 patient did not have any improvement | No AEs |
| Green and Sadoff (2002) [41] | 259 with 229 evaluable | Taz 0.1 % gel hs +/− am steroid (fluocinonide 0.05 % ung, 0.1 % mometasone furoate ung, 0.05 % diflorasone diacetate ung, 0.05 % betamethasone dipropionate cr, 0.005 % fluticasone propionate ung, or 0.05 % diflorasone diacetate cr) × 12 weeks | The greatest efficacy was seen with betamethasone dipropionate cr (50 % mean reduction vs. 20 % with monotherapy, $p \leq 0.001$), followed by mometasone furoate ung (41 % reduction, $p \leq 0.05$) and diflorasone diacetate ung (38 % reduction, $p \leq 0.05$). Maximal improvement at 8 weeks | The mometasone furoate ung regime was best tolerated (17 % incidence of drug-related AEs vs. 40 % with taz monotherapy). There were no treatment-related withdrawals due to AEs in the mometasone furoate ung regimen vs. 18 % on taz monotherapy |
| Koo and Martin (2001) [42] | 73 | Taz 0.1 % gel OD + mometasone furoate 0.1 % cr OD, or, mometasone furoate 0.1 % cr BID × up to 12 weeks with 12 weeks follow-up if clear by week 4 or ≥50 % better by week 12 | Greater, more rapid global improvement, plaque elevation and scaling with taz + steroid vs. steroid monotherapy ($p \leq 0.05$ by week 4 or 8) | 1 dermatitis on mometasone. Taz + steroid: 19 % Rx-related AEs at week 4, 17 % at week 8 and 0 % at week 12. Burning 11 %, pruritus 11 %, irritation 9 %, eruption 6 %, new psoriasis or exacerbation 6 % |

(continued)

**Table 7.1** (continued)

| Study | # Patients | Treatment | Efficacy | Safety |
|---|---|---|---|---|
| Guenther et al. (2000) [43] | 120 | Taz 0.1 % + 0.1 % mometasone furoate OD or, calcipotriene 0.005 % BID × 8 weeks + 12 weeks follow-up if clear at week 2 or 4, or week 8 ≥50 % better | At week 2, ≥75 % improvement in 45 % on taz + steroid vs. 26 % on calcipotriene ($p \leq 0.05$). Also greater reduction in BSA, elevation, scaling and erythema | Greater AEs with taz + steroid. [42 % vs. 8 % burning, 32 % vs. 13 % pruritus, 28 % vs. 12 % irritation, 25 % vs. 7 % erythema ($p \leq 0.05$) for each AE] |
| Bowman et al. (2002) [47] | 15 with 28 lesion pairs | Taz 0.1 % gel OD + calcipotriene 0.005 % gel BID, or, clobetasol ung BID × 2 weeks, then 4 weeks follow-up (open-label) | Marked reduction in scaling, elevation and overall lesional severity on both sides ($p < 0.0001$) with no difference between the 2 sides. More improvement of erythema with clobetasol ($p < 0.01$) | No Rx withdrawal due to AEs<br>No Rx-related AEs with clobetasol<br>Taz/calcipotriene: asymptomatic erythema in 53 %, peeling in 33 %, pruritus in 7 and irritation in 7 % |
| Tanghetti et al. (2000) [45] | 1,393 | Taz 0.05 % or 0.1 % gel OD for up to 12 weeks either as monotherapy or in combination with other topicals (open label) | Increased efficacy with adjunctive emollient and/or corticosteroid<br>Adjunctive mid- or high-potency steroid is at least as efficacious and often superior to superpotent steroid | Increased tolerability with adjunctive steroid<br>More AEs with monotherapy (22 % at week 4) vs. 13 % with mid- or high-potency steroid or 12 % with super-potent steroid |
| Koo (2000) [49] | 54 patients with 108 target lesions | Broad band UVB 3×/week | Time to 50 % improvement reduced by ½ (25 days vs. 53 days) | Taz + UVB: No photosensitivity or phototoxicity |
| | | ½ body with + 2/3: no topical, vehicle, or taz 0.1 % gel OD × 2 weeks pre-UV, then 3×/week | Cumulative UVB reduced by 76 % | 16.7 % had Rx-related AEs (irritation, burning and pruritus) |
| Stege et al. (1998) [51] | 20 | 0.1 % taz gel or 5 % salicylic acid 1 week before & during 3 weeks narrow band (nb) UVB | Significantly greater efficacy in ½ body treated with taz | |
| Behrens et al. (2000) [50] | 10 | ½ body hs taz 0.05 % gel or emollient + 311 nm UVB 5×/week | After 4 weeks, 64 % PASI reduction taz vs. 48 % | Mild irritation with taz, but no phototoxicity |
| Behrens et al. (1999) [53] | 12 patients | ½ body taz 0.05 % gel or vehicle + bath PUVA 4×/week | Faster and greater efficacy with taz. At 3 weeks, 76.5 % median PASI reduction vs. 58.5 %. ($p < 0.05$) | No photo-toxicity. With taz, mild irritation (transient burning and erythema) |
| Tzaneva et al. (2002) [54] | 31 | Oral PUVA 4×/weeks + 0.1 % taz gel (0.05 % if not tolerated) 1 lesion 1 side, tacalcitol ung 1 lesion opposite side | Similar efficacy with taz and tacalcitol. Compared to PUVA mono-therapy, the cumulative UVA was less with taz or tacalcitol ($p < 0.01$) | Tacalcitol: 1 mild irritant dermatitis, 1 hypertrichosis<br>Taz: 7 had AEs (dryness, irritant dermatitis, pruritus, burning); resolved after changed to 0.05 % |

up period in 18 % in the 0.1 % arm, 37 % in the 0.05 % tazarotene arm, and 55 % in the fluocinonide arm ($p<0.05$ % between tazarotene 0.1 % gel and fluocinonide). A small right/left study showed similar efficacy of tazarotene 0.1 % gel once daily + emollient once daily and calcipotriene BID, and however tazarotene was more irritating, but had a better maintenance effect after treatment discontinuation (overall severity $p=0.007$, erythema $p=0.01$, scaling $p<0.001$, elevation $p<0.001$) [33]. In a small open label right/left pilot study of 20 patients, twice daily calcipotriene was also found to be comparable to once daily 0.1 % tazarotene, but was more efficacious than once daily 0.05 % tazarotene [34]. A small ($n=30$) open-label right/left study showed that tazarotene and 5 % crude coal tar ointment had similar efficacy as measured by erythema, scaling and induration (ESI) [35].

Addition of a mid-potency corticosteroid (mometasone furoate 0.1 % cream) or high potency cream (fluocinonide 0.05 % cream) improved efficacy and reduced adverse effects [36]. At least 50 % improvement was noted in 91 % and 95 % in the mid- and high-potency steroid arms respectively compared to 80 % in the placebo arm. The cumulative rates of burning were only 61 % as frequent in the mid-potency steroid arm (14 %), and 52 % as frequent in the high-potency steroid arm (12 %) compared to the placebo arm (23 % rate). Addition of a low-potency steroid (fluocinolone acetonide 0.01 %) had minimal additive benefit. Tazarotene can also reduce the development of steroid-induced epidermal atrophy. In a 4-week long study of healthy volunteers, epidermal thickness was reduced by 43 % with diflorasone diacetate ointment monotherapy vs. 28 % when used in combination with tazarotene 0.1 % gel ($p \leq 0.003$) [37]. Another study showed that combination therapy with tazarotene 0.1 % gel used alternate evenings with betamethasone valerate 0.1 % enhanced efficacy and tolerance [38, 39]. The foam formulation of betamethasone valerate (0.12 %) was studied in a small open-label study involving 10 patients; all but 1 had improvement and 4 were clear at week 8 [40]. In an effort to determine the optimal steroid to use with tazarotene, tazarotene monotherapy was compared to combination therapy with 3 different high-potency and 3 different mid-high-potency steroids [41]. Greatest efficacy was seen when tazarotene 0.1 % gel was used in combination with betamethasone dipropionate 0.05 % cream, followed by mometasone furoate 0.1 % ung and diflorasone diacetate 0.05 % ung. The best tolerated regimen was the tazarotene + mometasone furoate 0.1 % ung, making this regimen the one with the optimal balance of efficacy and tolerability. Tazarotene 0.1 % gel in combination with mometasone furoate 0.1 % cream once daily was shown to be more efficacious than twice daily mometasone furoate cream [42] and twice daily calcipotriene 0.005 % ointment [43].

A large ($n=1{,}393$) open-label effectiveness study also showed that mid- to high-potency steroids were optimal potencies to be used in combination with tazarotene, and that superpotent steroids were not superior [44]. A subset of 166 patients were switched from calcipotriene +/− a steroid to tazarotene + a steroid. There was a substantial improvement in efficacy and patient satisfaction of these patients with 71 % having at least a 1 grade improvement in overall psoriasis severity [45]. In another similar subset study involving 246 patients switched from calcipotriene + steroid at baseline to tazarotene + steroid, 75 % achieved at least 50 % global improvement at the final visit (up to 12 weeks) [46]. A small open-label right/left comparison pilot study ($n=15$) showed similar efficacy of tazarotene + calcipotriene ointment, and the superpotent steroid clobetasol ointment [47].

Tazarotene can be used to maintain improvement. After a 6 weeks open-label treatment phase with tazarotene 0.1 % gel + clobetasol propionate 0.05 % ointment, a double-blind 5 months maintenance phase showed that those on tazarotene Monday, Wednesday, Friday + clobetasol Tuesday, Thursday maintained 75 % global improvement ($p \leq 0.001$ vs. vehicle group, $p \leq 0.05$ % vs. tazarotene/vehicle), those on tazarotene Monday, Wednesday, Friday + vehicle Tuesday, Thursday 50 % improvement, and those on vehicle Monday, Wednesday, Friday + white petrolatum Tuesday, Thursday, 25 % improvement [48].

Addition of tazarotene to phototherapy can enhance efficacy and decrease the total dose of ultraviolet (UV) radiation. Daily pre-treatment with 0.1 % tazarotene gel for 2 weeks, then three times a week immediately after broad band UVB treatment, increased the rapidity of improvement and overall efficacy [49]. The time to reach 50 % improvement decreased from 53 days to 25 days with an associated 76 % reduction in median cumulative UVB exposure (390 vs. 1,644 mJ/cm$^2$). The time to reach 75 % improvement was 28 days earlier. By day 81, 75 % improvement or better occurred in 50 % on UVB monotherapy versus 82 % on UVB + tazarotene 0.1 % gel. No treatment related photosensitivity or phototoxicity were noted. Similar results were seen with narrow-band (nb) UVB. In a small study (n = 10), after 4 weeks of 5×/week nb UVB, the psoriasis area and severity index (PASI) score decreased from 18.3 to 6.5 (95 % confidence interval (CI) 5.29–7.91) with the addition of tazarotene 0.05 % gel hs, compared to 9.5 (95 % CI 7.70–11.70) with emollient ($p < 0.05$) [50]. In a half body study involving 20 patients, tazarotene in combination with nb UVB was more efficacious than 5 % salicylic acid with nb UVB [51]. Tazarotene nb UVB combination therapy was found to be similar to calcipotriene nb UVB combination therapy in a study of 10 patients [52].

Psoralen ultraviolet A (PUVA) studies have also shown added benefit with topical tazarotene. In a ½ body bath PUVA study (n = 12), the side treated with tazarotene improved faster and to a greater extent [53]. After 3 weeks, the median PASI reduction was 76.5 % (95 % confidence interval (CI) 65–86) compared to 58.5 % (95 % CI 50–69). No phototoxic effects were seen. In an oral PUVA study (n = 31) addition of tazarotene gel or tacalcitol ointment resulted in faster clearing and 14 rather than 16 PUVA exposures [54].

## Other Types of Psoriasis (Palmoplantar, Nail)

Tazarotene is efficacious in the treatment of palmoplantar and nail psoriasis. In a 12-week randomized trial with 30 patients with palmoplantar psoriasis randomized to once daily 0.1 % tazarotene cream or 0.05 % clobetasol propionate cream, there was no significant difference in the reduction in the erythema scaling fissures and induration (ESFI) score between the two groups (83.2 and 89.1 % respectively) and complete clearance (52.9 and 61.5 % respectively) [55].

A double-blind, vehicle-controlled 24-week study (n = 31) showed greater reduction in onycholysis ($p \leq 0.05$ % weeks 4 and 12) and pitting ($p \leq 0.05$ at week 24) in occluded and nonoccluded tazarotene 0.1 % gel treated nails [56]. An open-label study (35) showed fingernail improvement after only 4 weeks with nonoccluded tazarotene 0.1 % gel applied to the nail plates, nail folds and periungual skin [57]. Hyperkeratosis and oil drop changes responded faster; pitting was the most persistent. After 12 weeks of treatment of fingernails and toenails, the mean visual assessment score for onycholysis decreased from 26 to 2, hyperkeratosis 25 to 2, oil spots 18 to 3, and pitting 13 to 1 ($p < 0.0001$ for each change.) A case report in a 6-year-old child showed that 8 weeks treatment with nonoccluded 0.05 % tazarotene gel improved nail psoriasis, especially hyperkeratosis [58]. Occluded tazarotene 0.1 % cream and clobetasol propionate 0.05 % cream had similar efficacy in a double-blind study of 46 patients with nail psoriasis [59]. Both treatments showed significant improvement in onycholysis, hyperkeratosis, salmon patches and pitting.

## Application Tips

Since tazarotene is photostable, it can be applied at any time of day [60]. When used in combination with a topical steroid, both compounds can be used at the same time of day without adversely affecting each other's stability [61]. The gel and cream formulations rub in well and do not stain. Only a small quantity is needed; larger amounts can increase the risk of irritation [62]. A cotton-tipped applicator to apply tazarotene and application of moisturizer around psoriatic lesions can minimize perilesional irritation from inadvertent application to unaffected skin. The gel and cream should be dry before clothes are worn to minimize

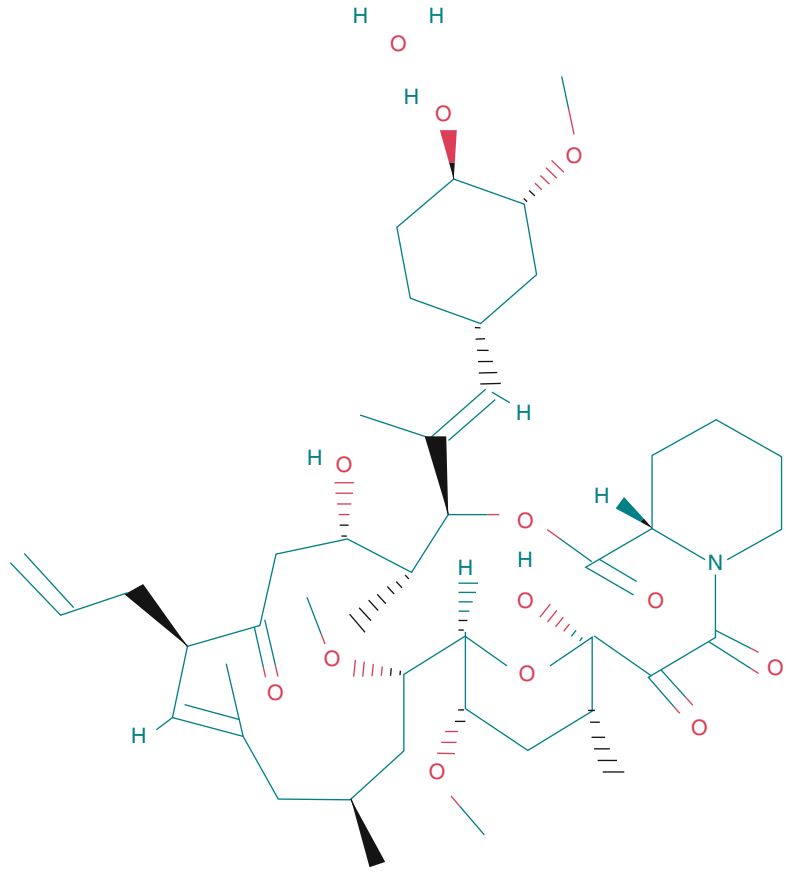

**Fig 7.2** Also known as: TACROLIMUS MONOHYDRATE, Protopic (TN), 109581-93-3, FK-506 monohydrate, Tacrolimus (USAN/INN), Tacrolimus hydrate (JP16), F4679_SIGMA
Molecular Formula: $C_{44}H_{71}NO_{13}$
Molecular Weight: 822.03344
A macrolide isolated from the culture broth of a strain of Streptomyces tsukabaensis that has stron immunosuppressive activity in vivo and prevents the activation of T-lymphocytes in response to antigenic or mitogenic stimulation in vitro

spread onto unaffected skin. The 0.05 % formulation should be considered for individuals with sensitive skin [62]. If irritation should occur, use of the 0.05 % cream formulation rather than the gel, alternate day treatment, and short contact treatment for as little as 5 min followed by a corticosteroid or emollient immediately after the tazarotene has been washed off, should be considered [62].

## Topical Calcineurin Inhibitors (Immunomodulators) Pimecrolimus and Tacrolimus

Topical pimecrolimus is available as a 1 % cream and tacrolimus as a 0.03 and 0.1 % ointment. They are indicated to treat atopic dermatitis. Although they are not FDA approved for the treatment of psoriasis, they are efficacious in the treatment of intertriginous, facial and genital psoriasis [63] (Fig. 7.2).

### Mechanism of Action

After binding to macrophilin-12, topical calcineurin inhibitors inhibit the calcium-dependent phosphatase calcineurin, which in turn results in inhibition of translocation of nuclear factor of activated T cells (NFAT) and down regulation of cytokine synthesis [7].

### Toxicity

Application site burning is the most frequent adverse drug reaction [7]. The FDA issued a controversial lymphoma “black box” warning [111]. This warning noted that, although a causal

relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors. In contrast to topical steroids, calcineurin inhibitors are not atrophogenic [64]. Pimecrolimus and tacrolimus have been given a Category C FDA pregnancy designation and should be avoided in individuals who are breastfeeding since they are both excreted in human milk [111].

## Clinical Studies in Psoriasis

In the treatment of plaque psoriasis, non-occluded tacrolimus was effective in two small studies (one monotherapy [65] and one with concurrent 6 % salicylic acid gel [66]) but not in another [67], while occluded tacrolimus [65, 68] and pimecrolimus [69] were.

Studies in inverse psoriasis are summarized in Table 7.2. In a small study (n = 57), after 2 weeks of 1 % pimecrolimus, 71.4 % were clear/almost clear vs. 20.7 % on vehicle ($p < .0001$) [70]. Only 1 patient on pimecrolimus had a treatment-related AE (paresthesia). However a 4-week study did not show superiority of pimecrolimus over vehicle [71]. In an 8-week open label study of 21 patients with intertriginous and/or facial psoriasis treated with 0.1 % tacrolimus, all patients had at least 75 % improvement and 81 % were clear [72]. In a study of 167 patients with intertriginous and/or facial psoriasis, by day eight 24.8 % treated with 0.1 % tacrolimus vs. 6 % on vehicle were at least 90 % better ($p = .004$); by 8 weeks, the numbers had risen to 66.7 and 36.8 % respectively ($p < .0001$) [73]. The face and intertriginous areas showed similar improvement (42 % with facial and 48 % with intertriginous lesions were clear) [74]. Similar efficacy (47.6 % clear) was seen in an open label facial study (n = 21), although 5/10 with complete clearing had recurrences during 1 month of follow-up [75]. Adverse effects of tacrolimus were not significantly different than in the placebo arm [73]. Studies in children have also shown efficacy of tacrolimus in facial and intertriginous psoriasis [76, 77]. In one open label study, marked improvement was noted in all 10 patients with long-standing genital and facial psoriasis after 1 week of 0.1 % tacrolimus ointment [78], and in another one (n = 12), male genital PASI decreased from 15.8 to 1.2 ($p < .001$) after 8 weeks of twice daily tacrolimus 0.1 % ointment [79]. Success in male genital psoriasis has also been reported with pimecrolimus [80].

## Tar

Although the German Guidelines [7] do not recommend tar for psoriasis treatment and describe it as "obsolete," tar is still widely used in many parts of the world [81]. Tar has been used for more than 2,000 years and became standard treatment with ultraviolet B phototherapy after Goeckerman's report in 1925 [81]. There are 3 types of tar, coal tar, wood tar (pine, beech, birch, juniper), and shale (ichthammols, bituminous tars) [82]. Coal tar comes from coal distillation in the manufacture of coke and contains approximately 10,000 compounds including polycyclic aromatic hydrocarbons such as benzenes, naphthalenes, creosoles and phenols [83]. The temperature of the distillation and type of coal used affect the final composition [84]. Liquor Carbonis Detergens (LCD) is an alcoholic extract of coal tar that can be mixed in cream, ointment or lotions bases, usually in a concentration of 5–15 % [83].

## Mechanism of Action

Tar inhibits DNA synthesis which in turn results in decreased epidermal proliferation [81]. It is also said to be vasoconstrictive, antifungal, antiparasitic, and antipruritic [81].

## Toxicity

Coal tar is malodorous, can stain hair and fabric and unlike wood and shale tars, is photosensitizing at wavelengths of 330–550 nm [81]. It can also

**Table 7.2** Studies of calcineurin inhibitors in inverse psoriasis

| Study | # Patients | Treatment | Efficacy | Safety |
|---|---|---|---|---|
| Gribetz et al. (2004) [70] | 57 | Pimecrolimus (P) 1 % cream or vehicle (V) BID × 8 weeks | Clear/almost clear:<br>Day 3: 14.3 % on P, 0 % on V, p = .0477<br>Week 8: 71.4 % on P, 20.7 % on V, p < .0001 | 1 mild application site paresthesia with P<br>1 moderate tenderness with V. No withdrawal due to AEs |
| Kreuter et al. (2006) [71] | 80 | P 1 % cream or calcipotriene (C) 0.005 % or 0.1 % betamethasone valerate (B) or vehicle (V) × 4 weeks | Mean M-PASI score reduction: B: 86.4 %, C: 62.4 %, P: 39.7 %, V: 21.1 %. No significant difference between B and C, P and C, and P and V. B better than P, p < .05 and V, p < .01. C better than V, p < .01. | P: 5/20 mild itching and burning<br>C: 2/20 increased erythema, warmth, irritation<br>B: No AEs<br>V: 1/20 herpes genitalis |
| Freeman et al. (2003) [72] | 21 intertriginous and/or facial psoriasis (2/21 face only) | 0.1 % tacrolimus (tac) × 8 weeks (open label) | Complete clearing in 81 and 75–99 % clearing in 19 % (N.B. includes 2 pts with only facial lesions) | 2 had itching and a feeling of warmth |
| Lebwohl et al. (2004, 2005) [73, 74] | 104 intertriginous 167 with intertriginous and/or facial psoriasis | 0.1 % tac ung or V BID × 8 weeks | 48 % with intertriginous psoriasis on tac were clear vs. 14 % on V (p < .001) | Burning in 8 % on tac, 7.3 % on V, hyperesthesia in 4.5 % on tac and 0 % on V, itching in 7.1 % on tac and 1.8 % on V. all NS |
| Steele et al. (2005) [76] | 13 children | 12 with 0.1 % tac, 1 with 0.03 % tac (retrospective review) | 12/12 on 0.1 % tac had complete clearance within 2 weeks<br>No improvement in 1 patient on 0.03 % | 1 on 0.03 % had burning and irritation |
| Martin Ezquerra et al. (2006) [65] | 15 | 0.1 % tac ung × 60 days (open label) | Erythema decreased from 2.9 at baseline to 0.19, infiltration from 2.1 to 0.11 and desquamation from 1.8 to 0.07. (for each, p < .001) N.B. Includes face + genital psoriasis | 2 had a transient warm sensation |
| Brune et al. (2007) [77] | 8 children with intertriginous/11 with face and/or intertriginous psoriasis | 0.1 % tac BID × 180 days (open label) | Reduction in overall severity incl. face (1.63 to 0.71, p < .0001) in the 8 who completed | Pruritus in 1 |

cause burning, stinging ("tar smarts"), folliculitis, acneiform eruptions, irritation, allergic contact dermatitis, erythroderma, tar keratoses and keratoacanthomas [81]. Acute tar intoxication may occur if tar is ingested, or if large amounts of tar are absorbed after topical application; erythrodermic psoriasis patients and young children are at a higher risk [81]. Carcinogenicity concerns arose after Sir Percival Pott, a London surgeon, linked the increased risk of scrotal cancer in chimney sweeps to soot [85], however there was no increase in the expected rate of skin cancer a study of 719 patients with psoriasis [86] and a 25-year follow-up study of 280 patients treated with crude coal tar and UVB [87].

## Clinical Studies in Psoriasis

Tar extract in oil was superior to the oil base in 5 subjects [88], however coal tar was significantly less effective than betamethasone valerate (38 % mean PASI reduction vs. 69 %) in another study [89]. Concentrations of 1 and 6 % crude coal tar have similar efficacy when used with UVB [90]. Daily UVB and tar ointment three times a day for an average of 20 days yielded good to excellent improvement in 95 % of 123 patients with remission rates of 2 months to 8 years (average 1.7 years) [91]. In a similar study, 60 % of patients were still in remission 2 years after treatment [92]. With erythemogenic doses of UVB, a number of studies failed to show increased efficacy with tar compared to petrolatum [93–97]. Studies with suberythemogenic UVB showed less UVB energy and fewer side effects with tar oil vs. emollients in one study [98], faster improvement with 1 % crude coal tar in petrolatum vs. petrolatum (22 %/week vs. 14.7 %/week, $p<0.0005$) and 5 % tar extract in oil vs. oil base (19.6 %/week vs. 11.4 %/week, $p<0.0005$) in another [96], and no benefit in another [99]. Menkes et al. showed similar efficacy of suberythemogenic UVB with tar oil, and maximally erythemogenic UVB with emollients in a study of 49 patients with psoriasis, however the total UVB dose to clearing was 44 % less in the suberythemogenic UVB with tar group [100].

## Anthralin

Anthralin (1,8-dihydroxyanthrone) was first synthesized in 1916 by Galewsky in Germany, after chysarobine, a related compound from Goa powder produced from the araroba tree in Brazil, was noted to be an effective treatment for psoriasis [101]. In the 1930s Ingram used anthralin in Lassar's paste (petrolatum, salicylic acid, zinc oxide, starch) with tar baths and UVB to treat psoriasis [101]. The Ingram regimen was in common use for several decades, but is now rarely used. Anthralin has also been formulated as an ointment [101], gel [102] and in a cream base which washes off easily and has minimal staining [103]. Commercial formulations are no longer available in Canada due to the development of efficacious, convenient, more cosmetically acceptable alternatives.

## Mechanism of Action

In vitro, anthralin has been shown to inhibit DNA replication and DNA repair synthesis [104], interfere with mitochondria [105], decrease keratinocyte transforming growth factor-α expression and epidermal growth factor (EGF) receptor binding [106], inhibit leukotriene production by neutrophils [107], and inhibit monocyte secretion of interleukin (IL)-6, IL-8 and tumour necrosis factor (TNF)-α [108].

## Toxicity

Adverse effects include staining of skin, nails and clothing due to oxidation of anthralin, burning, and irritant and allergic contact dermatitis [101]. In order to minimize irritation, care should be taken to avoid application to uninvolved skin and intertriginous areas should not be treated.

## Clinical Studies

The benefits of the Ingram regime in 2,120 patients were reported by Maclennan and Hellier

in 1961; 95 % were clear in a mean time of 15.2 days as inpatients and 19.5 days as outpatients [109]. Average clearance times in other inpatient series have varied from 11.0 to 20 days [101]. Short contact anthralin ointment with a 10 min to 1 h contact time was tried in an effort to minimize staining and irritation [110]. It was as effective as conventional treatment with anthralin ointment [111], difluorosone acetate [111], and twice daily calcipotriene [112]. If anthralin is considered in the outpatient setting, short contact application (20–30 min) with an initial 1 % concentration, increasing the concentration as tolerated, has been recommended [63].

## Moisturizers and Keratolytics

Moisturizers and keratolytics such as salicylic acid and urea are considered 'Basic Therapy' of psoriasis [7], although there are no placebo-controlled studies supporting their use. Moisturizers decrease scaling, limit painful fissuring and are anti-pruritic. Salicylic acid should be not used with oral salicylates since systemic toxicity might occur. Systemic toxicity might also occur after topical application, especially if applied to >20 % of the body surface, or to patients with impaired renal or hepatic function [63].

### Conclusions

Although tazarotene is efficacious as monotherapy, it is more commonly used in combination with a mid- to high-potency topical steroid since tolerance and efficacy are increased and the steroid's atrophogenic potential decreased with such a combination [113]. Use with broad band narrow band UVB can enhance efficacy and decrease the cumulative dose of UV. Although phototoxicity was not noted in clinical studies, if tazarotene is added to ongoing phototherapy, it might be prudent to reduce the UVB dose by 30–50 % or UVA dose by 2 J/cm$^2$ once scaling and induration are reduced, since one study showed that application of tazarotene for 2 weeks prior to phototesting significantly decreased the average UVB MED from 56.25 to 42.5 mJ/cm$^2$ ($p<0.01$) [114]. Palmoplantar and nail disease, particularly nail bed disease, also respond to tazarotene.

The calcineurin inhibitors, particularly tacrolimus, are efficacious and well-tolerated in the treatment of inverse, facial and genital psoriasis. They are minimally effective in plaque psoriasis and do not cause skin atrophy.

The use of tar and anthralin has declined with the introduction of more cosmetically elegant, efficacious products. Several studies have questioned the efficacy of tar; there does not appear to be any benefit of adding tar to erythemogenic UVB.

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# Ultraviolet Therapy for Psoriasis

8

Tien V. Nguyen and John Y.M. Koo

**Abstract**

Total-body ultraviolet therapy (UV) for moderate-to-severe psoriasis consists of narrowband and broadband-UVB, psoralen plus UVA (PUVA – where psoralen can be ingested orally or applied topically), inpatient phototherapy (i.e. Goeckerman Therapy, Ingram therapy), non-office-based phototherapy (i.e. use of commercial sunlamps/sunbeds or home UVB for psoriasis treatment, heliotherapy, climatotherapy), and combined UVB/PUVA with retinoid or biologic agents. For each type of UV therapy discussed in this chapter, essential information regarding dosage and administration, efficacy (including comparator data if available), short-term side effects, and long-term photocarcinogenic risks are discussed. A well-balanced understanding of the advantages and drawbacks of each photo-therapeutic option can help phototherapy practitioners optimize clinical outcomes as well as enhance the quality of life for patients affected by this chronic skin condition.

**Keywords**

Ultraviolet therapy • NB-UVB • BB-UVB • PUVA • Goeckerman Therapy • Ingram therapy • Tanning • Home UVB • Heliotherapy • Climatotherapy • Combination therapy

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## UVB Phototherapy

UVB phototherapy has been used worldwide since the twentieth century. It consists of narrowband UVB (NB-UVB) and broadband UVB (BB-UVB), which are still the most commonly chosen phototherapeutic options for patients with psoriasis.

## Dosage and Administration

The calculation of the initial UVB dose can be done after assessment of the MED (the minimal erythema dose that induces barely perceptible erythema on non-involved skin) or the Fitzpatrick skin type of each patient [1]. Skin testing to determine MED can add significant time to the first phototherapy visit. Therefore, dosimetry is often based on estimation of Fitzpatrick skin types. Subsequent dosing depends on response of psoriasis and phototoxic reactions to previous doses. For example, if a patient experiences mild-to-moderate pruritus or discomfort (but no skin burns), he or she should be treated with the same light dose until these reactions resolve [1]. If skin burns or intense skin inflammation (i.e. "beefy red" erythema, severe pruritus, etc.) develops, light treatment should be withheld from patients for days or even weeks. In the latter case, phototherapists might consider the use of "cooling procedures" to calm intense skin inflammation, for example, with topical steroids, before re-instituting phototherapy. Please see Table 8.1 [2] and Table 8.2 [2].

The optimal number of UVB exposures per week is three, since less than three treatments per week may result in lower efficacy, and more than three treatments per week have not been shown to be more effective [3]. Once patients have achieved marked improvements of their psoriasis, therapeutic regimen can be tapered slowly to once weekly. Since this maintenance therapy is less intensive and well tolerated, it may be continued for as long as possible in order to prevent rebound of psoriasis [1, 3].

Figures 8.1, 8.2, and 8.3 are intended to illustrate the office-based practice of UVB phototherapy.

**Table 8.1** Dosing guidelines for broadband ultraviolet B

| According to skin type: | | |
|---|---|---|
| Skin type | Initial UVB dose, mJ/cm$^2$ | UVB increase after each treatment, mJ/cm$^2$ |
| I | 20 | 5 |
| II | 25 | 10 |
| III | 30 | 15 |
| IV | 40 | 20 |
| V | 50 | 25 |
| VI | 60 | 30 |
| According to MED: | | |
| Initial UVB | 50 % of MED | |
| Treatments 1–10 | Increase by 25 % of initial MED | |
| Treatments 11–20 | Increase by 10 % of initial MED | |
| Treatments ≥21 | As ordered by physician | |
| If subsequent treatments are missed for: | | |
| 4–7 days | Keep dose same | |
| 1–2 weeks | Decrease dose by 50 % | |
| 2–3 weeks | Decrease dose by 75 % | |
| 3–4 weeks | Start over | |

Reproduced with permission from Menter et al. [2]
Administered 3–5×/week
*MED* minimal erythema dose, *UV* ultraviolet

## Efficacy

Rare comparator studies have documented a much larger difference in efficacy between broadband and narrowband UVB than what is typically observed in practice. In a study by Green et al., 52 patients with plaque psoriasis treated with NB-UVB achieved clearance in 6.6 weeks, whereas 25 patients treated with BB-UVB achieved clearance in 22 weeks [4]. At 1-year follow-up, 38 % of the NB-UVB cohort retained clearance, compared with 5 % of the BB-UVB cohort. Such magnitude of efficacy difference has not yet been replicated by other studies.

More moderate results can be found in another study involving 22 patients with psoriasis who received half-body exposure to BB- or NB-UVB. After 3 weeks of treatment, clinical resolution occurred in 86 % of NB-UVB-treated plaques

**Table 8.2** Dosing guidelines for narrowband ultraviolet B

| According to skin type: | | | |
|---|---|---|---|
| Skin type | Initial UVB dose, mJ/cm$^2$ | UVB increase after each treatment, mJ/cm$^2$ | Maximum dose, mJ/cm$^2$ |
| I | 130 | 15 | 2,000 |
| II | 220 | 25 | 2,000 |
| III | 260 | 40 | 3,000 |
| IV | 330 | 45 | 3,000 |
| V | 350 | 60 | 5,000 |
| VI | 400 | 65 | 5,000 |
| According to MED: | | | |
| Initial UVB | 50 % of MED | | |
| Treatments 1–20 | Increase by 10 % of initial MED | | |
| Treatments ≥21 | Increase as ordered by physician | | |
| If subsequent treatments are missed for: | | | |
| 4–7 days | Keep dose same | | |
| 1–2 weeks | Decrease dose by 25 % | | |
| 2–3 weeks | Decrease dose by 50 % or start over | | |
| 3–4 weeks | Start over | | |
| Maintenance therapy for NB-UVB after >95 % clearance: | | | |
| 1×/week | NB-UVB for 4 weeks | Keep dose same | |
| 1×/2 weeks | NB-UVB for 4 weeks | Decrease dose by 25 % | |
| 1×/4 weeks | NB-UVB | 50 % of highest dose | |

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Administered 3–5×/week. Because there is broad range of MED for NB-UVB by skin type, MED testing is generally recommended. It is critically important to meter UVB machine once weekly. UVB lamps steadily lose power. If UV output is not periodically measured and actual output calibrated into machine, clinician may have false impression that patient can be treated with higher doses when machine is actually delivering much lower dose than number entered. Minimum frequency of phototherapy sessions required per week for successful maintenance as well as length of maintenance period varies tremendously between individuals. Above table represents most ideal situation where patient can taper off phototherapy. In reality, many patients require 1×/week NB-UVB phototherapy indefinitely for successful long-term maintenance
*MED* minimal erythema dose, *NB* narrowband, *UV* ultraviolet


**Fig. 8.1** Nurse stations and light boxes for office-based UVB phototherapy

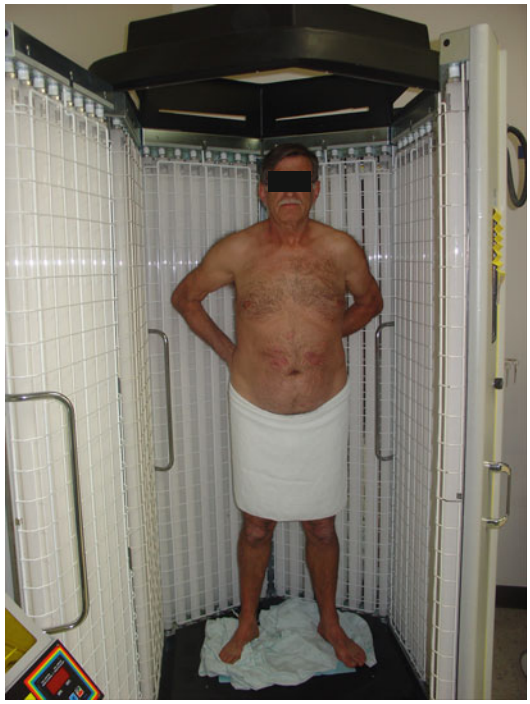

**Fig. 8.2** Eye protection for whole-body UVB irradiation

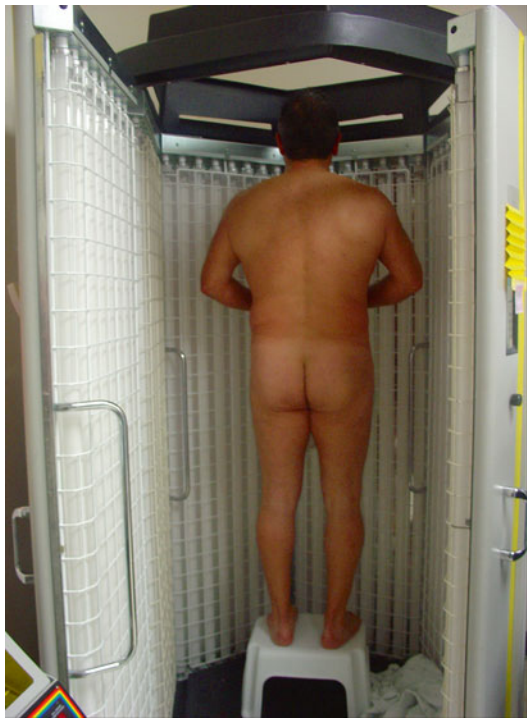

**Fig. 8.3** Whole-body UVB irradiation using a stool to increase lower-body exposure

and 73 % of the BB-UVB-treated plaques [5]. With regards to Long-term efficacy of NB-UVB, Karawaka et al reported that 56 % of their 52-patient cohort retained PASI 50 response for at least 1 year after a 4-week course of NB-UVB phototherapy [6].

The difference in efficacy between BB-UVB and NB-UVB – where the latter is, to some extent, superior as a treatment for psoriasis – deserves explication. Some of the UV rays emitted by BB-UVB lamps (i.e. 254, 280, or 294 nm rays) are less effective than UV rays with longer wavelengths (i.e. 311 or 312 nm rays) at clearing psoriasis [7]. The 311 nm rays emitted by NB-UVB lamps are capable of clearing psoriatic plaques with a little as 0.4 times the MED. Furthermore, NB-UVB therapy confers the benefit of causing fewer phototoxic reactions for patients than BB-UVB therapy at the same doses.

## Side Effects and Safety

Side effects of UVB phototherapy include visible erythema, burning, blistering, discomfort, and post-inflammatory hyperpigmentation [1, 5, 8]. In addition, "over-exposure" to UVB has been associated with precipitation of erythrodermic psoriasis in two reported cases [9].

## Photocarcinogenicity of UVB Phototherapy

Studies with mice have often not mirrored human exposure to UVB. They should not be extrapolated at face value to determine the carcinogenic risk of UVB phototherapy in humans. For instance, UVB irradiation of 30 hairless, lightly pigmented mice who are not cancer-prone for 30 weeks was linked with an 83 % rate of squamous cell carcinoma (SCC) development [10]. This study lacked a control mice group. Moreover, the mice received UVB 5 days per week, while humans with psoriasis are optimally treated three times weekly.

In another study using hairless, lightly pigmented mice, all mice developed skin tumors,

while mice receiving 311 nm UVB developed skin tumors earlier than mice treated with BB-UVB [11]. Of note, some of the mice had *total-body* exposure to UVB at doses that were multitudes of the MED (also known as "supra-erythemogenic" doses). In humans, intense UVB irradiation of non-involved skin is likely to result in frequent, severe skin burns, which can increase the risk of skin cancer.

Meanwhile, review of the worldwide literature on human experience revealed no convincing data of an increased photocarcinogenic risk of long-term UVB phototherapy for psoriasis. In a publication by Lee et al., no increased carcinogenic risk associated with UVB phototherapy was appreciated in 10 out of the 11 studies in the medical literature [12]. One exception is the report featuring a 30-case/137-control sub-cohort from a large-scale Finnish study in psoriasis patients, where the relative risk ratio of developing SCC in patients with a history of UVB treatments was 1.6. This risk is slightly elevated but not statistically significant [13].

In addition, there was no increased risk of skin cancer in 484 Northern Irish patients who had at least 18 NB-UVB exposures individually [14]. A larger retrospective study involving 3,886 patients treated with UVB at a Scottish hospital found 27 basal cell carcinoma (BCC), 7 SCC, and 6 melanomas, which were comparable to expected incidences for the three types of skin cancer, respectively, in the matched populations [15]. In this study, only patients who received both NB-UVB and PUVA had a higher incidence of BCC (27) than the expected incidence (14) in the general Scottish population [15].

In a follow-up study of 195 patients who received either BB- or NB-UVB treatment for psoriasis, only one patient developed melanoma in situ. This patient's tumor was diagnosed in the same year phototherapy was instituted; hence, its development may have been unrelated to the limited UVB exposure [16]. Another study followed 1908 Scottish patients who had long-term UVB treatment for an average of 4 years. Remarkably, the study found no incidence of melanoma SCC [17]. Ten patients developed BCC mostly on the face compared with the expected incidence of 4.7 in the matched population [17]. The predilection of BCC for the face attested to the possible increase in solar exposure as an uncontrolled variable, since patients with psoriasis often engage in this practice to augment office-based phototherapy. For office-based phototherapy, the patient's face is typically covered to avoid unnecessary exposure.

## PUVA (Psoralen Plus Puva)

### Dosage and Administration

PUVA is the combination of the plant-originated compound psoralen and UVA (320–400 nm) irradiation for the treatment of psoriasis. Available as Oxsoralen Ultra® 10 mg capsules in the US, psoralen can be taken orally or diluted in a bath solution for topical administration within the hour before UVA irradiation. In the beginning of their treatment course, patients are encouraged to undergo PUVA treatment thrice weekly. For the purpose of maintaining marked improvement or clearance of psoriasis, the number of weekly office visits for PUVA can be tapered slowly to once weekly, once every other week, or even a less frequent schedule. Dosimetry of PUVA is described in Table 8.3 [2] and Table 8.4 [2] Information about dosage following missed PUVA exposures can be found in Table 8.5.

Please refer to Fig. 8.4 for an illustration of "hands" PUVA (PUVA just for the hands) and to Figs. 8.5, 8.6, 8.7, and 8.8 for an illustration of bath PUVA.

**Table 8.3** Dosing of 8-methoxypsoralen for oral psoralen plus ultraviolet A

| Patient weight | | |
|---|---|---|
| lb | kg | Drug dose, mg |
| <66 | <30 | 10 |
| 66–143 | 30–65 | 20 |
| 144–200 | 66–91 | 30 |
| >200 | >91 | 40 |

Reproduced with permission from Menter et al. [2]

**Table 8.4** Dosing of ultraviolet A radiation for oral psoralen plus ultraviolet A

| Skin type | Initial dose, J/cm$^2$ | Increments, J/cm$^2$ | Maximum dose, J/cm$^2$ |
|---|---|---|---|
| I | 0.5 | 0.5 | 8 |
| II | 1.0 | 0.5 | 8 |
| III | 1.5 | 1.0 | 12 |
| IV | 2.0 | 1.0 | 12 |
| V | 2.5 | 1.5 | 20 |
| VI | 3.0 | 1.5 | 20 |

Reproduced with permission from Menter et al. [2]

**Table 8.5** Subsequent dosing protocol for PUVA

| Number of missed days | Subsequent dosing |
|---|---|
| 3–5 | Continue routine dosing increase |
| 6–14 | Hold dose |
| 15–21 | Decreased dose by 25 % |
| 22–28 | Decreased dose by 50 % |
| >28 | Re-institute phototherapy and dosimetry |

Adapted from UCSF Psoriasis Center with permission of the author (JK)

**Fig. 8.4** PUVA for the hands/feet psoriasis or eczema

**Fig. 8.5** Oxsoralen Ultra® 10 mg capsules for bath PUVA

**Fig. 8.6** Boiled water to dissolve Oxsoralen Ultra*** 10 mg capsules

## Efficacy

Following activation by UVA irradiation, psoralen cross-links with DNA of various cell types in psoriatic skin (i.e. keratinocytes, T cells, etc.) to inhibit inflammation and cell proliferation. A recent randomized, double-blind, placebo-controlled trial involving 40 psoriasis patients revealed an 86 % PASI 75 response rate in the PUVA arm versus 0 % PASI 75 response rate in the UVA arm after 12 weeks of therapy [18]. In another study, 88.8 % of 3,175 patients with psoriasis achieved 95–100 % clearance after an average of 20 PUVA exposures [19].

When compared against NB-UVB phototherapy, PUVA demonstrates inferior efficacy in small-scale studies but superior efficacy in large-scale studies. A comparator trial involving only 17 patients reported a PASI score reduction of 45 % in the PUVA-treated cohort compared with 77 % in the NB-UVB-treated cohort [20]. In this study, both PUVA and NB-UVB irradiation were done thrice weekly for a maximum of 30

**Fig. 8.7** Concentrated solution made by dissolving Oxsoralen Ultra 10 mg capsules in hot water

**Fig. 8.8** Measuring water level for bath PUVA. The water level corresponding to 100 L is indicated on the ruler

exposures or clearance, whichever came first. In another study of 28 patients with psoriasis, 54 % of the PUVA-treated cohort versus 78 % of the NB-UVB-treated cohort achieved clearance after a maximum of 30 exposures [21]. Interestingly, in this study PUVA was administered twice weekly, which is not the optimal regimen to achieve rapid clearance of psoriasis.

In terms of a larger "head to head" comparitor study, Gordon et al. treated 100 patients thrice weekly with either PUVA or NB-UVB phototherapy. Eighty-four percent of the PUVA-treated cohort achieved clearance of psoriasis after 16.7 exposures compared with 63 % of NB-UVB-treated cohort after 25.3 exposures [22]. Moreover, the number of PUVA-treated patients who retained clearance 6 months after therapy was almost double that of NB-UVB-treated patients [22]. A similar study involving 93 patients showed an 84 % clearance rate in the PUVA arm after 17.0 exposures compared with 65 % in the NB-UVB arm after 28.5 exposures [23]. Sixty-eight percent of the PUVA-treated subjects versus 35 % of the NB-UVB-treated subjects remained in remission for 6 months after treatments had ended. Evidence from these large, randomized trials seem to support superior efficacy of PUVA over NB-UVB, especially with regard to duration of therapeutic effects.

## Side Effects

Dose-dependent effects of PUVA include skin irritation, skin burns, and tanning. In addition, ingestion of psoralen has been associated with nausea, headaches, dizziness, and extremely rare instances of psychiatric disturbance (i.e. insomnia, depression) [8]. To minimize nausea, patients can try decreasing the dose of psoralen and/or ingesting psoralen with food later in the day [8].

After decades of use, the association of PUVA with an increased risk of cataracts has not been substantiated in an evidence-based fashion [24]. The author (JK) feels that an ophthalmic examination is mainly useful for documenting the presence or absence of pre-existing cataracts. Therefore, for the author (JK), even the presence of pre-PUVA cataracts does not necessarily constitute an absolute contraindication for initiating PUVA therapy. There is no convincing human data after decades of worldwide use to prove that PUVA increases the risk of cataracts, provided that the patient is compliant with UVA eye protection measures for 24 h after psoralen ingestion.

Long-term exposure to PUVA is associated with photoaging marked by premature cutaneous degeneration and pigmentation [25].

## Photocarcinogenicity of PUVA

Long-term UVA irradiation exposure has been associated with melanocytic atypia (i.e. large, angular hyperchromatic nuclei and binucleated melanocytes), suggesting aberrant cellular kinetics [26]. A list of 25 PUVA follow-up studies conducted worldwide can be found in Table 8.6. Out of 25 published studies, 24 did not show an elevated risk of melanoma associated with long-term PUVA exposure. However, one study published by Stern et al. recorded an increased risk of cutaneous melanoma associated with PUVA. In this study, 1,380 patients across the USA were monitored for up to 21 years during and after photochemotherapy. During the first 15 years of follow-up, the relative incidence of melanoma was not different than expected in the general US population, based on cancer statistics from the SEER (Surveillance, Epidemiology, and End Results) Program [49]. In the next 5 years of follow-up, seven new cases of melanoma were diagnosed, giving a relative risk ratio of 5.4 [49]. The authors thus hypothesized that a period of latency exists before the risk of melanoma related to long-term PUVA treatment becomes recognizable.

Comprehensive knowledge of how SEER derives its cancer statistics can influence how one interprets Stern et al.'s results and the implications of their study. SEER approximates melanoma prevalence in the general US population based on chart reviews of hospitals and "search of private laboratory records" in designated regions, which, as of 1990, comprised 9.6 % of the total US population. Unlike systemic cancers for which SEER database was primarily intended, many cases of melanoma in situ and early-stage invasive melanoma are excised on an outpatient basis by community dermatologists without being registered into any of the above databases [53, 54]. As a result, data generated by SEER may underestimate the actual prevalence of melanoma in the general US population. This could inflate the melanoma risk for PUVA that was calculated in Stern et al.'s study. Additionally, the study lacked a matched control group to account for confounding variables such as a history of sunburns, family history of skin neoplasm, other UV light treatments, or medications that possess carcinogenic risk, etc.

An extension of the original study by five more years followed the same cohort of 1,380 PUVA-treated patients. The relative risk ratio within this latest 5-year period is 7.4, once again based on cancer statistics from SEER [50]. In contrast, the largest PUVA study that has been published to date was conducted in Sweden by Lindelof et al., who examined a cohort of 4,799 PUVA-treated psoriasis patients. The data published by Lindelof et al. revealed no increased risk of melanoma compared to the general Swedish population during an average 15–16 years of follow-up [51]. There was not even an increased risk of melanoma in a subcohort of 1,867 patients who were followed up for longer than 15 years [51] – this is where Stern et al. claimed to have observed an increased carcinogenic risk of PUVA. The prevalence of melanoma used to calculate relative risk ratio of melanoma in Lindelof et al.' study comes from the Swedish Cancer Registry. It is likely to reflect the actual prevalence in the Swedish population, since reporting of melanoma diagnoses in Sweden is compulsory – unlike the situation in the USA, where no melanoma-reporting requirement exists.

Concerning the risk of NMSC, the results of Lindelof et al.'s study supported an increased risk of SCC associated with long-term PUVA use: relative risk ratios were 3.6 for women and 5.6 for men [51]. Furthermore, analysis of the 1,380-patient US PUVA cohort by Nijsten and Stern revealed higher than expected incidences of SCC and BCC compared with the general US population (based on SEER statistics). This NMSC risk is particularly notable in patients with more than 200 lifetime PUVA treatments [55]. Conversely, a follow-up study in 944 Swedish and Finnish psoriasis patients treated only with *bath* PUVA, not systemic PUVA, did

**Table 8.6** Risk of melanoma associated with PUVA treatment

| Authors (Year) | Country | Number of subjects | Number of melanoma cases | Follow-up periods (years) | Mean or median follow-up | Relative risk of invasive melanoma |
|---|---|---|---|---|---|---|
| Honigsmann et al. (1980) [27] | Austria | 418 | 0 | 1–5 | [a] | [a] |
| Lobel et al. (1981) [28] | Australia | 489 | 0 | [a] | [a] | [a] |
| Lassus et al. (1981) [29] | Finland | 525 | 0 | 1–3.6 | 2.2 | [a] |
| Lindskov (1983) [30] | Denmark | 198 | 0 | 1–6 | 3.5 | [a] |
| Ros et al. (1983) [31] | Sweden | 250 | 0 | 0–7 | 4.1 | [a] |
| Reshad et al. (1984) [32] | United Kingdom | 216 | 0 | 0–7 | 4.8 | [a] |
| Eskelinen et al. (1985) [33] | Finland | 1,047 | 0 | 0–8 | [a] | [a] |
| Tanew et al. (1986) [34] | Austria | 297 | 0 | 3.4–8.0 | 5.3 | [a] |
| Henseler et al. (1987) [35] | Europe | 1,643 | 1 invasive | 0–11 | 8.0 | [a] |
| Barth et al. (1987) [36] | Germany | 6,820 | 0 | 0–10 | [a] | [a] |
| Cox et al. (1987) [37] | United Kingdom | 95 | 0 | 0–8 | [a] | [a] |
| Torinuki and Tagami (1988) [38] | Japan | 151 | 0 | 0–10 | [a] | [a] |
| Abdullah and Keczkes (1989) [39] | United Kingdom | 198 | 1 in situ | 0–10 | [a] | [a] |
| Forman et al. (1989) [40] | United States | 551 | 1 invasive | 0–10 | 4.8 | [a] |
| Bryunzeel et al. (1991) [41] | Netherlands | 260 | 0 | 0–12.8 | 8.7 | [a] |
| Chuang et al. (1992) [42] | United States | 492 | 0 | 0–14 | 5.4 | [a] |
| Lever and Farr (1994) [43] | United Kingdom | 54 | 0 | 6–15 | 11.2 | [a] |
| Gritiyarangsan et al. (1995) [44] | Thailand | 113 | 0 | 2–14 | 6.2 | [a] |
| Maier et al. (1996) [45] | Austria | 496 | 0 | 0.4–17.2 | 6.2 | [a] |
| McKenna et al. (1996) [46] | Northern Ireland | 245 | 0 | 2–15 | 9.5 | [a] |
| Hannuksela et al. (1996) [47][b] | Finland | 527 | 0 | 0–16 | 11 | [a] |
| Cockayne and August (1997) [48] | United Kingdom | 150 | 0 | 5–17 | [a] | [a] |
| Stern et al. (1997) [49] and Stern (2001) [50] | United States | 1,380 | 18 invasive<br>7 in situ<br>1 ocular | 0–24 | 19 [49] | 1975–1990: 1.0<br>1991–1996: 4.7 (1.4–16.1)<br>1996–1999: 7.4 (2.2–25.1) |
| Lindelof et al. (1999) [51] | Sweden | 4,799 | | 0–21 | 16 | M: 1.1 (0.4–2.3)<br>F: 1.0 (0.5–2.2) |
| Hannuksela-Svahn et al. (1999) [52][b] | Sweden, Finland | 944 | 0 | 0–18 | 14.7 | M: 0.7 (0.0–3.8)<br>F: 1.3 (0.0–7.2) |

[a]Information not provided or not able to be calculated from data
[b]Bath PUVA only

not show any increased risk of SCC or malignant melanoma after a mean follow-up period of 14.7 years [52]. Whether different cellular mechanisms are involved or the total UVA dose is lower, bath PUVA appears to have less photocarcinogenic risk than oral PUVA.

It is important to recognize that available data about long-term safety of PUVA therapy mostly come from studies involving Caucasians. Murase et al. conducted the only review of PUVA-related skin cancer incidence in non-Caucasian patients with various photosensitive dermatoses. Their analysis included 4,294 long-term PUVA patients who had at least 5 years of follow-up in studies conducted in Japan, Korea, Thailand, Egypt, and Tunisia. The relative risk of developing skin neoplasm in these patients compared to the general dermatology outpatient population was 0.86 (with a confidence interval of 0.36–1.35). This means that the increased risk of skin cancer related to long-term PUVA in Asian and North African patients has yet to be demonstrated [56]. Further investigation into the protective nature of darker skin phototypes is needed.

## Inpatient Phototherapy

### Goeckerman Therapy

Formulated in 1925, Goeckerman's eponymous therapy is one of the oldest forms of phototherapy for the treatment of psoriasis [57] and enjoyed widespread use in the USA until the Diagnostically Related Groups (DRG) made prolonged hospitalization for dermatologic conditions impossible. It is still considered by many dermatologists as the gold standard treatment based on high efficacy and induction of prolonged remission times. Furthermore, Goeckerman therapy can be used to treat patients who have failed a number of therapeutic modalities beyond topical steroids, such as PUVA, UVB, and biologics [58]. Also, it lacks the steroid-related side effects and internal adverse risks associated with systemic therapies.

#### Dosage and Administration

Goeckerman therapy is an intensive therapy requiring all-day, everyday continuous participation for typically 4–6 weeks in a hospital unit or psoriasis day care center (Figs. 8.9 and 8.10) [59]. The treatment regimen begins each day with UVB irradiation, since UV light will not penetrate after application of crude coal tar (CCT). The second step is to lather the patient's skin with CCT in petroleum (Fig. 8.11), which comes in 2, 5, and 10 % preparations, and to soak the patient's scalp in 20 % liquor carbonis detergens (LCD) in Neutraderm® lotion (Fig. 8.12) [59]. Twenty percent LCD in Aquaphor ointment is applied to the total body of each patient before he/she leaves the facility. It is also sent home with the patient to be done once more at bedtime. If the patient's condition is so severe that tar plus UVB do not provide adequate control, then compounded anthralin and even topical PUVA can be added [1]. Infrequently, truly recalcitrant psoriasis might necessitate the concomitant use of retinoids and topical vitamin D derivatives in order to achieve clearance [1].

#### Efficacy

Goeckerman therapy has high efficacy for recalcitrant psoriasis, even when single or multiple biological agents have failed to show improvements [58]. In a prospective study, 95 and 100 % of 25 psoriasis patients who were treated with Goeckerman therapy reached PASI 75 by week 8 and week 12, respectively [60]. In another study, clearance of psoriasis has been documented in 90 % of 300 patients after only 18 days of treatment. Eight-month remission was recorded in 90 % of these subjects [59]. It should be noted that the second study featured a more intensive treatment regimen than the commonly practiced Goeckerman therapy: UVB and tar therapy were administered twice daily, and patients attended the program 6 instead of 5 days a week [59]. This may explain their significantly rapid clearance rate.

In 1979 DesGroseilliers et al. implemented a modified design to render Goeckerman therapy less time-intensive and more cost-effective. 200 patients were treated with coal tar application at home plus office-based UVB irradiation the following day 5 days a week. After 1 month of

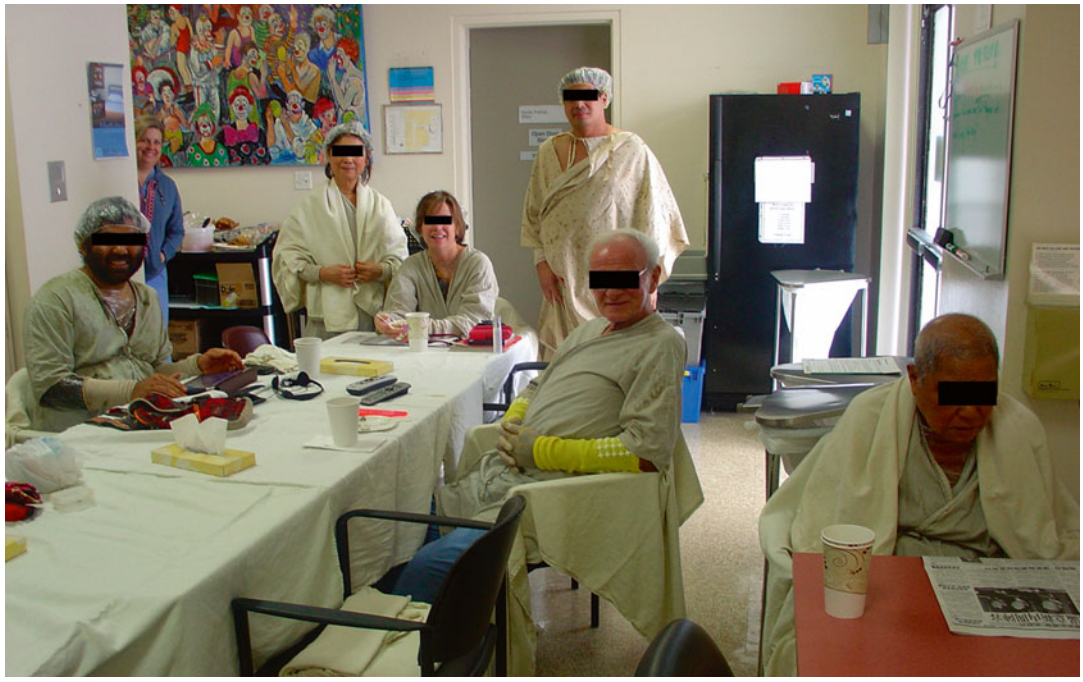

**Fig. 8.9** The common area for Goeckerman Therapy patients at a psoriasis day care center, which often turns into a therapeutic milieu (i.e. where the ambient supportive atmosphere is experienced by the patients as therapeutic)

**Fig. 8.10** Physicians performing rounds on a patient undergoing Goeckerman Therapy

treatment, 86 % of patients in this cohort achieved clearance of their psoriasis [61]. The mean remission duration of 5.1 months was calculated based on 185 patients who experienced relapse during the observation period [61]. However, there were 15 patients in the study who did not relapse during the entire observation period. Had these 15 patients been included, the calculated mean remission duration would have been longer than 5.1 months.

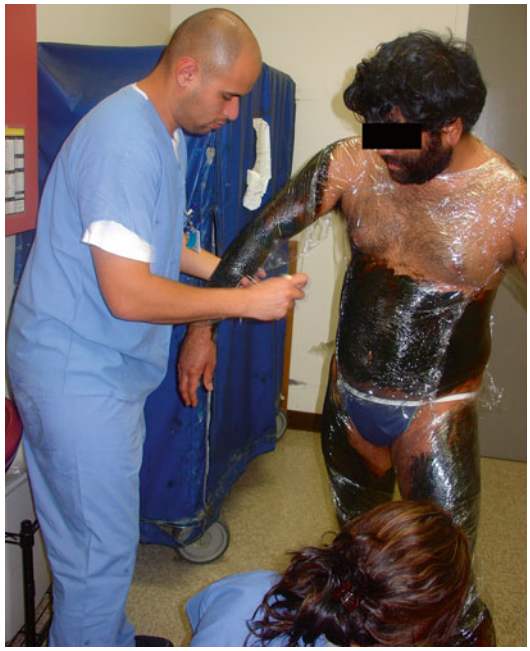

**Fig. 8.11** Nursing staff applying crude coal tar with occlusion to psoriatic skin

**Fig. 8.12** Nursing staff applying 20 % liquor carbonis detergens in Neutraderm lotion to a psoriasis patient's scalp

### Side Effects and Long-Term Safety

Side effects of Goeckerman therapy include folliculitis and phototoxic reactions, which are can be managed by dose adjustment of UVB and tar. The pustules associated with Goeckerman therapy can develop on non-involved skin and are therefore distinct from pustular psoriatic lesions [62]. Rarely, precipitation of erythrodermic psoriasis has been documented in patients allergic to crude coal tar [63]. To investigate long-term safety, a 25-year follow-up study was conducted in 280 psoriasis patients treated with Goeckerman therapy over a 5-year period. The results consisted of 1 melanoma, 22 BCC, 7 SCC, and 3 tumors of unknown type [64]. Based on cancer statistics from a matched population, there was no increase in the risk of skin cancer in these patients [64].

## Ingram Therapy

Ingram therapy is the inpatient treatment of psoriasis with UV irradiation and anthralin, which was introduced to dermatology in 1916 [65]. It consists of a succession of tar bath, light treatment, and application of anthralin paste or ointment to involved skin. Adding crude coal tar to anthralin has been shown to reduce skin irritation without compromising antipsoriatic efficacy [66]. In a retrospective study by De Bersaques, 275 psoriasis patients who were treated in a hospital with Ingram therapy achieved clearance after an average of 25 days [65]. Patients did not need another treatment or hospitalization for 8–11 months after therapy [65]. However, being a single center study, these results might have been influenced by loss to follow-up of patients who sought care from other practitioners due to early relapse.

**Table 8.7** Meta-analysis of all studies included

| Exposure | Number of studies | Summary relative risk (95 % CI) | Heterogeneity[a] P-value $\chi^2$ | H |
|---|---|---|---|---|
| Ever use of indoor tanning facility | 19 | 1.15 (1.00–1.31) | 0.013 | 1.37 |
| First exposure in youth | 7 | 1.75 (1.35–2.26) | 0.55 | 0.91 |
| Exposure distant in time | 5 | 1.49 (0.93–2.38) | 0.018 | 1.65 |
| Exposure recent in time | 5 | 1.10 (0.76–1.60) | 0.81 | 0.67 |

Reproduced with permission from the IARC [68]
[a]The degrees of freedom for the Chi-square are given by the number of databases included minus one, not by the number of studies

**Table 8.8** Meta-analysis of the cohort and population-based case–control studies included

| Exposure | Number of studies | Summary relative risk (95 % CI) | Heterogeneity[a] P-value $\chi^2$ | H |
|---|---|---|---|---|
| Ever use of indoor tanning facility | 10 | 1.17 (0.96–1.42) | 0.011 | 1.540 |
| First exposure in youth | 5 | 1.71 (1.25–2.33) | 0.435 | 0.973 |
| Exposure distant in time | 2 | 1.58 (0.25–9.98)[a] | 0.502 | 0.830 |
| Exposure recent in time | 2 | 1.24 (0.52–2.94) | 0.762 | 0.521 |

Reproduced with permission from the IARC [68]
[a]The confidence interval is very wide because this analysis includes only two studies, one of which has two estimates

## Non-Office-Based Phototherapy

### Commercial Tanning Therapy

In commercial tanning facilities, phototherapy for psoriasis can be conducted using "tanning beds" that emit high-intensity UVA rays mixed with small quantities of contaminant UVB. This is different from office-based, outpatient UVB phototherapy, where healthcare professionals frequently perform clinical assessments and light dose adjustments. For 16 out of 20 psoriasis patients treated with tanning beds, the initial mean PASI score of 7.96 (±1.77) was diminished to 5.04 (±2.5) after 6 weeks of treatment [67]. Even those who did not complete the entire treatment course had a 23.5 % improvement of their PASI scores [67]. Furthermore, most patients reported significant improvements in health-related quality of life, while mild burning and transient pruritus were infrequent and well-tolerated [67].

There is controversy surrounding the existence of an association between exposure to commercial UV tanning devices (i.e. sunlamps, sunbeds) and an increased risk of melanoma. In 2006 the International Agency for Research on Cancer issued a detailed report on the photocarcinogenic risk of artificial UV exposure, which addressed 23 case-control studies related to indoor tanning and melanoma. The risks for melanoma associated with "ever use" (any exposure to sunlamps/sunbeds in one's lifetime), "first use in youth" (exposure to sunlamps/sunbeds starting at 35 years old or younger), "distant use" (5 years or more from the time of the interview), and "recent use" (less than 5 years from the time of the interview) of indoor tanning devices were compared and contrasted using reported relative risk ratios. Meta-analysis of 19 of these 23 studies (Table 8.7) revealed a calculated summative relative risk of 1.15 (95 % confidence interval: 1.00–1.31) for "ever use" of indoor tanning facility [68]. The same relative risk becomes slightly elevated to 1.17 (0.96–1.42) when data only from cohort and population-based case-control studies were employed for calculation (Table 8.8) [68]. In both meta-analyses the summative relative risk

is higher for first exposure in youth than for "ever use" of indoor tanning facility and also higher for "distant" exposure versus "recent" exposure [68].

In a systematic review of case-control studies, 6 out of 19 studies reported a dose-response relationship between tanning lamp/bed exposure and melanoma risk [69]. Another review of 10 case-control studies reported that the odds ratios spanned anywhere from 0.7 (0.5–1.0) to 2.9 (1.3–6.4) for "ever use" versus "never use" (no exposure at all during one's lifetime) of sunlamps/sunbeds [70]. Of note, the dose-dependent risk for invasive melanoma is likely to be more profound in Caucasian *female* users with more than ten lifetime tanning sessions compared with those having less than ten sessions [71]. The results of this study do not apply to Caucasian male users, possibly due to the fact that they visit tanning facilities less frequently than their female counterparts [71]. In addition, this cut-off of ten tanning sessions is an arbitrary proposal based on the results of one study. More convincing data is needed to establish a photocarcinogenic threshold for UVB exposure through tanning devices.

### Home UVB Therapy

Most devices employed in home phototherapy emit UVB. This form of phototherapy is tailored to patients with stable psoriasis and logistical difficulty, such as lack of time to do office phototherapy or no access to nearby dermatology practices with UVB capacity. In a randomized trial involving 196 psoriasis patients, 70 % of patients receiving home UVB therapy reached PASI 50 compared to 73 % in the outpatient group [72]. Short-term safety profiles were not notably different between the groups. [72] Moreover, the burden of therapy (a function of method and time commitment) was significantly lower for home phototherapy patients than for office-based outpatients [73].

### Heliotherapy

Heliotherapy is the therapeutic use of sunlight to treat psoriasis and other photosensitive dermatoses. There are not many large, randomized, controlled studies to determine the efficacy of heliotherapy, let alone comparator studies involving other forms of phototherapy. In a study with 373 subjects, the rate of clearance of psoriasis was 22 % and that of PASI 75 response was 84 % after 1 month of treatment [74]. The median remission time was 2.6 months (80 days) [74]. Short-term side effects are similar to other phototherapeutic modalities: skin burns, irritation, pruritus, erythema, heat, etc. Skin cancer risks associated with long-term heliotherapy in patients with psoriasis have not been studied.

### Climatotherapy at the Dead Sea

Climatotherapy is the exposure of skin to a special kind of climate for the treatment of psoriasis. Its efficacy was established in a study involving 64 patients: PASI 75 response after 1 month of climatotherapy at the Dead Sea was 75.9 %, and the median duration of remission was 5.8 months (23.1 weeks) [75]. Analysis of skin cancer data from a cohort of 1,738 Danish patients who were followed up for an average of 6.1 years revealed no association between climatotherapy and an increased risk of melanoma [76]. There were, however, 8 SCC and 28 BCC compared with 0.8 expected SCC and 6.6 expected BCC. [76] It was later discovered that the subjects in this follow-up study had received more than three times the necessary amount of UVB to achieve therapeutic results [77]. This important information might partially explain the significant difference between observed and expected incidence of non-melanoma skin cancer.

## Combination Therapy

For patients with severe psoriasis based on large BSA coverage and/or resistance to traditional single therapies, combinations of therapies are available as treatment options.

### UVB and Retinoid Therapy

Acitretin, an oral retinoid agent, has been shown to enhance the efficacy of UVB phototherapy.

In an 8-week, randomized, comparator study involving 82 psoriasis patients, 60 % of the combined BB-UVB and acitretin cohort (re-UVB) versus 24 % of the BB-UVB cohort reached PASI 75 [78]. Phototherapy was administered three to five times weekly, and acitretin was available as 25 mg tablets taken once daily [78]. Treatment with acitretin 25 mg plus thrice weekly NB-UVB resulted in 75 % improvement of psoriasis in 30 out of 40 patients from another study [79].

The phenomenon "delayed retinoid burn" was described in 2011 after a psoriasis patient experienced a severe phototoxic reaction as a result of adding acitretin 25 mg daily to a previously tolerated UVB dose [80]. Since acitretin induces cell differentiation and leads to sloughing of keratin layers from psoriatic plaques, the end result is too much light penetration causing phototoxicity. Therefore, phototherapy providers should consider reducing UV dose when starting concomitant retinoid therapy. The authors recommended cutting UVB dose by 50 % as soon as acitretin is added [80]. How this is conducted in each phototherapy provider's office is a judgment call.

## PUVA and Retinoid Therapy

Similarly, rapid improvement of recalcitrant psoriasis might be achieved by adding oral retinoid agents to PUVA. In a study comparing the efficacies of combined PUVA plus acitretin dosed at 1 mg/kg body weight/day (re-PUVA) versus PUVA lone, clearance was achieved in 96 % of the combination cohort and 80 % of the PUVA cohort after 11 weeks of treatment [81]. Had the 48 subjects of this study undergone PUVA treatment three instead of four times weekly, the clearance rates in both arms might not have been as high and their difference easier to appreciate.

Furthermore, another head-to-head comparitor study between re-PUVA and re-UVB showed 100 % clearance rate in the re-PUVA cohort compared with 93 % in the re-UVB cohort after a 6-week treatment course [82]. Etretinate dosed at 1 mg/kg body weight/day was used instead of acitretin. The duration of therapeutic effects was longer for the re-PUVA patients than the re-UVB patients [82]. However, this study was limited by its small size (each cohort consisted of 15 patients) and the fact that PUVA and UVB was done twice weekly, respectively, for each combination therapy.

When photo(chemo)therapy was instituted at the optimal treatment regimen (thrice weekly) in 60 psoriasis patients, clearance was achieved in 63.3 % of the re-PUVA cohort versus 56.6 % of the re-UVB cohort. [83] The reported clearance rates were lower in this study than in the previous studies because acitretin was dosed at 0.3–0.5 mg instead of 1 mg/kg body weight/day. In spite of the dosing differences between these comparitor studies, all consistently proved that re-PUVA is more effective at reducing the clinical severity of psoriasis than re-UVB combination therapy.

## UVB and Biologics

UVB therapy can be added to biological agents to expedite clearance of moderate-to-severe psoriasis. A 6-week study involving 14 patients showed that combined UVB and etanercept helped patients achieve a 64 ± 28.8 % reduction of their modified PASI scores compared with the 53.7 ± 36.9 % PASI score reduction in patients treated with etanercept alone [84]. UVB was given thrice weekly, and etanercept was dosed at 25 mg twice weekly. De Simone et al. performed a single-arm, open label study in which 33 patients with moderate-to-severe psoriasis were treated for 8 weeks with etanercept 50 mg once weekly plus NB-UVB thrice weekly, after which only etanercept was continued for another 4 weeks. At Weeks 4, 8, and 12 of treatment, PASI 75 was reached in 24.2, 66.7, and 81.8 % of the study participants, respectively [85].

The results of a single-arm, single-center, open-label study involving 20 patients with severe psoriasis were promising: after 12 weeks of combined adalimumab 40 mg every other week and NB-UVB three times weekly, 95 and 85 % of the patients reached PASI 75 and clearance, respectively [86]. Moreover, 65 % of patients retained PASI 75 response 12 weeks following the end of treatment [86]. A similar but larger trial (known by the acronym "UNITE") with NB-UVB thrice weekly plus etanercept

50 mg twice weekly also showcased high efficacy of combination therapy: at Week 12, 84.9 % of 86 psoriasis patients reached PASI 75 [87]. There was also an equally important and significant improvement in health-related quality of life in almost all of the UNITE study subjects [87].

## Photocarcinogenicity of Combination Therapy

Oral retinoid agents can lower the skin cancer risk associated with phototherapy through promotion of keratinocyte differentiation. There is a case report of one patient on once daily acitretin 25 mg whose number of squamous cell carcinomas decreased while on acitretin and increased when taken off acitretin [88]. In addition, the results of a 15-year follow-up study in 135 psoriasis patients who received PUVA and acitretin/etretinate for more than 6 months seemed convincing: the numbers of SCC diagnosed during the time of using versus not using acitretin/etretinate were 196 and 302, respectively [89]. The adjusted incidence rate ratio of SCC was calculated to be 0.79, which implicates the potential of oral retinoid agents to decrease non-melanoma skin cancer risk in phototherapy patients [89]. Whether or not these agents have any effect on melanoma risk is a question that has not yet been addressed in the literature.

The carcinogenicity of combined phototherapy plus biological agents is an on-going concern. In 2011, Gamblicher et al. compared psoriatic plaques that were treated with either BB-UVB at two MED or combined BB-UVB at two MED plus a one-time administration of etanercept 50 mg in 11 study subjects. Punch biopsies of the treated areas were taken at 1, 24, and 72 h after BB-UVB treatment [90]. Immunohistochemical analysis revealed increased expression of survivin (a tumor marker) and decreased activity of cyclin D and p53 (regulators of tumor development) in BB-UVB-plus-etanercept-treated sites compared with BB-UVB-treated sites [90]. Large randomized, controlled trials are needed to determine if an increased risk of melanoma or NMSC exists in psoriasis patients treated with combined photo(chemo)therapy and biologics.

### Conclusion

All-day, everyday Goeckerman therapy is one of the most effective regimens for moderate-to-severe psoriasis, and it still maintains an appealing safety profile. [91, 92] PUVA has been shown to result in high clearance rates, but the association of PUVA with an increased risk of NMSC in fair-skin Caucasian patients has rendered it less popular nowadays than narrowband UVB [92]. Until this date whether or not PUVA causes an increase in melanoma risk is a controversial topic that centers more or less on interpretation of existing follow-up data. Fortunately, adding oral retinoid agents to PUVA therapy can confer some chemo-protective effect limited to periods of retinoid use [92].

In terms of efficacy, both forms of UVB therapy are not as effective as Goeckerman or PUVA but fare better than heliotherapy [91–93]. The combination of UVB and oral retinoid or biological agents can lead to more successful therapy for patients than any of these modalities alone. Short-term side effects of UVB phototherapy are well-tolerated, and no studies so far have convincingly demonstrated any relationships between long-term UVB treatment and an increased risk of skin cancer. If office UVB is not feasible, climatotherapy, commercial and home UV therapies should still be considered as useful alternatives in the care of patients with stable psoriasis.

Finally, excimer laser therapy, to which another chapter of this book is dedicated, has been conducted worldwide for more than 10 years to target recalcitrant plaque psoriasis (Fig. 8.13). Current data on its efficacy revealed that fewer exposures to light are needed to induce remission [94–97]. No signal regarding an increased risk of skin cancer from therapeutic use of excimer laser has been reported. Furthermore, excimer laser spares non-involved skin, so there is a possibility, in terms of cutaneous malignancy safety, that this targeted phototherapy may even be better than traditional total-body irradiation exposure with UVB or PUVA.

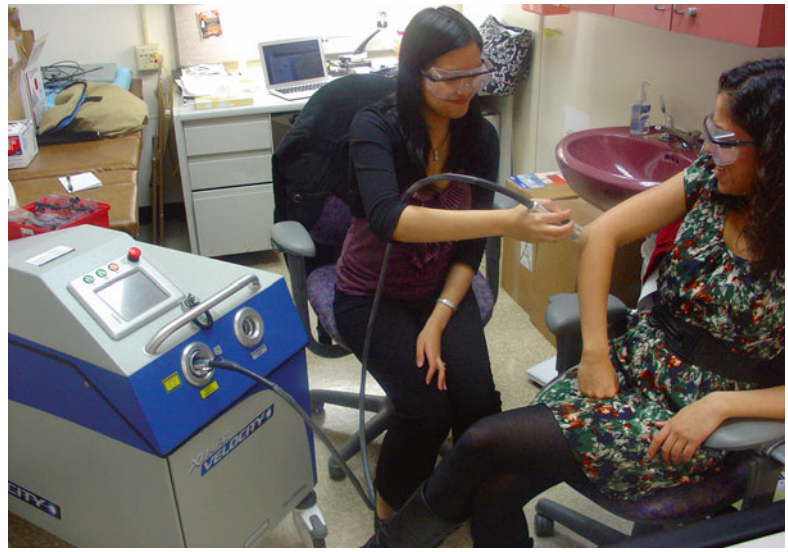

**Fig. 8.13** Excimer laser therapy requires the most powerful excimer laser machine to adequately treat moderate-to-severe psoriasis

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# Laser Therapy for Psoriasis

9

Amylynne J. Frankel and Ellen Henrie Frankel

**Abstract**

Psoriasis is a chronic disease that can affect the skin, joints and nails and seriously affect quality of life. There are many treatments available to treat, but not cure this common disorder, including topical therapies as well as systemic treatments. When limited psoriatic plaques fail to respond to traditional therapies, one option is laser therapy. Laser therapy provides the ability for targeting lesional skin and sparing non-lesional skin. In unresponsive areas such as the scalp, shins, gluteal crease and palms and soles, laser therapy is an ideal option. Laser therapy can be applied in combination with other treatment modalities to yield more complete clearance of plaques. Examples of laser therapy include Excimer laser, Pulsed dye laser, and $CO_2$ laser.

**Keywords**

Psoriasis • Laser treatment • Excimer laser • Pulsed dye laser • Recalcitrant plaques

Psoriasis is a chronic inflammatory disorder that affects approximately 2 % of the population. Psoriasis affects skin, joints, nails and quality of life. The most common form of cutaneous disease is plaque psoriasis. Traditional first line therapies for psoriasis include topical corticosteroids, vitamin D analogues, phototherapy, and systemic agents such as methotrexate or biologic agents. Despite newer and more targeted therapies, some plaques remain recalcitrant to treatment.

When limited plaques fail to respond to traditional therapies, one option is laser therapy. Laser therapy provides the ability for targeting lesional skin and sparing non-lesional skin. In unresponsive areas such as the scalp, shins, gluteal crease and palms and soles, laser therapy is an ideal option. Laser therapy can be applied in

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combination with other treatment modalities to yield more complete clearance of plaques (Table 9.1).

There are many lasers available for dermatologic use, many of which have been studied in the treatment of psoriasis. Choosing the appropriate laser light wavelength and pulse duration allows for selective destruction of various epidermal and subepidermal structures. Parrish and Jaenicke demonstrated that the best spectrum of wavelength for treating psoriasis is 300–313 nm, which targets epidermal proliferation and inflammation [1]. Other lasers that target superficially located microvasculature, such as the pulsed dye laser (585-nm), may also prove beneficial in treating psoriatic plaques, in which primary pathology includes dilated tortuous microvessels [2] (Table 9.2).

**Table 9.1** When to consider laser therapy for psoriasis

| |
|---|
| 1. Localized disease only |
| 2. Disease recalcitrant to conventional therapies |
| 3. Concomitant therapy in problematic areas (e.g. scalp, palms/soles, gluteal crease) |
| 4. Contraindications to current therapies including NBUVB |

## Excimer Laser

The most commonly used laser approved by the FDA for the treatment of psoriasis is the 308-nm excimer laser (Xtrac; PhotoMedex, Radner, PA). It generates single-wavelength UVB radiation with a spot size of 2×2 cm and a pulse-repetition rate ≤200 Hz. The pulse width is 30 ns. The average

**Table 9.2** Laser manufacturer contact information

| **Excimer lasers** | **Manufacturer** | **Contact info** |
|---|---|---|
| Pulsemaster 800 series | Light Machinery Inc | lasers@lightmachinery.com (613) 749-4895 |
| Ipex-800 series | Light Machinery Inc | LightMachinery Inc. 80 Colonnade Road Ottawa, Ontario, Canada, K2E 7L2 |
| Pharos EX-308 | RA Medical Systems | Ra Medical Systems, Inc<br>2270-L Camino Vida Roble<br>Carlsban, CA 92011<br>1-877-635-1800<br>info@ramed.com |
| Xtrac | Photomedex | 147 Keystone Drive<br>Montgomeryville, PA 18936<br>215-619-3600<br>info@photomedex.com |
| **Nd:YAG** | **Manufacturer** | **Contact info** |
| GentleYAG | Candela | 3 Goodyear Unit A<br>Irvine, CA 92618<br>949-716-6670 |
| **$CO_2$ lasers** | **Manufacturer** | **Contact info** |
| Impact series | Light Machinery Inc | See above |
| LaserMark Series | Light Machinery Inc | See above |
| $CO_2$RE | Candela | Syneron Inc.<br>3 Goodyear Unit A<br>Irvine, CA 92618<br>949-716-6670 |
| **PDL lasers** | **Manufacturer** | **Contact info** |
| Vbeam | Candela | Syneron Inc.<br>3 Goodyear Unit A<br>Irvine, CA 92618<br>949-716-6670 |

**Table 9.3** Factors influencing response to excimer laser therapy

| |
|---|
| 1. Localization/location of plaques (scalp vs. intertriginous) |
| 2. Laser settings (fluence rather than number of treatments) |
| 3. Individual plaque characteristics (thickness, scale) |

laser power delivered by the hand pieces is 2–3 W. Exposure time is varied by changing a setting on the laser termed minimal erythema dose (MED) [3]. Excimer laser prevents replication of epidermal cells and induces localized suppression of immune function by depleting T cells [4].

The 308-nm excimer laser has been shown to be very effective in clearing psoriatic plaques after a small number of treatments in a relatively short period of time [5]. In one early multicenter study, PASI 75 in was achieved in 72 % of subjects after an average of 6.2 treatments. PASI 90 was achieved by 35 % in an average of 7.5 treatments [6]. Another study showed PASI 100 after an average of 8.6 treatments [7]. In these studies, higher fluencies were used, whereas current guidelines recommend using medium doses (about three times MED, thereby decreasing the risk of potential side effects). Studies using this medium fluence continued to show good results in short periods of time [8]. In one recent study, PASI 70 was achieved in 60.2 % of subjects after an average of 17 sessions and an average cumulative dose of 6.46 J/cm$^2$ [3]. However, a review of seven prospective studies describing excimer efficacy for psoriasis found no consensus for a single protocol (high fluency versus medium fluency), so practitioners should continue to consider individual plaques when determining the best fluency for an individual patient [9].

There are many factors that may factor in to the response of a given plaque to excimer therapy (Table 9.3). Location of a given plaque may determine clinical response [4]. For example, scalp psoriasis may require more treatments to achieve clearance compared to inverse psoriasis [10, 11]. Additionally, individual plaque characteristics could contribute to clinical response, with thicker, scalier plaques responding more slowly than thinner plaques without scale [5, 8].

As this is targeted UVB therapy, it is not surprising that clinical results are similar to NB-UVB therapy. Potential adverse effects include pain, erythema, blistering, and discoloration, not unlike NB-UVB therapy. However, given excimer therapy affords targeted treatment to lesional sites only and reduction of cumulative exposure, this modality of treatment may be safer than conventional UVB therapy in regard to skin aging and carcinogenesis [3].

## Pulsed Dye Laser (PDL)

PDL is a 585-nm laser that targets the underlying vasculature in psoriatic plaques. PDL treatment is based on the selective absorption of short pulses of 585 nm light by oxy-hemoglobin inducing photothermolysis of the dermal vasculature, leaving other nearby structures in the skin undamaged. Clinical improvement of psoriasis after PDL treatment is accompanied by alterations in certain classical markers of psoriasis disease activity, including expression of VEGFR2, VEGFR3, E-selectin and down regulation of TNF-$\propto$ and IL-23 [12], as well as a decrease in the number of dermal papillary microvessels and normalization of vasculature of psoriatic lesions [13].

Several studies have shown partial or complete clearance of psoriatic plaques, including recalcitrant plaques, by PDL [12, 14]. PDL also proved effective in the treatment of nail psoriasis, improving the matrix and nail bed [15]. Many studies have shown that approximately 50 % of subjects respond to PDL therapy, but prognostic factors are not yet elucidated to identify ahead of time who will respond [16, 17].

Drawbacks to PDL treatment of psoriasis include small laser spot size, pain induced by treatment, transient purpura and hyperpigmentation. However, this therapy appears to be very safe, as long-term side effects of PDL have yet to be reported. Larger, randomized controlled studies are needed with longer, more standardized treatment and follow-up periods to more accurately assess the role of PDT in treatment of psoriasis.

## $CO_2$ and Nd:YAG Laser

The neodymium-doped yttrium aluminum garnet laser (Nd:YAG) emits infrared light with a wavelength of 1,064 nm and can penetrate the skin up to a depth of 7 mm. Under the assumption that target endothelial structures in psoriasis are located up to a few millimeters deep in the psoriatic skin, and knowing that psoriatic blood vessels are key in the pathogenesis of the disease, it was thought that this therapy might be beneficial in the treatment of psoriasis.

A pilot study evaluation the clinical efficacy and tolerability of the Nd:YAG versus an established topical therapy in an intra-patient, left-to-right comparison was conducted which showed no benefit with regards to the Nd:YAG in the treatment of psoriasis. These results differed from several anecdotal reports in which psoriatic plaques responded to low-energy Nd:YAG treatment (1,320 nm) [2, 18]. In another study with 12 subjects with plaque psoriasis, ablation of the entire epidermis and papillary dermis with $CO_2$ laser was generally ineffective in treating recalcitrant psoriatic plaques [19].

However, given the paucity of data using this modality, it is not an appropriate therapy option at this time.

## Comparative Studies

In a study comparing excimer laser versus NB-UVB, the number of treatments was 3.6 times fewer, and the duration of exposure was 2.27 times shorter with excimer laser than with the 311-nm narrowband UVB therapy. Additionally, the cumulative dose needed for clearing was 6.47 times less with excimer therapy. Given the current school of thought that side effects increase with increasing exposure to UVB, excimer laser treatment might not only be more efficacious for limited disease, but also safer than NB-UVB.

In a study comparing excimer versus PDL in the treatment of 22 psoriatic patients, 13/22 responded best to excimer versus 2/22 who responded best to PDL and 7 who responded equally to the two methods. In this study, the excimer laser was superior to PDL therapy [16].

In a study comparing PDL and class II topical steroids, PDL showed significantly higher efficacy [20].

In a single-blind prospective paired randomized controlled study, PDL was shown to be non-inferior to NV-UVB therapy. Furthermore, combining the two therapies does not confer additional benefit [17].

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# Traditional Systemic Therapy I: Methotrexate and Cyclosporine

10

Robert M. Bacigalupi and Erin Boh

**Abstract**

This chapter will review the traditional systemic drugs, methotrexate and cyclosporine, both of which are used in treating patients with moderate to severe psoriasis or recalcitrant psoriasis. Systemic therapies are also used in patients with psoriatic arthritis and disease not amenable to topical or light therapy. Methotrexate, a folic acid analogue, has become "the gold standard" of systemic therapies for moderate to severe psoriasis. It is often the initial systemic therapy started and has become the most widely used. Cyclosporine, a T-cell inhibitor that downregulates IL-2, is highly effective and highly efficient. It is often used in short durations when rapid control is desired. The pharmacology and use of these drugs in the treatment of patients with psoriasis will be covered as well as the parameters to screen patients, monitoring guidelines and adverse effects associated with each.

**Keywords**

Psoriasis • Methotrexate • Cyclosporine • Traditional systemic therapies • Systemic therapy

## Introduction

Psoriasis is a chronic inflammatory disease affecting nearly seven million individuals. It can be debilitating and associated with systemic co-morbidities such as arthritis, hypertension, hyperlipidemia and insulin resistance [1–3]. Recently, it has been suggested that psoriasis may be associated with or part of the metabolic syndrome [4–6]. In addition to topical therapy and phototherapy, systemic agents, including a newly developed class referred to as biologics, have been used for its treatment. Systemic therapies are often reserved for patients with moderate to severe psoriasis. The goals of treatment are to quickly clear or reduce psoriatic lesions, to make the patient comfortable by alleviating symptoms and to provide long-term maintenance with minimal toxicity for the patient.

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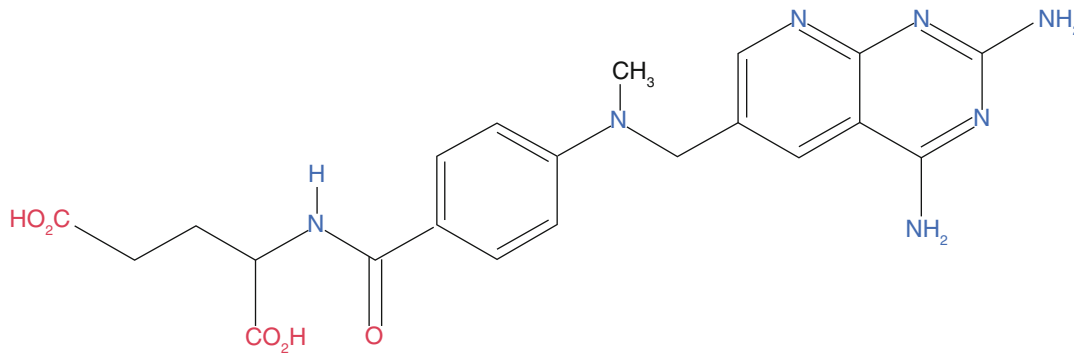


**Fig. 10.1** Structure of methotrexate

In the past, systemic therapy has been used for those individuals with moderate to severe psoriasis as defined by greater than 10 % body surface area or debilitating disease. With the appearance of biologic agents, the treatment algorithm has expanded tremendously. While these agents have a very good safety and efficacy profile, they have been slow to replace traditional agents for the treatment of psoriasis. Contraindications due to comorbid conditions as well as cost are the most limiting factors for the use of these biologic agents.

This chapter will review the traditional systemic drugs, methotrexate and cyclosporine, both of which are used in treating patients with moderate to severe or recalcitrant psoriasis.

## Methotrexate

### Introduction

Methotrexate is the most widely used systemic treatment for moderate to severe psoriasis. The National Psoriasis Foundation and American Academy of Dermatology recently published detailed dosing and monitoring guidelines [7, 8]. Methotrexate is a synthetic analogue of folic acid, which exhibits immunosuppressive as well as anti-inflammatory properties. It has been used successfully to treat psoriasis for over 50 years. While Gubner et al. in 1951 [9] first reported clearance of psoriasis in cancer patients being treated with aminopterin, a precursor to methotrexate, Edmunson and Guy first reported methotrexate's efficacy in treating psoriasis in 1958 [10]. The FDA approved methotrexate in 1972 for the indication of psoriasis [11]. Interestingly, it was not until the early 1980s that methotrexate was approved for rheumatoid arthritis. Since these early years, methotrexate has become the "gold standard" for treating moderate to severe psoriasis and psoriatic arthritis [11, 12]. Over the years, dosing has been modified to minimize the toxicity associated with methotrexate [7, 8].

### Mechanism of Action

Methotrexate has anti-proliferative, anti-inflammatory and immunosuppressive actions. As a synthetic analogue of folic acid, methotrexate competitively inhibits dihydrofolate reductase, an enzyme responsible for conversion of folic acid to reduced folate (tetrahydrofolate) (Fig. 10.1). Tetrahydrofolate is required for the transfer of 1-carbon units in the thymidylate and purine synthesis pathway [13]. This inhibition blocks synthesis of deoxythymidylic acid, which is required for DNA synthesis. As a consequence, methotrexate causes the arrest of cell division in the S phase.

Studies have shown that the anti-proliferative effects of high-dose methotrexate can be reversed by high doses of folic acid, thus supporting the mechanism of inhibition of DNA synthesis [13, 14]. Low-dose methotrexate may exhibit other mechanisms of action, including anti-inflammatory and immunomodulatory effects.

This observation is supported by the widespread practice by dermatologists and rheumatologists of administering low doses of folic acid (i.e. 1 mg/day) to patients on methotrexate to minimize adverse effects without compromising efficacy [15].

While high-dose methotrexate inhibits DNA synthesis, primarily through the inhibition of dihydrofolate reductase, lower doses as used in treatment of psoriasis have more anti-inflammatory effects. These anti-inflammatory effects seem to involve the formation of intracellular metabolites of methotrexate [13, 16]. Once absorbed, methotrexate is metabolized intracellularly to polyglutamate derivatives, potent inhibitors of a number of folate-dependent enzymes leading to the accumulation of intracellular imidazole products. These inhibit adenosine deaminase, ultimately resulting in accumulation of adenosine [16]. Adenosine suppresses the secretion of inflammatory cytokines by macrophages and neutrophils, as well as diminishes the expression of adhesion molecules. Additionally, adenosine, through binding to the A2 receptor, exhibits potent anti-inflammatory effects by inhibiting neutrophil leukotriene synthesis [13]. Activated T cells play a pivotal role in psoriasis, and it appears that methotrexate not only inhibits DNA replication of these T-cells but also diminishes antigen-stimulated T-cell proliferation. By inhibiting mitogen-activated T-cells, these cells become more susceptible to apoptosis [17]. Johnston et al. recently refuted this notion of increased susceptibility to apoptosis [18]. These authors propose that methotrexate exerts its effects through both folate-dependent (decreased synthesis of antigen stimulated T-cells) and folate-independent mechanisms (altered adhesion molecule expression through alterations in adenosine). Most likely, the benefits seen involve both processes, and methotrexate should be viewed as an immunosuppressing and immunomodulating agent. At this point in our understanding, methotrexate appears to have multiple mechanisms of action at play.

## Absorption and Bioavailability

Methotrexate may be given orally, intramuscularly, subcutaneously or intravenously. Food intake does not influence absorption in adults but may in children [14]. Once absorbed, methotrexate is actively transported into cells where it is metabolized into polyglutamate imidazole products, which appear to be the more active drug. These products accumulate, resulting in increased adenosine contributing both to toxicity and efficacy [16]. Current data suggests that methotrexate is metabolized intracellularly, including in the liver, to form polyglutamate metabolites that exert effects on various tissues.

Peak levels are attained fairly rapidly, approximately 1 h after oral administration, slower relative to other modes of administration. Absorption after ingestion may be affected by dosing: higher doses having incomplete or variable absorption. Steady-state levels of methotrexate may be more reliable in smaller doses over the course of 12–24 h 1 day/week. Plasma levels have a triphasic response. Once the drug is absorbed, plasma levels decrease rapidly within the first hour, reflecting distribution throughout body tissues. The second phase of reduction reflects renal excretion over the next 2–4 h. Importantly, renal function such as glomerular filtration and tubular secretion can significantly affect blood levels. The final phase occurs through slow release from the tissues over 10–27 h after ingestion reflecting its half-life (T½).

Approximately 50 % of methotrexate is transported bound to plasma proteins. The free or unbound portion is the active form of the drug. Plasma levels can be affected by the binding of other drugs to these plasma proteins either displacing or blocking methotrexate, resulting in elevated blood levels. Drug interactions will be discussed below.

## Use in Psoriasis

Methotrexate is FDA-approved for the treatment of moderate and moderate-to-severe psoriasis in adults and psoriatic arthritis [11]. The first treatment guidelines on the use of MTX in psoriasis were published by Roenigk et al. in 1973 [19]; and, since that time, many newer treatment guidelines for the use of methotrexate and other systemic agents in psoriasis have been published [7, 8, 14, 20]. The most recent guidelines for the

**Table 10.1** Contraindications to methotrexate therapy

| Absolute contraindications | Relative contraindications |
|---|---|
| Excessive alcohol consumption, resulting in liver damage | Renal insufficiency |
| Alcoholic liver disease or other chronic liver diseases, including hepatitis B or C | Advanced age |
| Bone marrow abnormalities: anemia, thrombocytopenia, leucopenia | Alcohol consumption<br>History of or current alcohol consumption) |
| Immunodeficiency | Peptic ulcer disease |
| Nursing mothers | Concomitant use of hepatotoxic drugs |
| Pregnancy | Family history of inheritable liver disease |
| Methotrexate hypersensitivity | Diabetes mellitus |
| Active infection | Hyperlipidemia<br>Morbid obesity<br>Active infection |

treatment of psoriasis with methotrexate were published by the National Psoriasis Foundation and by the American Academy of Dermatology in 2009 [7, 8]. These guidelines, as well as a systematic review of the literature, has led to evidence-based recommendations on the use of methotrexate in psoriasis including specific guidance on dosing, route of administration, risk and monitoring of liver toxicity [8, 21].

There are several important parameters to consider when choosing methotrexate as a form of therapy. These include the severity of the disease, the patient's co-morbidities such as associated arthritis, socioeconomic factors, and the ability of the patient to participate in treatment. As a general rule, methotrexate is suggested for patients with at least 10 % body surface area (BSA) affected, who have failed or can no longer perform topical therapy, or who have failed or have contraindications to phototherapy. Absolute and relative contraindications to methotrexate therapy, listed in Table 10.1, should be reviewed carefully and discussed with the patient prior to initiation of the drug. Considerations for patient selection should be based on patient history, laboratory findings and co-morbidities. Absolute contraindications mandate an alternative form of therapy. Methotrexate is a teratogen, and women of childbearing potential should use birth control. It is contraindicated in pregnancy as well as during breastfeeding. Men should also be counseled on not impregnating a woman until 3 months off therapy. Relative contraindications include Type 2 diabetes, insulin resistance, alcohol consumption, obesity and hypertriglyceridemia. As a general rule, these patients should be evaluated for other treatments. Patients with relative contraindications can use methotrexate with appropriate precautions. For instance, patients with renal disease may be treated with a lower dose; patients with peptic ulcer disease may be treated with concomitant proton pump inhibitor therapy. The decision to treat should be based on the patient's individual situation.

## Dosing

Methotrexate is generally given as a single weekly oral dose administered over a 12–24 h period. It is available as a 2.5 mg tablet and an injectable 25 mg/ml solution. Dosing is equivalent whether the oral or injectable form is used. A test dose of 5 mg of methotrexate is initially given with blood tests (complete blood count with platelets and renal and liver function tests) drawn 6 days later. If blood work is within normal limits, treatment doses are started at 10–15 mg once weekly. Methotrexate can be increased by 2.5–5 mg every 2–4 weeks until a response is seen, up to approximately 25 mg weekly, the maximum recommended dose. A 1 mg/day folic acid supplement is recommended based on expert evaluation [15]. Some practitioners recommend not taking folic acid on the day patients dose with methotrexate, but the significance of this has not been studied. There are published reports suggesting that folic acid protects against gastric upset, nausea, oral ulcerations and may even impact bone marrow toxicity, especially in rheumatoid arthritis patients [15]. For those patients who cannot tolerate the oral formulation because of nausea or other reasons, methotrexate can be administered by a subcuta-

**Table 10.2** Monitoring methotrexate guidelines

| |
|---|
| Baseline |
| History and physical |
| Careful review of drug history and evaluation of low risk versus high-risk patients |
| Laboratory |
| Complete blood count with differential and platelet counts (CBC) |
| Comprehensive metabolic panel- renal and hepatic (CMP) |
| Hepatitis B and C screening |
| Tuberculosis screening with PPD or blood test |
| Serum or urine pregnancy screening |
| On-going monitoring |
| Periodic review of drug history |
| Physical exam |
| Laboratory |
| CBC with differential and platelets q month for 3 months then every 3 months |
| CMP q month for 3 months, then every 3 months |
| Tuberculosis screening every year |

neous or intramuscular route. Subcutaneous injection is equally effective and can be self-administered at home. All dosing schedules should be adjusted to the individual patient to obtain or maintain adequate disease control with minimal side effects. In order to ensure some degree of safety, monitoring should be done on a continuous basis.

## Monitoring Guidelines

Prior to initiation of methotrexate treatment, the patient should have pretreatment blood tests, tuberculosis screening, a complete medical history with emphasis on medications and co-morbidities, and a complete physical examination performed. Patients should be counseled on methotrexate and its potential side effects. Documentation should include the type of psoriasis, past treatments, patient's quality of life measures, the body surface affected, risk factors for hepatotoxicity and other potential toxicities. Patients taking methotrexate should be monitored regularly for potential organ toxicity. Baseline and ongoing monitoring guidelines are listed in Table 10.2.

Monitoring of the blood parameters should be done approximately 2–4 weeks after adjusting the dose. It is important to remain at the minimal effective dose and to record the total cumulative dose of methotrexate while maintaining disease control and medication tolerance. It is also important to consider a liver biopsy in those patients on long-term therapy.

While practitioners have their individual styles of practice, it is advisable to perform a periodic history and physical exam on patients on methotrexate therapy to ensure the highest quality of care and to minimize potential adverse events. If laboratory abnormalities occur, blood tests may be repeated and more frequent monitoring may be necessary. Liver function tests should be drawn at a 5-day interval from the last dose since values may be elevated 1–2 days after ingestion of methotrexate. If a significant persistent abnormality in liver chemistry develops, methotrexate therapy should be withheld for 1–2 weeks and repeat blood work should be performed. Discuss with the patient if any new medications were prescribed or other situations have developed.

### Liver Biopsy

Guidelines for biopsying the liver in psoriasis patients were published in 1998 and updated in the American Academy of Dermatology (AAD) guidelines for treatment of psoriasis in 2009 [8, 15]. Initially, guidelines suggested liver biopsy at the start of therapy and after every 1.5 g cumulative dose thereafter [19]. The AAD and National Psoriasis Foundation guidelines for monitoring have been updated to differentiate patients at low risk for hepatotoxicity from those at high risk [7, 8]. Table 10.3 outlines those patients at high risk for hepatotoxicity. For low-risk patients, methotrexate can be initiated without performing a baseline liver biopsy. A liver biopsy should be performed after approximately a 3.5–4.0 g cumulative dose. High-risk patients should obtain a liver biopsy after approximately a 300–600 mg cumulative dose to ensure a response to therapy before subjecting the patient to the risks of a biopsy. Table 10.4 summarizes the grading system proposed by Roenigk et al. for interpretation of

**Table 10.3** High risk factors for hepatic toxicity from methotrexate

| |
|---|
| History of or current alcohol consumption |
| Persistent abnormal liver chemistry studies |
| History of liver disease, including chronic hepatitis B or C |
| Family history of inheritable liver disease |
| Diabetes mellitus |
| Obesity |
| History of significant exposure to hepatotoxic drugs or chemicals |
| Potential significant drug interactions |
| Lack of folate supplementation |
| Hyperlipidemia |

**Table 10.4** Evaluation of liver biopsy findings [22]

| Grade | Findings | Disposition |
|---|---|---|
| I | Fatty infiltration; mild; nuclear variability; mild; portal inflammation | Normal<br>Continue methotrexate |
| II | Moderate to severe fatty infiltration; moderate to severe nuclear variability; portal tract expansion; portal tract inflammation and necrosis | Continue methotrexate |
| IIIA | Mild fibrosis; slight enlargement of portal tracts without disruption | Fibrosis<br>Discontinue methotrexate<br>Repeat biopsy sooner |
| IIIB | Moderate to severe fibrosis; cirrhosis | Fibrosis<br>Discontinue methotrexate |
| IV | Cirrhosis | Cirrhosis<br>Discontinue methotrexate |

liver biopsy histologic results [15]. As a general rule, patients with grade I and II can continue methotrexate. Those with grade IIIA may cautiously continue therapy with more stringent monitoring if better alternatives are not available. Only those patients without other options should continue methotrexate. Patients with grade IIIB and IV should discontinue the drug regardless. It is important to closely work with a hepatologist who is also up to date with the current published guidelines.

## Adverse Effects

There are a number of common and uncommon adverse effects reported with methotrexate usage. Common minor complaints by patients include fatigue, nausea, vomiting, headache and stomatitis. Many of these adverse effects are eliminated by administration of folic acid. If gastrointestinal symptoms persist, methotrexate can be administered by injection, subcutaneously or intramuscularly. Dosing may also be administered in divided doses over a 24-h period. The three primary areas of potential major toxicity include hepatotoxicity, myelosuppression and pulmonary fibrosis.

### Hepatotoxicity

There are both acute and chronic hepatotoxic adverse effects. Acute hepatocellular damage, as manifested by elevated liver enzymes, may result from high blood levels of methotrexate. High blood levels occur when the dose exceeds 25 mg/week or when levels are increased by a significant drug interaction or displacement of bound methotrexate by another medication. Acute hepatocellular damage almost always results in abnormal liver enzyme studies. However, chronic damage to the liver may occur even when liver blood studies remain normal. Chronic hepatotoxicity results from the cumulative effects of methotrexate on the portal system resulting in fibrosis. The histologic damage and subsequent fibrosis can only be assessed by liver biopsy. As discussed above, biopsy of the liver can be delayed in those patients who are at low risk of hepatotoxicity but should be done at an earlier interval if the patient is at high risk. The histopathologic features of methotrexate-induced liver toxicity resemble nonalcoholic steatohepatitis (NASH), a similar pattern observed in patients who are obese, hyperlipidemic or diabetic. Methotrexate likely aggravates preexisting steatohepatitis. Serum assays for assessing liver fibrosis, such as the measurement of the amino-terminal peptide of procollagen III, have been used in Europe as an alternative to liver biopsy but are not currently available in the United States [22]. Currently, there are no blood assays or diagnostic tests adequate to monitor for chronic liver toxicity other than biopsy.

### Myelosuppression

Myelosuppression is potentially a very significant toxicity associated with methotrexate administration. Methotrexate can cause leukopenia, thrombocytopenia and anemia. It is usually dose-dependent and due to direct toxic action on the bone marrow. Rarely, there is an idiosyncratic myelosuppression, which occurs early in treatment. Idiosyncratic reactions may be more likely in patients with advanced age, renal insufficiency, underlying bone marrow disease, hypoalbuminemia, concomitant medications or folate deficiency. For this reason, physicians administer the test dose of methotrexate. It is imperative to screen patients appropriately before starting methotrexate therapy as well as monitor while on therapy to minimize these risks. If anemia, thrombocytopenia or leucopenia occurs acutely, it can be reversed with folic acid administration or in severe cases, folinic acid (leucovorin) rescue. High dose folic or folinic acid can be given by mouth or intravenously at doses of 15 mg every 6 h for 1–2 days or until the methotrexate levels approach zero. Administration of daily folic acid while on methotrexate may minimize gastrointestinal and liver toxicity, but its impact on the bone marrow toxicity remains controversial [15, 23].

### Pulmonary Fibrosis

Pulmonary fibrosis and interstitial pneumonitis may uncommonly occur in patients with psoriasis being treated with methotrexate, but is more common in patients being treated for rheumatoid arthritis. Pulmonary fibrosis is more commonly associated with high dose methotrexate therapy. Patients should be monitored for signs and symptoms such as dry cough, dyspnea at rest and low-grade fever. Other very uncommon pulmonary complications include bronchiolitis obliterans organizing pneumonia (BOOP), pleuritis and pleural effusions.

### Drug Interactions

Methotrexate has many reported and presumptive drug interactions that may result in decreased or increased levels of methotrexate and potentiate end-organ toxicity. Therefore, it is very important to take a complete medication history as part of pre-methotrexate screening. It is also important to counsel patients regarding possible drug interactions, especially with regards to over-the-counter and commonly prescribed drugs. Table 10.5 has some of the common potential drug interactions. There are numerous medications that increase or decrease blood methotrexate levels either by displacing it from protein binding sties, blocking its binding, and altering the metabolism of it through the cytochrome P-450 system. Other medications may also have an additive effect on end-organ damage.

**Table 10.5** Common drug interactions with methotrexate

| Antibiotics | Anticonvulsants/ antipsychotics | Miscellaneous |
|---|---|---|
| Trimethoprim | Phenytoin | Salicylates |
| Sulfonamides | Phenothiazines | NSAIDs |
| Chloramphenicol | | Systemic retinoids |
| Tetracyclines | | Probenecid |
| Dapsone | | Triamterene |

## Cyclosporine

### Introduction

Cyclosporine, a cyclic peptide of 11 amino acids, was isolated from the soil fungus Tolypocladium inflatum Gams in 1970 (Fig. 10.2). Cyclosporine's immunosuppressive properties have been well known and used in solid organ transplantation since 1983 [24]. In 1979, Mueller and Hermann reported serendipitous clearing of psoriasis lesions during a clinical trial evaluating cyclosporine A for rheumatoid and psoriatic arthritis [25]. This important observation led to its subsequent use in psoriasis. The original formulation (Sandimmune) had considerable variations in absorption and bioavailability. Newer microemulsion formulations (Neoral) have better and more predictable bioavailability and are more cost effective. Neoral was FDA approved in 1997

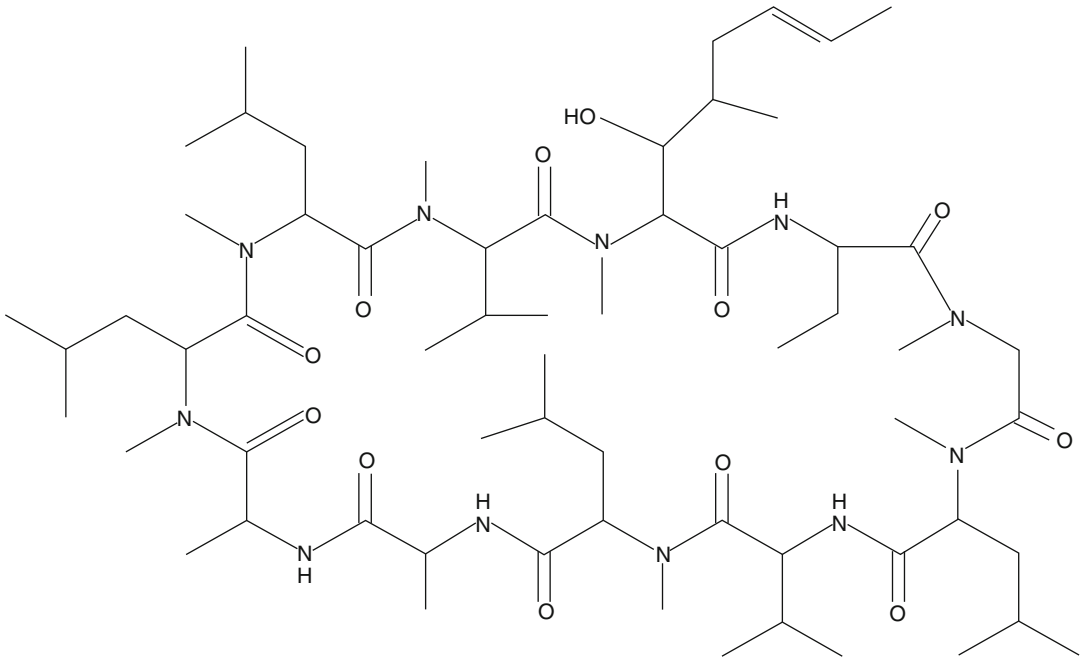


**Fig. 10.2** Structure of cyclosporine

for psoriasis and rheumatoid arthritis. Despite published guidelines for use in psoriasis, there still remains controversy and disagreement over treatment strategy and monitoring [8, 26, 27]. In contrast to other traditional agents such as methotrexate and hydroxyurea, cyclosporine is not remarkably cytotoxic, does not suppress the bone marrow and is not teratogenic [26, 28]. Despite its rapid effect and efficacy, many dermatologists are reluctant to use cyclosporine, owing to its potential side effects and perceived lack of safety.

## Mechanism of Action

Cyclosporine primarily acts by inhibiting T-cell function and interleukin (IL-2) [26, 28]. After an antigen-presenting cell binds to a T cell, intracytoplasmic levels of calcium increase leading to calmodulin activation of calcineurin phosphatase. Calcineurin phosphatase dephosphorylates cytoplasmic nuclear factor of activated T cells allowing translocation into the nucleus and enabling transcription of proinflammatory genes, including IL-2, IL-4, interferon gamma and transforming growth factor beta.

Calcineurin inhibition by a cyclosporine-cyclophilin complex prevents activation of calcineurin phosphatase, thus preventing downstream transcription of proinflammatory genes, most notably IL-2, and the up-regulation of the IL-2 receptor [26, 27]. As a consequence, T-cell activation and production of inflammatory cytokines is impaired. It is now widely accepted that psoriasis is mediated by these activated T cells and their cytokine products. Cyclosporine appears to also dampen expression of intercellular adhesion molecule (ICAM)-1 on keratinocytes and endothelial cells. This down-regulation of ICAM-1 prevents recruitment of inflammatory cells. Cyclosporine also decreases tumor necrosis factor, a key cytokine in psoriasis pathogenesis, and suppresses the Th17 genes, IL-17, IL-22 and the IL-23p19 subunit, all of which are overexpressed in psoriatic skin [29].

## Absorption and Bioavailability

Cyclosporine is lipophilic and exhibits very poor solubility in water. As a consequence, suspension and microemulsion forms of the drug have been

developed for oral administration and for injection. The first formulation, Sandimmune, was produced in 1983. It had variable and unpredictable bioavailability among patients secondary to its high dependence on bile solubility. This was improved by the introduction of a microemulsion formulation, Neoral, in July 1995. Several other cyclosporine formulations have subsequently been brought to market. The bioavailability of generic cyclosporine is approximately 30 % that may be slightly increased with some branded versions. Cyclosporine capsules and liquid oral formulations are considered bioequivalent. There are few published reports comparing bioavailability and efficacy among different generic formulations although the perception that differences in these agents exists is prevalent [30]. Since cyclosporine has a narrow therapeutic window, careful monitoring and consistency in generic formulations is required.

Cyclosporine is absorbed in the small intestine with peak concentrations occurring from 1 to 8 h. The absorption is dependent on bile salts, increased with fatty foods. Metabolism is affected with concurrent grapefruit juice ingestion [31]. Cyclosporine distributes through multiple organ systems, including the skin, and can be found in breast milk. It crosses the placenta but not the blood brain barrier.

Cyclosporine is metabolized by the hepatic cytochrome P-450 3A4 (CYP3A4) enzyme system, and almost completely excreted in bile through the feces. The dose may need to be reduced in patients with hepatic insufficiency but not in renal insufficiency or with hemodialysis. The elimination half-life of cyclosporine is about 19 h, and its metabolism is age-dependent with a twofold increase in half-life in adults compared to children.

## Use in Psoriasis

Cyclosporine is FDA approved for severe psoriasis, resistant/recalcitrant psoriasis and disabling psoriasis. Numerous studies have been published on cyclosporine evaluating its efficacy, its comparison to methotrexate and etretinate, and its long-term maintenance/remission data. In a randomized study comparing methotrexate and cyclosporine after 16 weeks, cyclosporine and methotrexate appeared to be equally effective, with PASI 75 improvement being 71 and 60 %, respectively [32]. In a study comparing the oral retinoid etretinate with cyclosporine, PASI 75 improvement was seen in only 47 % of patients on etretinate compared to 71 % on cyclosporine [33]. Cyclosporine rapidly controls psoriasis, but rapid withdrawal may result in rebound. Open label studies evaluating discontinuation of cyclosporine after 1 year of therapy with a gradual (1 mg/kg/week) taper or abrupt cessation were published in 1999 and 2001 [34, 35]. No significant rebound was noted in either group, and the median time to relapse was not significantly different. Since more than 50 % of patients will relapse after 4 months, new treatments should be added at the time of taper or once psoriasis returns.

According to recently published recommendations by the National Psoriasis Foundation, cyclosporine should be used with caution and for the most severe cases [26, 27]. For reasons not totally understood, dermatologists do not use cyclosporine often for recalcitrant psoriasis and view it only as a rescue drug treatment. The drug is very safe to use if proper patient selection is done, with knowledge of the patient's co-morbidities and medications and with proper clinical monitoring. Since the drug is very effective with rapid onset of action, offering dramatic clearance in as little as 2–4 weeks, it can be used to clear patients quickly allowing time to plan and transition to a long-term maintenance regimen. It has also been used successfully for erythrodermic and pustular psoriasis. While cyclosporine's beneficial effects on psoriasis were first observed during trials for rheumatoid arthritis, it is not as useful for arthritis as for psoriasis lesions.

While not approved for children or pregnant women, cyclosporine has been used with good results in these patient populations. It is considered category C and should be used with caution in pregnancy and during lactation [36]. Cyclosporine has been associated with low birth weight (<2,500 g) and prematurity (<37 weeks) when used in renal transplant patients. Limited information is known about

the effect of cyclosporine in pregnant women with psoriasis, who typically are prescribed lower doses. Cyclosporine does not appear to be a teratogen and has been used in pregnant women with successful outcomes. Overall, it is the author's opinion that cyclosporine is safe to use in high risk psoriasis patients during pregnancy if the benefits far outweigh the risks in severely debilitating disease, but should not be used routinely. If cyclosporine is used in a pregnant patient, the mother and fetus should be carefully followed by high-risk obstetrician. Cyclosporine has been used in children uncommonly but appears to be safe and efficacious [26, 27, 37, 38]. Doses are similar to that used in the adult population, 2.5–3.0 mg/kg/day in divided doses. Treatment courses should be limited to 6-month intervals [38]. Risks of malignancy and lymphoproliferative disorders seem to be minimal in children treated for skin diseases due to limited courses of therapy and dosages that are below 5 mg/kg/day.

Cyclosporine is contraindicated in patients with uncontrolled or difficult to control hypertension and in those individuals with significant renal disease or frequent infections. Careful attention should be paid to individuals with a personal history of cutaneous malignancies as cyclosporine can increase the numbers of skin cancers over time. Particular caution should be given with patients who have had extensive PUVA therapy (greater than 200 treatments) as the risk of nonmelanoma skin cancers, particularly squamous cell carcinoma, may be slightly increased [39]. As with methotrexate, the decision to use cyclosporine should be made based on a patient's individual situation.

## Dosing

Generally, patients are treated with 2.5–3 mg/kg/day, usually in divided doses. The package insert suggests dosing at ideal body weight; but, in the author's experience, dosing is subtherapeutic at ideal weights in significantly obese patients. Dosing may need to be adjusted, especially in the first few weeks as bioavailability is variable and may vary with different generics. Patients should be consistent with dosing regimens, same time and amount of food ingested. Absorption may even be improved slightly with food, but levels may be decreased with grapefruit juice [31]. Unlike transplantation patients, peak and trough levels do not need to be routinely done to ensure adequate blood levels in psoriasis patients. Levels may be checked if there is a question of compliance or issues with absorption. Cyclosporine therapy is generally used on a short-term basis to control severe flares, rarely more than 6–12 months.

**Table 10.6** Monitoring guidelines for cyclosporine

| |
|---|
| Baseline |
| History and physical |
| Careful review of drug history |
| Blood pressure evaluation |
| Laboratory |
| Complete blood count with differential and platelet counts (CBC) |
| Comprehensive metabolic panel- renal and hepatic (CMP) |
| Hepatitis B and C screening |
| Tuberculosis screening with PPD or blood test |
| Serum or urine pregnancy screening |
| On going monitoring at q 2 weeks × 1 then q 4-weeks × 3 months then q 2 months |
| Periodic review of drug history |
| Physical exam |
| BP at every visit and home monitoring if warranted |
| Laboratory |
| CBC with differential and platelets at 2 weeks then q month for 3 months then every 2 months |
| CMP at 2 weeks then q month for 3 months then every 2 months |
| Tuberculosis screening every year |

## Monitoring Guidelines

Prior to initiating cyclosporine therapy, the patient should have pretreatment blood tests, urinalysis, tuberculosis screening, a complete medical history with emphasis on medications and co-morbidities, and a complete physical exam with special attention to elevations in blood pressure performed. Patients should be counseled on adverse effects and the need for careful monitoring. Baseline and ongoing monitoring guidelines are listed in Table 10.6.

Frequent monitoring, especially for iatrogenic hypertension and signs of renal insufficiency, is required. Usually office visits with repeated counseling and education parallel the blood evaluation schedule. If warranted, patients can also monitor blood pressure at home. The package insert recommends stopping cyclosporine if the blood pressure remains elevated after an attempt to lower the dose on several occasions. An alternative is to start the patient on an anti-hypertensive agent and monitor the pressure. Because of possible permanent damage to the kidney and loss of renal function in patients on long-term therapy, cyclosporine is a drug that requires careful patient selection and subsequent monitoring to be used safely. Therefore, a careful assessment of psoriasis disease severity is critical when assessing the risk-benefit ratio of treatment with cyclosporine. With the wide availability of other useful agents for psoriasis, it is reasonable to consider an alternative if the blood pressure or kidney function remains elevated after two readings. Patients on cyclosporine are also immunosuppressed and are more susceptible to infections, bacterial, viral and fungal. Patients should be examined and screened for these types of infection before as well as during treatment.

## Adverse Effects

While the frequency and severity of side effects is reduced when used at doses for psoriasis, the major toxicities associated with cyclosporine remain renal insufficiency and hypertension. The most common side effects associated with cyclosporine administration include headaches (15 %), hypertrichosis (6 %), and gingival hyperplasia, which is seen more frequently in transplant patients but can uncommonly occur in psoriasis patients. Other side effects include hirsutism, tremor, diarrhea, hypertriglyceridemia, hypomagnesemia, nausea/vomiting, paresthesias and influenza-like symptoms. Blood abnormalities include hypomagnesemia, hyperlipidemia and hyperuricemia. As a consequence of these abnormalities, magnesium and uric acid levels should be obtained regularly. Lipid monitoring is less frequently needed but should be considered in patients on longer treatment periods. Rare side effects include neurologic complaints, including lowering the seizure threshold, transient gastrointestinal complaints and respiratory complaints of cough and rhinitis.

### Nephrotoxicity

Nephrotoxicity is the most common and clinically significant adverse effect and can present as acute azotemia or as a chronic, slowly progressive renal failure. Although reversible changes in the kidney may be related to the vascular effect, long-term therapy may lead to permanent scarring with loss of renal function. Therefore, it is very important to routinely monitor the renal function with a serum creatinine and a urinalysis as well as the blood pressure in patients on cyclosporine. It is important to remember that elderly patients may have a decrease in the glomerular filtration rate (GFR) without a decrease in creatinine. Patients who are on cyclosporine for a year are suggested to get an annual GFR. This is not routinely done, since patients do not usually remain on cyclosporine for greater than a year at a time. Patients with elevations of serum creatinine greater than 25 % from baseline on two occasions (separated by 2 weeks) should have a 25–50 % decrease in their dosage. If the creatinine level remains elevated, the cyclosporine dose should once again be decreased by 25–50 %. If after these changes, the creatinine does not return close to baseline, cyclosporine should be discontinued.

### Hypertension

Hypertension is caused by renal vasoconstriction and sodium retention, and usually presents early in the course of treatment. Dose reduction or addition of an anti-hypertensive such as amlodipine can ameliorate this adverse effect. Caution the patient that they may experience dependent edema, a side effect common to both cyclosporine and amlodipine. Since amlodipine has been reported to be renal protective in the transplant population on cyclosporine, the addition of amlodipine at this juncture is reasonable. In fact, many clinicians familiar with using the drug will start

**Table 10.7** Potential cyclosporine (CyA) drug-drug interactions

| Drug class | Increases CyA | Decreases CyA | Drug levels increased by CyA |
|---|---|---|---|
| Antiarythmics | Amiodarone | | |
| CCB[a] | Diltiazem; verapamil | | Verapamil; diltiazem |
| Diuretics | Thiazodes; furosemide | | |
| Antifungals | Azoles | Griseofulvin | |
| Antibiotics | Quinolones; cephalosporins doxycycline | Beta-lactams; nafcillin; rifampin | |
| Anti-HIV | PI[b] | Efavirenz | |
| Anti-malarials | Hydroxychloroquine | | |
| SSRI[c] | Fluoxetine; sertraline | | |
| Foods | Grapefruit | | |
| Anti-neoplastic | Imatinib | | |
| Steroids | Dexamethasone; methylprednisolone | | |
| Anti-convulsants | | Phenytoin; phenobarbital; valproic acid | |
| Others | OCP[d] | | Statins |
| Retinoids | | Bexarotene | |

[a]Calcium channel blockers
[b]Protease inhibitors
[c]Selective Serotonin Reuptake Inhibitors
[d]Oral contraceptive pills

amlodipine at low doses such as 5 mg q day even in normotensive individuals as a prophylactic measure at onset of therapy [40, 41].

## Drug Interactions

Since cyclosporine is metabolized by the hepatic CYP3A4 system, a variety of drug interactions can occur. Table 10.7 has a list of some common drug interactions seen with cyclosporine administration. Concomitant use of medications also metabolized by the CYP3A4 system compete as substrates and may increase serum levels and potentiate toxicity. Induction or inhibition of the enzyme may decrease or increase serum levels, respectively. Foods usually do not affect cyclosporine levels but grapefruit juice increase levels of cyclosporine by CYP3A4 inhibition. Interactions may also occur with over the counter nutraceuticals, herbal and vitamin preparations. For instance, St John's wort may decrease cyclosporine concentrations. In patients who have severe liver disease, metabolism may be decreased, leading to higher drug levels. Although heavy alcohol intake increase cyclosporine levels, mild to moderate alcohol consumption has little effect.

Cyclosporine is also an inhibitor of CYP3A4 affecting other drugs such as calcium channel blockers, erectile dysfunction drugs, and statins. Reports of serious rhabdomyolysis occurring in patients who are concurrently treated with a statin have been described [42]. Medications that may potentiate renal toxicity such as aminoglycosides or nonsteroidal anti-inflammatory drugs as well as medications that may elevate potassium levels should be restricted. Given the long list of possible drug interactions, a thorough medication history must be obtained for all patients before initiating treatment, and patients should be educated regarding the introduction of new drugs with continued therapy.

As a general rule, drugs that alter the cytochrome P450 system should be introduced cautiously and potentially nephrotoxic drugs, such as nonsteroidal anti-inflammatory drugs, aminoglycosides, ciprofloxacin, clotrimazole, and fibrates

that can impair renal function during cyclosporine treatment should be avoided if possible.

## Summary

Both methotrexate and cyclosporine improve psoriasis by decreasing inflammation and suppression of T-cell mediated production of inflammatory cytokines that are known to be pivotal in the pathogenesis of psoriasis. While methotrexate and cyclosporine are safe and reliable treatments for psoriasis with proper patient selection and monitoring, the risk of serious potential complications remains. Patients and physicians should be aware of these side effects and discuss risks and benefits prior to starting therapy. From the physician's perspective, careful selection of the patient is paramount to eliminate potential complications. From the patient's perspective, the importance of follow-up appointments and appropriate, timely blood monitoring needs to be understood.

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# Traditional Systemic Therapy II: Retinoids and Others

11

Misha Koshelev, Fareesa Shuja, and Ted Rosen

**Abstract**

Some patients with psoriasis either do not respond to or develop significant toxicities from the well-recognized first-line systemic therapeutic agents. However, there are a number of second-line systemic agents which may be effective. For example, acitretin is particularly effective in erythrodermic psoriasis and palmoplantar pustulosis, as well being the consensus treatment of choice for generalized pustular psoriasis. Since acitretin does not induce immunocompromise, it is useful in the management of severe psoriasis associated with HIV infection. Concomitant UVB or PUVA may be synergistic with acitretin. Although not FDA-approved to treat psoriasis, hydroxyurea has shown some efficacy in treating chronic plaque psoriasis and, in short bursts, may be useful to stop the earliest flare of pustular psoriasis.

Mycophenolate mofetil may be utilized to treat moderate-to-severe chronic plaque psoriasis, most often as a maintenance therapy for patients needing cyclosporine for initial disease control. 6-thioguanine is used to treat plaque psoriasis and palmoplantar pustulosis which is resistant to more commonly utilized systemic agents, but is not recommended for long-term maintenance due to the risk of hepatotoxicity. Systemic tacrolimus is best used to treat severe, recalcitrant, chronic plaque psoriasis at a gradually increasing dose (to a maximum of 0.15 mg/kg/day); nephrotoxicity may be a limiting factor in long-term use. Though usually used in the management of rheumatoid arthritis, leflunomide can also be considered for patients with treatment-resistant, widespread, chronic plaque psoriasis

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or psoriatic arthritis. Penicillin V or erythromycin can be used to treat guttate psoriasis when the latter is related to or associated with a bacterial infection, usually of the upper respiratory system.

**Keywords**
Acitretin • Hydroxyurea • Mycophenolate mofetil • Tacrolimus • Leflunomide • Penicillin

Psoriasis occurs in approximately 1 out of 50 individuals and prominently affects the skin, nails, and joints. Patients with psoriasis are treated most commonly with topical agents, and in about 70–80 % of patients, topical therapy is sufficient. Systemic treatments tend to be reserved for patients with more than 10 % body surface area involvement or severe psoriasis of the scalp, palms and soles, genitalia, or intertriginous sites. In the era of biologics, traditional systemic therapies continue to remain both useful and appropriate for some patients, as these drugs offer comparatively inexpensive, orally administered alternatives with well-known short and long-term risks. For those patients who either do not respond to the recognized first-line agents methotrexate and cyclosporine, or who develop significant toxicities when using them, the second-line systemic agents discussed herein are reasonable treatment options.

Retinoids such as acitretin are particularly effective in erythrodermic psoriasis and palmoplantar pustulosis as well being the treatment of choice for generalized pustular psoriasis and severe psoriasis in HIV. Acitretin is a well-tolerated and efficacious second-line agent for chronic plaque psoriasis in responsive patients. Its efficacy can be maximized in combination regimens such as acitretin plus UVB or PUVA. Retinoids are teratogenic and thus contraindicated in women who are pregnant or plan to become pregnant within 3 years after stopping acitretin.

Hydroxyurea is not FDA-approved to treat psoriasis. However, historically it has shown some efficacy in treating chronic plaque psoriasis and can safely be combined with cyclosporine. Other systemic agents that can be used to treat chronic plaque psoriasis include mycophenolate mofetil, 6-thioguanine, systemic tacrolimus, and leflunomide. Penicillin V and erythromycin are often used to treat *Streptococcus pyogenes-associated* guttate psoriasis, particularly in the pediatric age group. The structures of the various agents discussed in this chapter are illustrated in Figs. 11.1 and 11.2.

## Acitretin

### FDA-Approved Indication(s)

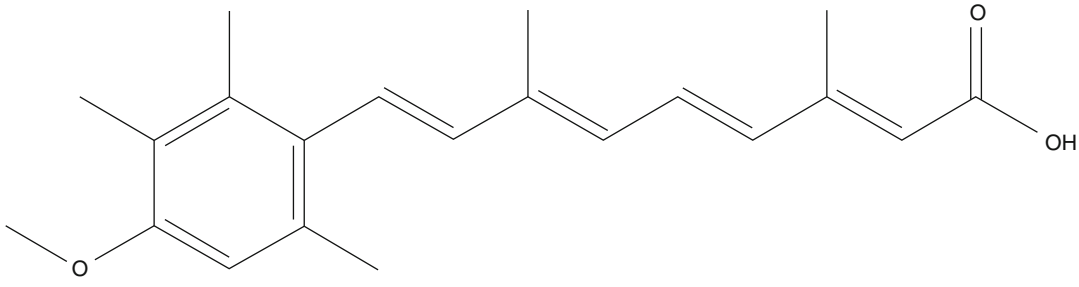
Acitretin is FDA-approved for the treatment of severe psoriasis in adults [1]. In women of childbearing potential, acitretin is only advised for non-pregnant individuals who do not respond to other psoriasis medications or have contraindications to their use.

### Mechanism of Action

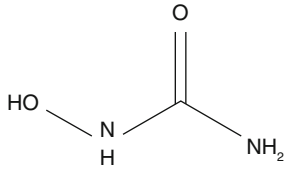
The exact mechanism of action of acitretin in psoriasis is unknown though it is likely related to its ability to decrease epidermal proliferation and induce differentiation [1].

### When Best to Use

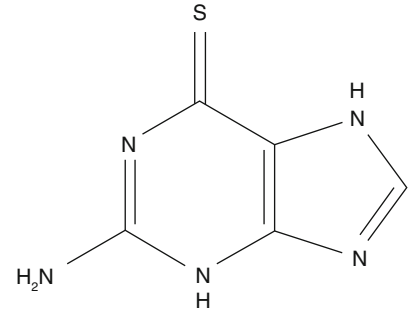
Acitretin is the treatment of choice for generalized pustular psoriasis and is an effective treatment for exfoliative erythrodermic psoriasis [8]. It is also the first-line therapy for severe psoriasis in the setting of human immunodeficiency virus (HIV) infection as it does not cause significant immunosuppression [9]. In palmoplantar pustulosis, it both ameliorates hyperkeratosis as well as decreases the pustulation, making it a highly utilized treatment for this psoriasis sub-type. For



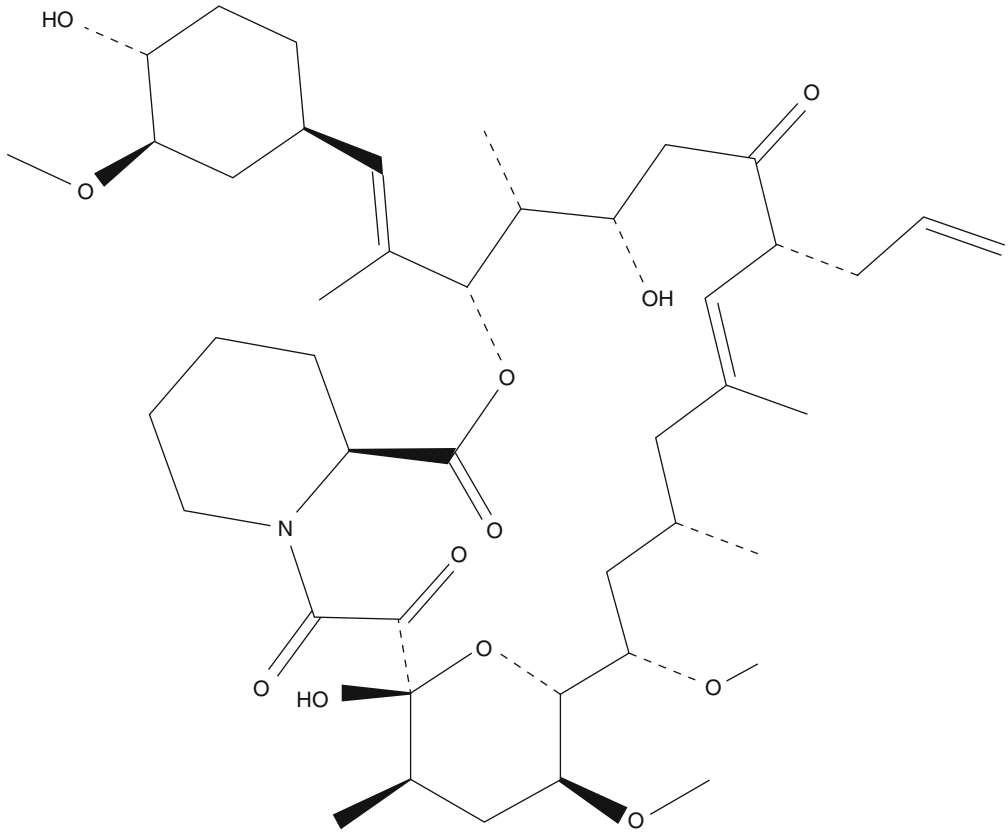

Acitretin




Hydroxyurea




6-Thioguanine




Tacrolimus

**Fig. 11.1** Chemical structures of acitretin, hydroxyurea, 6-thioguanine, and tacrolimus; adapted from the package inserts for the corresponding medications [1–4]

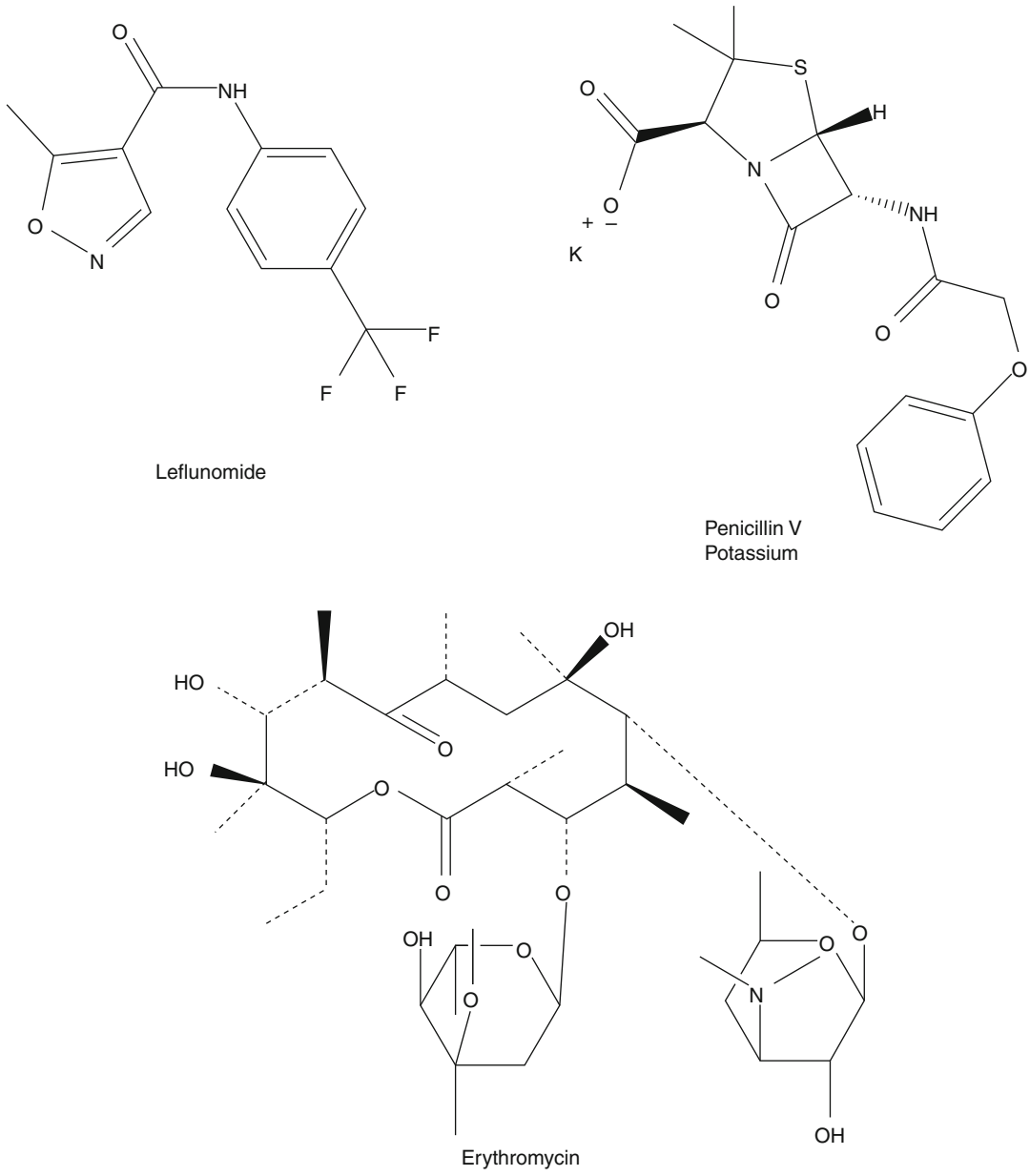



**Fig. 11.2** Chemical structures of leflunomide, penicillin V potassium, and erythromycin; adapted from the package inserts for the corresponding medications [5–7]

acitretin-responsive patients with chronic plaque psoriasis, it can be an effective maintenance therapy for many. It is notable, however, that not all chronic plaque psoriasis patients respond sufficiently to this drug [9].

Acitretin can also safely be combined with certain other systemic agents, and it potentiates the effectiveness of phototherapy. It has been successfully combined with TNF-alfa (TNF-α) inhibitors to treat chronic plaque psoriasis [10]. Although seemingly contraindicated by the acitretin prescribing information which warns of the risk of hepatotoxicity, acitretin and methotrexate have been combined when monotherapy

was inadequate. It is crucial to monitor liver function closely with this combination [1, 11]. Acitretin has been used with cyclosporine for short-term treatment albeit with frequent monitoring of lipids. Acitretin has also been combined with hydroxyurea to treat recalcitrant palmoplantar pustulosis.

### Dosage

The general acitretin dose ranges from 10 to 50 mg daily, administered with meals [1, 9]. Generalized pustular psoriasis typically requires an acitretin dose of 25–50 mg [8]. After clinical response, the dose is tapered to 10–25 mg daily. Exfoliative erythrodermic psoriasis requires an acitretin dose of 25–50 mg daily.

Clinical trials have employed varying acitretin doses to treat chronic plaque psoriasis [9]. A daily dose of 25 mg or less minimizes adverse events. Initiation of therapy should begin with a low dose and progressively increase to avoid an initial disease flare, as well as to improve tolerability [1, 12]. Maximal response is usually seen after 3–6 months of treatment [9].

When acitretin is combined with phototherapy, the drug is usually given by itself for 2 weeks prior to starting light treatments [9]. If a patient is already receiving UVB or PUVA, acitretin can be added at a dose of 25 mg daily while the UVB/UVA dose is concomitantly decreased by 30–50 % to minimize UV-induced erythema [1, 9]. After 1 week on acitretin, the UVB/UVA dose can be increased, as tolerated [9]. Patients given PUVA and acitretin have a decreased incidence of squamous cell cancer compared to individuals given PUVA alone, as might be expected due to chemopreventative features of this drug (and retinoids in general).

Based on clinical experience, acitretin is administered in low doses to reduce adverse events [9, 13]. A 2011 publication revisited data from two randomized trials with an 8-week double-blinded placebo-controlled phase and a 16-week open-label phase [13]. Patients received placebo or 75, 50, 25, or 10 mg of acitretin in the double-blinded phase; during the open-label phase, doses were adjusted according to clinical response, and patients were grouped into low and high dose categories. Low-dose treatment was defined as approximately 25 mg/day, whereas high-dose treatment was defined as approximately 50 mg/day. After 16 weeks, cumulative improvement of psoriasis based on investigator static global assessment was 47 % in patients given low-dose acitretin in both phases versus 29–33 % in the other groups. Similarly, there was a 73 % decrease in affected body surface area in the group receiving low-dose acitretin in both phases versus 28–54 % in the others. This data suggests that low-dose acitretin is not only safer than high-dose acitretin, but may also be more efficacious in the treatment of psoriasis.

### Adverse Events

See Table 11.1 and the "Perils and Pitfalls" section below.

**Table 11.1** Frequency of selected adverse events reported in clinical trials of acitretin [1, 9]

| Percent of patients reporting event(s) | Adverse event(s) reported |
|---|---|
| More than 75 % | Cheilitis |
| 50–75 % | Alopecia |
| | Skin peeling |
| 25–50 % | Rhinitis |
| | Xerosis |
| | Nail disorder |
| | Pruritus |
| 10–25 % | Rigors |
| | Xerophthalmia |
| | Xerostomia |
| | Epistaxis |
| | Arthralgia |
| | Spinal hyperostosis |
| | Erythematous rash |
| | Hyperesthesia |
| | Paresthesia |
| | Paronychia |
| | Skin atrophy |
| | Sticky skin |
| Less than 10 % | Nausea |
| | Abdominal pain |
| | Decreased night vision |
| | Headache |
| | Myalgia |

### Recommended Monitoring

Obtain a history and physical examination, CBC with platelets, BUN/Cr, LFTs, lipid profile, and a pregnancy test if indicated before starting acitretin [9, 14]. The clinician should perform a physical examination and obtain a CBC with platelets, BUN/Cr, LFTs, and lipid profile monthly for the first 3–6 months, then every 3 months [14]. BUN/Cr and CBC with platelets may be ordered every other monitoring period if desired. Pregnancy tests may be done monthly, if indicated.

### Perils and Pitfalls

Acitretin is contraindicated in patients with hypersensitivity to retinoids, chronically elevated lipids, severely impaired kidney or liver function, nursing mothers, and women who are pregnant [1]. The average half-life of acitretin is 49 h and that of its isomer cis-acitretin is 63 h; however, in the presence of alcohol, etretinate, whose average half-life is 120 days, can form. Etretinate has been detected 2.1–2.9 years after stopping therapy, most likely due to storage in fatty tissue. This is why acitretin is contraindicated in women who plan to become pregnant within 3 years of stopping the medication and is given with extreme caution (if at all) in women of child-bearing potential. Patients are also advised against donating blood from the initiation of treatment to 3 years after discontinuation. Fetal abnormalities reported with retinoid use include meningomyelocele, meningoencephalocele, decreased cranial volume, and cardiovascular malformations.

Acitretin may interact with a number of medications. It interferes with the contraceptive effects of the microdose progestin minipill [1, 9]. When given with tetracyclines, the combination raises the risk of increased intracranial pressure and manifest pseudotumor cerebri [1]. Acitretin can potentiate the glucose-lowering effects of glibenclamide and may reduce phenytoin protein binding [9]. Acitretin should not be given with other oral retinoids nor with excessive vitamin A supplementation to avoid hypervitaminosis A [1, 9].

Hepatobiliary abnormalities such as elevated serum bilirubin and transaminases, toxic hepatitis, acute reversible hepatic injury, and cirrhosis have been associated with acitretin [1]. In clinical trials, 66 % of patients treated with acitretin had triglyceride elevations; of note, these patients were likely to have increased alcohol intake, diabetes mellitus, obesity, pre-existing disturbances of lipid metabolism, or a family history of these conditions. Acitretin-induced serum triglyceride levels above 800 mg/dL have been associated with fatal fulminant pancreatitis. Acitretin-induced pancreatitis without an increase in serum triglycerides has also been reported. Forty percent of patients treated with acitretin in clinical trials had decreased HDL levels and one-third had serum cholesterol elevations. Changes in lipid levels resolved after stopping acitretin. Thromboembolic events, acute myocardial infarction, and pseudotumor cerebri have been reported, as have depression, thoughts of self-harm, aggressive feelings, and other psychiatric symptoms. Adults receiving acitretin have rarely experienced abnormal ossification.

The various adverse events associated with this drug are summarized in Table 11.1.

### Strength of Evidence

Acitretin can be an effective maintenance therapy for chronic plaque psoriasis [9, 12]. A multicenter Canadian trial involving 37 patients treated with acitretin, 50 mg daily for 4 weeks followed by dosage adjustment according to clinical response, was conducted for 11 months [12]. Seventy-nine percent of patients achieved PASI 75. A 2008 prospective study enrolled 17 patients with plaque psoriasis who had failed treatment with methotrexate, cyclosporine, or PUVA, or who had at least 10 % body surface area involvement [15]. Acitretin was started at 0.3 mg/kg/day and could be increased to 0.5 mg/kg/day after 1 month depending on clinical response; the mean dose was 0.4 mg/kg/day. After 4 months, the mean PASI reduction was 59.4 %.

There are no head-to-head trials comparing the effectiveness of acitretin to methotrexate or cyclosporine in the treatment of chronic plaque psoriasis, but there is general consensus agreement that acitretin is a considerably less effective monotherapy [9]. A 1993 comparison between cyclosporine and etretinate, the pro-drug of acitretin, showed that cyclosporine was more

efficacious in the treatment of severe plaque psoriasis [16].

Acitretin has been studied in the treatment of palmoplantar pustulosis [8, 17]. In one study, patients received 10 mg/day for 4 weeks followed by dosage adjustment based on clinical response for 8 weeks [17]. After the 12 weeks, patients had an average of 3.9 pustules versus 57.8 at baseline.

Acitretin is more, and possibly most, efficacious when combined with phototherapy [9]. In patients with moderate-to-severe psoriasis involving 20–80 % body surface area, 50 mg acitretin daily with concomitant broadband-UVB (BB-UVB) led to a 74 % reduction in psoriasis severity scores after 12 weeks, versus a 42 % reduction with acitretin alone and a 35 % reduction with UVB alone [18]. Another study reported the use of 35 mg acitretin daily for 4 weeks followed by 25 mg acitretin daily plus BB-UVB in patients with generalized chronic plaque or exanthematic-type pustular psoriasis [19]. The psoriasis severity index decreased 79 % with acitretin and UVB versus 35 % with placebo and UVB. The median cumulative UVB dose needed to reach 75 % improvement was 41 % lower for the acitretin and UVB group than for the placebo and UVB group. Of note, though these studies look at BB-UVB, narrow-band UVB is taking the place of BB-UVB in most practices.

As biologics are increasingly being used for psoriasis, a 2008 randomized controlled investigator-blinded trial studied the efficacy of combining acitretin with the TNF-α inhibitor etanercept versus acitretin alone in 60 adults with moderate-to-severe chronic plaque psoriasis over 6 months [10]. Twenty patients received 0.4 mg/kg oral acitretin daily, 22 patients received 25 mg etanercept subcutaneously twice a week, and 18 patients received 0.4 mg/kg oral acitretin daily with etanercept 25 mg subcutaneously once a week. Thirty percent of patients in the acitretin group achieved PASI 75, compared to 45 % of patients treated with etanercept alone and 44 % of patients treated with both etanercept and acitretin. Thus it appears that acitretin is less effective than etanercept and that adding acitretin to etanercept achieves an efficacy rate similar to that of etanercept alone. The results, of course, might well be drug-dose-dependent.

## Hydroxyurea

### FDA-Approved Indication(s)

Hydroxyurea is FDA-approved to treat melanoma; recurrent, metastatic, or inoperable ovarian cancer; resistant chronic myelocytic leukemia; and sickle cell anemia [2]. It is also FDA-approved to control local primary squamous cell carcinoma of the head and neck, excluding the lip, in conjunction with radiotherapy [20].

### Mechanism of Action

The precise mechanism of action of hydroxyurea in psoriasis is unknown [2, 9, 21, 22]. Hydroxyurea inhibits ribonucleotide reductase and suppresses DNA synthesis.

### When Best to Use

Hydroxyurea has been given to patients with moderate-to-severe chronic plaque psoriasis who have received the recommended cumulative dose of methotrexate or who cannot tolerate adverse events related to methotrexate [23]. Hydroxyurea has also been used with low-dose cyclosporine in short-course therapy to treat recalcitrant, severe psoriasis and with acitretin to treat recalcitrant palmoplantar pustulosis [11]. Hydroxyurea may also be beneficial in generalized pustular psoriasis [21].

### Dosage

Hydroxyurea is initiated at a dose of 500 mg twice daily, and increased to 3 g daily as tolerated [9, 21]. Dosing at 3–4.5 g weekly has also been used [9, 23]. The senior author has utilized hydroxyurea as a short-term "rescue" drug during flares of von Zumbusch type pustular psoriasis, starting at 3.0 g as a daily dose and decreasing by 500 mg daily, for a 1 week total course.

### Adverse Events

See Table 11.2 and the "Perils and Pitfalls" section below.

**Table 11.2** Selected adverse events reported with the use of hydroxyurea; events reported in psoriasis patients are marked with an asterisk (*) [9, 20, 21, 23, 24]

| |
|---|
| Myelosuppression, including anemia*, leukopenia*, and thrombocytopenia* |
| Gastrointestinal symptoms, including diarrhea*, aphthous ulcers*, nausea, vomiting, constipation, anorexia, and stomatitis |
| Dermatological symptoms, including nail pigmentation*, alopecia*, pruritus*, dermatomyositis-like skin changes, rash, and ulceration |
| Systemic symptoms, including edema*, asthenia, chills, malaise, and fever |
| Neurologic symptoms, including hallucinations, dizziness, headache, disorientation, and convulsions |
| Serum creatinine, BUN, and uric acid elevations with temporary impairment of renal tubular function |
| LFT elevations |
| Rare pulmonary fibrosis |
| Rare dysuria |
| Nonfatal and fatal pancreatitis and hepatotoxicity, severe peripheral neuropathy in HIV patients given hydroxyurea with other antiretrovirals |

### Recommended Monitoring

Before starting hydroxyurea, the clinician should obtain a good history and perform a general physical examination, CBC, and pregnancy test (if indicated) [9]. Weekly CBCs are obtained until a stable dose is achieved and monthly thereafter as long as treatment with this agent is continued. Repeat physical examination, focusing on skin cancer and checking for enlarged lymph nodes, should be done biannually. Periodic pregnancy testing is performed if indicated.

### Perils and Pitfalls

Hydroxyurea is contraindicated in patients with known hypersensitivity to hydroxyurea; in patients with leukopenia, severe anemia, or thrombocytopenia; during pregnancy; and in nursing mothers [2, 9]. Hydroxyurea may raise uric acid levels and require changes in the doses of uricosuric medications to prevent a flare of gout [2]. Severe peripheral neuropathy, fatal and nonfatal pancreatitis, hepatotoxicity and fatal hepatic failure have been described in HIV patients given hydroxyurea and didanosine with or without stavudine. These adverse events are quite rare in normal hosts.

Patients given long-term hydroxyurea have reportedly developed both lymphoma and nonmelanoma skin cancer. In patients treated with hydroxyurea for myeloproliferative disorders, secondary leukemia has developed. These patients have also developed gangrene and vasculitic ulcerations, but most were simultaneously receiving interferon. Self-limiting megaloblastic erythropoiesis may occur early in the course of hydroxyurea therapy.

Myelosuppression may occur in patients treated with hydroxyurea. Leukopenia generally occurs first, followed by anemia or thrombocytopenia. Bone marrow recovery is rapid when treatment is stopped. Increased myelosuppression may be seen when hydroxyurea is used concurrently with radiotherapy or myelosuppressive drugs [9]. The various potential adverse events associated with hydroxyurea are summarized in Table 11.2.

### Strength of Evidence

Studies have reported variable efficacy of hydroxyurea in the treatment of psoriasis [9]. One study compared the efficacy and toxicity of hydroxyurea and methotrexate for the treatment of moderate-to-severe chronic plaque psoriasis [23]. Patients had at least 20 % body surface area involvement and a PASI of at least 10. Patients were assigned to treatment with either hydroxyurea or methotrexate. Patients given methotrexate received 15 mg weekly for 4 weeks; the dose was then increased up to 20 mg weekly in patients with less than 25 % PASI reduction. Patients receiving hydroxyurea were given 500 mg twice a day on 2 consecutive days for 1 week, then 500 mg three times a day on 2 consecutive days for 3 weeks. After 4 weeks, patients with less than 25 % PASI reduction were given 500 mg three times a day on 3 consecutive days. Ten of 15 patients treated with methotrexate and 2 of 15 patients treated with hydroxyurea achieved PASI 75 at 12 weeks. Though most patients treated with hydroxyurea did not achieve PASI 75, they did have a mean PASI reduction of 48.47 % while experiencing fewer adverse events than the methotrexate group.

A 2004 study evaluated the efficacy and safety of daily hydroxyurea in patients with chronic plaque psoriasis involving more than 20 % body

surface area in patients with erythrodermic psoriasis or generalized pustular psoriasis [21]. Patients had incompletely responded to conventional systemic and topical therapies. Thirty-four patients were started on 500 mg hydroxyurea twice daily. If hydroxyurea was tolerated and PASI reduction was less than 25 % after 2 weeks, it was increased to 1 and 1.5 g on alternate days, and then to 1.5 g daily as tolerated. If greater than 95 % clearance was achieved, treatment was tapered off over 4–8 weeks. Mean PASI reduction was 76 % at 10–12 weeks, although hydroxyurea was stopped in three patients who developed leukopenia.

In a 2001 study, 31 patients with chronic plaque psoriasis involving more than 20 % body surface area were started on hydroxyurea; 500 mg twice daily was given to patients who weighed no more than 60 kg, and 500 mg three times a day was given to the others [25]. In patients receiving the lower dose, hydroxyurea was increased to 500 mg three times daily if less than 35 % PASI reduction was seen after 3 weeks. After 8 weeks, treatment was stopped if PASI was reduced by less than 35 %. Otherwise, hydroxyurea was continued. Seventy-five percent of patients showed at least a 35 % PASI reduction within 8 weeks, and more than 50 % showed greater than 70 % PASI reduction by a mean of 11 weeks.

## Mycophenolate Mofetil (MMF)

### FDA-Approved Indication(s)

MMF is FDA-approved in combination with corticosteroids and cyclosporine to prevent organ rejection in liver, heart, and kidney transplant patients [26].

### Mechanism of Action

MMF is hydrolyzed to its active metabolite, mycophenolic acid, which inhibits de novo guanosine nucleotide synthesis and selectively suppresses lymphocyte growth and division [26].

### When Best to Use

MMF is utilized to treat moderate-to-severe chronic plaque psoriasis in patients who cannot tolerate any of the various first-line agents [27]. MMF can be given with cyclosporine, making it useful as maintenance therapy for patients needing cyclosporine for initial disease control [28].

### Dosage

MMF can be given as 1.0–2.0 g twice daily [9, 27].

### Adverse Events

Psoriasis patients given MMF reported abdominal cramping, diarrhea, nausea, elevated LFTs, severe hyperbilirubinemia, severe hypertension, life-threatening hyperuricemia, life-threatening hypokalemia, periorbital edema, urticaria, furunculosis, and pruritus [27, 29, 30]. Transplant patients given MMF reported vomiting, genitourinary urgency, genitourinary frequency, dysuria, sterile pyuria, headaches, insomnia, peripheral edema, hypercholesterolemia, hypophosphatemia, and hyperkalemia [9].

### Recommended Monitoring

The clinician should obtain a history, physical examination, CBC, platelet count, serum chemistry panel, LFTs, and pregnancy test (if indicated) before starting MMF [9, 26]. After initiation of therapy, complete blood and platelet counts should be checked weekly for 1 month, then every 2 weeks for 2 months, then monthly thereafter. It is wise to also obtain serum chemistries and LFTs monthly, a physical examination focusing on skin cancer and lymph nodes biannually, and ongoing pregnancy tests (if indicated).

### Perils and Pitfalls

MMF is contraindicated in patients with hypersensitivity to MMF or mycophenolic acid, during pregnancy, and in nursing mothers [9, 26]. MMF can cause first trimester spontaneous abortions and fetal malformations [26]. It can interact with acyclovir, ganciclovir, valganciclovir, probenecid, xanthine bronchodilators, high-dose salicylates, cholestyramine, phenytoin, antibiotics, calcium, iron, and aluminum or magnesium-containing antacids [9].

Patients given MMF have developed severe neutropenia. Two percent of kidney and heart

transplant patients and 5 % of liver transplant patients given MMF in clinical trials developed fatal infection/sepsis. Live attenuated vaccines should not be given to patients taking MMF [9, 26]. Pure red cell aplasia, anemia, leukopenia, and thrombocytopenia have also been reported [9].

Between 0.4 and 1 % of transplant patients given MMF with other immunosuppressive drugs developed lymphoma or lymphoproliferative disease [26]. Adults given prolonged MMF had increased risk of skin cancer. Fatal cases of progressive multifocal leukoencephalopathy (PML) with the use of MMF were reported in patients with risk factors such as pre-existing immune function impairment and treatment with other immunosuppressants.

### Strength of Evidence

A 2010 randomized, open-label clinical trial evaluated the efficacy and safety of MMF versus methotrexate in chronic plaque psoriasis patients with a PASI score of at least 10 and a history of inadequate response to topical therapy [27]. Seventeen patients received MMF 1 g twice daily for 12 weeks. Fifteen patients received methotrexate 7.5 mg/week for 1 week, then 15 mg/week for 3 weeks, and then 20 mg/week for 8 weeks. Ten of 17 patients (58.8 %) in the MMF group and 11 of 15 patients (73.3 %) in the methotrexate group achieved PASI 75. Possibly due to a small sample size, the difference between the two groups was not statistically significant.

A 2009 randomized open-label clinical trial evaluated the efficacy of MMF versus cyclosporine in chronic plaque psoriasis patients with a PASI score of at least 10 [29]. Sixteen patients received MMF 1 g twice daily for 6 weeks. Then they received 500 mg MMF twice daily if they had 60 % or greater PASI reduction, 1 g MMF twice daily if they had between 25 and 60 % PASI reduction, and 1.5 g MMF twice daily if they had 25 % or less PASI reduction. Twenty-one patients received 1.25 mg/kg cyclosporine twice daily for the first 6 weeks, and then either 1.25 mg/kg once daily, 1.25 mg/kg twice daily, or 2.5 mg/kg twice daily based on PASI reduction thresholds identical to those in the MMF group. After 12 weeks, mean PASI decreased from 22.4 to 10.6 in the MMF group and from 24.6 to 6.6 in the cyclosporine group.

Use of concomitant MMF and cyclosporine to treat severe recalcitrant psoriasis was described in nine patients who failed to clear on cyclosporine alone or could not tolerate higher cyclosporine doses [28]. Three patients showed good clinical improvement and four patients showed moderate disease control after a follow-up period of 3–11 months. No additional toxicity was seen after starting MMF in patients already taking cyclosporine. Notably, this study included a patient with erythrodermic psoriasis and another with generalized pustular psoriasis.

## 6-Thioguanine (6TG)

### FDA-Approved Indication(s)

6-thioguanine is FDA-approved to induce and sustain remission in patients with acute nonlymphocytic leukemia, most commonly in combination with other chemotherapeutic agents [3]. It is not recommended for long-term treatment due to a significant risk of hepatotoxicity.

### Mechanism of Action

6-thioguanine is a purine nucleotide analogue that interferes with nucleic acid synthesis [3].

### When Best to Use

Use 6-thioguanine to treat plaque psoriasis and palmoplantar pustulosis that are resistant to the more commonly utilized systemic agents [31].

### Dosage

6-thioguanine is given two to three times per week to reduce the risk of myelosuppression [9, 31, 32]. The starting dose of 6TG is 80 mg twice per week; the dose is then increased by 20 mg every 2–4 weeks [9]. The maximum dose is 160 mg three times per week.

### Adverse Events

According to various reports, 22–68 % of psoriasis patients given 6TG develop myelosuppression [32, 33]. Up to 12 % of patients given the drug

reported gastrointestinal adverse events, including nausea, vomiting, aphthous ulcers, gastric ulcers, gastroesophageal reflux, and dysgeusia [9, 32, 33]. One quarter of patients treated with 6TG for psoriasis experienced LFT elevations [9, 32]. Patients treated with this agent also developed headaches, fatigue, photodermatitis, herpes zoster, multiple warts, hyperuricemia, hepatic veno-occlusive disease, and non-melanoma skin cancer [9, 32, 33].

#### Recommended Monitoring

The clinician should obtain a history and physical examination, complete blood and platelet counts, serum chemistry panel, LFTs, hepatitis B and C tests, PPD, and pregnancy test (if indicated) before initiating 6TG therapy [3, 9]. After starting treatment, a complete blood and platelet counts should be checked every 2–4 weeks, serum chemistries every 3 months, and a physical examination focusing on lymph nodes and skin cancer biannually; periodic pregnancy tests should be performed, if indicated.

#### Perils and Pitfalls

6-thioguanine is contraindicated in patients with known hypersensitivity to the drug; in patients with liver disease, immunosuppression, anemia, leukopenia, and/or thrombocytopenia; during pregnancy; and in nursing mothers [9]. Psoriasis patients treated with 6-thioguanine have rarely developed hepatotoxicity, but in those who did, most cases resolved after stopping treatment [3, 9, 31, 32]. Treatment with 6TG may increase the risk of hepatic veno-occlusive disease and portal hypertension [3].

The cytoplasmic enzyme thiopurine methyltransferase (TPMT) metabolizes 6-thioguanine and other thiopurines [3, 33]. TPMT activity in Caucasians varies based on a genetic polymorphism. Specifically, 10 % of Caucasians have intermediate TPMT activity and one in approximately 300 Caucasian individuals has no TPMT activity [33]. Lower TPMT activity increases the risk of myelosuppression in patients taking 6-thioguanine. Aminosalicylate derivatives, such as olsalazine, mesalazine, and sulfasalazine, may inhibit TPMT [3, 9]. Life-threatening infections due to 6TG-induced granulocytopenia have been reported [3]. It has been recommended that physicians measure TPMT activity in all psoriasis patients before starting 6-thioguanine to determine initial dosage and assess the risk of myelosuppression [33].

#### Strength of Evidence

Studies have repeatedly demonstrated that 6TG is efficacious in the treatment of psoriasis [9, 22]. A 2001 retrospective 4-year review of the treatment of 18 psoriasis patients with 6-thioguanine reported 14 patients (78 %) had more than 90 % improvement, 3 patients (17 %) had 50–90 % improvement, and 1 patient had less than 50 % improvement [9, 33]. A 1999 study of two to three times weekly dosing reported marked improvement in 10 of 14 (71 %) patients [32]. A 1994 study reported the results of 6-thioguanine administration to 76 patients with plaque psoriasis and to 5 patients with palmoplantar pustulosis [31, 34]. In this study, which used varied dosing schedules, 78 % of patients had complete or almost complete clearing, 11 % had some improvement, and 11 % had little or no change in their psoriatic lesions [31, 34].

## Systemic Tacrolimus

#### FDA-Approved Indication(s)

Tacrolimus is FDA-approved, in conjunction with corticosteroids, to prevent organ rejection in patients with kidney, liver, or heart transplants [4]. Patients with kidney or heart transplants generally also receive azathioprine or mycophenolate mofetil.

#### Mechanism of Action

Tacrolimus inhibits the phosphatase activity of calcineurin and thereby suppresses T cell activation [4].

#### When Best to Use

Systemic tacrolimus is best used to treat severe, recalcitrant, chronic plaque psoriasis [35].

### Dosage

Systemic tacrolimus is started at a dose of 0.05 mg/kg/day [4, 9, 35]. The dose can be increased to 0.10 mg/kg/day after 3 weeks and to 0.15 mg/kg/day after 6 weeks.

### Adverse Events

Diarrhea, paresthesias, insomnia, pharyngitis, and headache were commonly reported in psoriasis patients treated with systemic tacrolimus [35]. Tremor, nausea, and abnormal renal function tests were commonly reported in transplant patients given tacrolimus [9]. Hyperglycemia, elevated LFTs, leukocytosis, dyspnea, anemia, edema, fever, and arthralgias were less commonly reported in transplant patients given tacrolimus [9].

### Recommended Monitoring

One should obtain a detailed medical history and perform a physical examination. A CBC count with differential, serum BUN and creatinine levels, LFTs, and pregnancy test (if indicated) should all be obtained before starting systemic tacrolimus [9]. After starting treatment, serial evaluations should be done of the patient's blood pressure, serum chemistries, BUN and creatinine, LFTs, and pregnancy test (if indicated) [4, 9, 35]. A monitoring frequency has not been firmly established [9].

### Perils and Pitfalls

Systemic tacrolimus is contraindicated in patients with known hypersensitivity to tacrolimus or to its metabolites and in nursing mothers [4, 9]. Tacrolimus causes fetal harm in pregnant animals [4, 9]. Transplant patients treated with tacrolimus have an increased risk of developing lymphoma and skin malignancies and an increased susceptibility to infection [4]. It can be presumed that, since psoriasis patients already have a increased baseline risk of lymphoma, this particular potential problem needs to be followed closely. Patients who receive systemic tacrolimus have developed new onset diabetes mellitus, acute and/or chronic nephrotoxicity, neurotoxicity, hyperkalemia, hypertension, myocardial hypertrophy, and pure red cell aplasia. The clinician must advise patients to take oral tacrolimus consistently either with or without food, as the presence of food affects the drug's bioavailability. The cytochrome P450 system metabolizes systemic tacrolimus, and it therefore interacts with many drugs [9]. One should not give systemic tacrolimus concurrently with cyclosporine; discontinue one drug at least 24 h before starting the other.

### Strength of Evidence

A randomized, placebo-controlled trial evaluated the safety and efficacy of systemic tacrolimus in patients with severe recalcitrant plaque psoriasis [9, 35]. Nine week PASIs decreased by 83 % in the tacrolimus group compared to 47 % in the placebo group ($P < 0.02$) [35].

## Leflunomide

### FDA-Approved Indication(s)

Leflunomide is FDA-approved to treat active rheumatoid arthritis in adults [5].

### Mechanism of Action

Leflunomide inhibits de novo pyrimidine synthesis and thereby suppresses cell proliferation and inflammation [5].

### When Best to Use

Leflunomide can be considered for patients with treatment-resistant, widespread, chronic plaque psoriasis or psoriatic arthritis [9, 36].

### Dosage

Leflunomide should be started at 100 mg/day for 3 days, and then maintained at a dose of 20 mg/day [5, 9, 36].

### Adverse Events

Diarrhea, elevated liver enzymes, tiredness/lethargy, and alopecia were commonly reported in psoriasis patients given leflunomide [36]. Nausea, weight loss, headache, and dizziness were reported in rheumatoid arthritis patients given leflunomide, but such side effects could reasonably be expected in psoriasis patients as well [9].

### Recommended Monitoring

The clinician should obtain a history and physical examination, CBC with differential, LFTs, and pregnancy test (if indicated) before starting leflunomide. [9] After starting treatment, a CBC with differential and LFTs should be checked monthly for 6 months, then every 6–8 weeks [5, 9]. If indicated, ongoing pregnancy tests should be checked [9].

### Perils and Pitfalls

Leflunomide is contraindicated in patients with hypersensitivity to leflunomide, during pregnancy, and in nursing mothers [5, 9]. Hepatotoxicity and fatal liver failure have been reported in patients treated with leflunomide, and it is well worth noting that concurrent methotrexate therapy increases the risk of hepatotoxicity. Patients given leflunomide have rarely developed pancytopenia, agranulocytosis, thrombocytopenia, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Concurrent rifampin use leads to increased and potentially toxic peak levels of leflunomide's active metabolite.

### Strength of Evidence

A randomized, placebo-controlled trial evaluated the safety and efficacy of leflunomide in patients with active psoriatic arthritis and psoriasis with at least 3 % skin involvement [9, 36]. Patients could concurrently use up to 10 mg/day of oral prednisone or the steroid equivalent. Seventeen percent of the leflunomide versus 8 % of the placebo group ($P = 0.048$) achieved PASI 75 and 59 % of the leflunomide versus 30 % of the placebo group ($P < 0.0001$) achieved a response by the Psoriatic Arthritis Response Criteria.

## Penicillin V and Erythromycin

### FDA-Approved Indication(s)

Among other indications, penicillin V and erythromycin are both approved to treat mild to moderate *Streptococcus pyogenes*-associated infections [6, 7].

### Mechanism of Action

Penicillin V inhibits cell-wall synthesis in penicillin-sensitive microorganisms [7]. Erythromycin inhibits protein synthesis in susceptible microorganisms [6].

### When Best to Use

Penicillin V or erythromycin can be used to treat guttate psoriasis when the latter is related to or associated with a bacterial infection, usually of an upper respiratory nature [37–39].

### Dosage

Both antibiotics (penicillin V or erythromycin) are given orally in a dosage of 250 mg four times daily, for 14 days [39].

### Adverse Events

Patients given penicillin V sometimes report nausea, vomiting, abdominal pain, diarrhea, and black hairy tongue [7]. Patients taking erythromycin often develop nausea, vomiting, abdominal pain, diarrhea, and anorexia [6].

### Recommended Monitoring

No specific hematologic or biochemical monitoring is recommended for short-term therapy with penicillin V or erythromycin [6, 7].

### Perils and Pitfalls

Penicillin is contraindicated in patients with hypersensitivity to the drug; reported hypersensitivity reactions have been fatal [7]. Patients receiving penicillin V have developed *Clostridium difficile* associated diarrhea. High dose penicillin has rarely been associated with leukopenia, anemia, thrombocytopenia, nephropathy, and neuropathy.

Erythromycin is contraindicated in patients taking terfenadine, astemizole, pimozide, or cisapride due to increased risk of fatal ventricular arrhythmia and also in patients with hypersensitivity to erythromycin [6]. Patients taking erythromycin have developed LFT abnormalities, hepatitis, pseudomembranous colitis, QT prolongation, ventricular arrhythmias, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, pancreatitis, convulsions, and reversible hearing loss.

Strength of Evidence

Despite the lack of evidence supporting treatment of guttate psoriasis with antibiotics, it is often routinely used for this purpose [37–39]. There is one small study comparing the use of phenoxymethylpenicillin versus erythromycin versus no treatment for 14 days; no benefit over placebo was seen in the groups treated with antibiotics [38].

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## Recommended Reading

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# Etanercept

# 12

Andrew F. Alexis and Charlotte M. Clark

**Abstract**

Etanercept is a soluble dimeric fusion protein that was the first anti-tumor necrosis factor (TNF-α(alpha)) drug to be approved for the treatment of psoriasis and psoriatic arthritis. It is administered subcutaneously by self-injection. As with other biologic drugs for psoriasis, etanercept offers a targeted approach to treatment that lacks end organ side effects of traditional systemic therapies such as methotrexate, cyclosporine, or acitretin. With over 8 years of postmarketing experience in psoriasis (and over 14 years since approval for moderate to severe RA in 1998), a large body of safety data exists for etanercept. Here, we review the safety and efficacy of etanercept in the treatment of plaque psoriasis and psoriatic arthritis, with emphasis on published Phase 3 and Phase 4 clinical trial data. Safety considerations, recommended monitoring, and studies of combination therapy are also discussed.

**Keywords**

Etanercept • TNF-alpha inhibitors • Psoriasis • Psoriatic arthritis • Clinical Trials • Safety data • Efficacy data • Combination therapy • Monitoring recommendations • Malignancies • Opportunistic infections • Demyelinating disorders • Congestive heart failure

## Introduction

Etanercept was the first anti-tumor necrosis factor (TNF-α(alpha)) drug to be approved for the treatment of psoriasis and psoriatic arthritis. As a TNF-α(alpha) blocking agent, etanercept modulates inflammatory processes of innate and extrinsic immune responses, cell trafficking, and acute and chronic inflammation that are aberrant in psoriasis. In this chapter, the safety and efficacy of etanercept in the treatment of plaque psoriasis and psoriatic arthritis will be reviewed, with emphasis on published Phase 3 and Phase 4 clinical trial data.

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## Background

Psoriasis is a chronic inflammatory disease, characterized by hyperkeratotic epidermal lesions formed in response to T cell activation and the associated release of proinflammatory cytokines [1]. Although the exact pathogenesis of psoriasis remains to be fully elucidated, TNF appears to play a key role in the inflammatory cascade associated with psoriasis and psoriatic arthritis. When compared to uninvolved skin, greater concentrations of TNF-α are expressed in the stratum corneum of psoriatic lesions [2].

Etanercept is a TNF-α inhibitor and FDA approved drug for the treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Etanercept is also approved for the treatment of other TNF mediated inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and polyarticular juvenile idiopathic arthritis.

## Structure and Mechanism of Action

Etanercept is a soluble dimeric fusion protein that includes two TNF-α receptors fused to the constant region (Fc) of human IgG1, allowing it to bind specifically with non-membranous bound TNF-α (see Fig. 12.1) [1, 3, 4]. Etanercept binds to and inactivates TNF [3]. Furthermore, etanercept modifies responses induced by TNF activity, such as adhesion molecule expression (needed for leukocyte migration) and blood cytokine levels [5]. Therapy is administered as a subcutaneous injection by patients at home. The peak absorption of etanercept is at 51 h, with a mean half-life of 68 h [4].

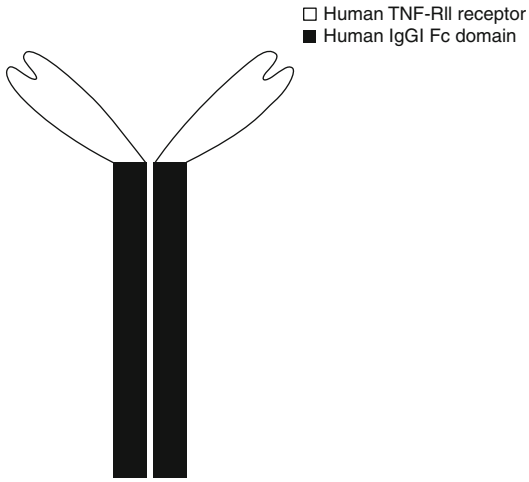


**Fig. 12.1** Illustration of structure of etanercept [3] (Used with permission from Elsevier Limited Publishing)

## Etanercept in the Treatment of Psoriatic Arthritis

Psoriatic skin lesions typically precede the onset of joint symptoms and therefore, dermatologists can potentially diagnose psoriatic arthritis in early stages through careful history and examination. Elevated TNF-α levels have been found in psoriatic arthritis joint fluid in comparison to osteoarthritis controls [2]. Psoriatic arthritis patients treated with etanercept have shown to have significant reductions in cutaneous psoriasis lesions as well as improvement of their arthritis [1, 6]. Etanercept (25 mg SC twice-weekly) has been shown to be efficacious in the treatment of psoriatic arthritis as evidenced by significantly greater percentages of subjects achieving a 20 % or greater reduction in American College of Rheumatology criteria (ACR20) scores [6]. Significant inhibition of radiographic disease progression (measured by mean change in modified total Sharp score) has also been shown in controlled clinical trials of etanercept in the treatment of psoriatic arthritis (see Fig. 12.2) [6, 7].

## Etanercept in the Treatment of Psoriasis

The safety and efficacy of etanercept has been shown in large double blinded placebo-controlled trials [8–10]. Based on US and Global phase III trial data the dosage approved by the US FDA for the treatment of plaque psoriasis is 50 mg SC twice weekly for 12 weeks followed by 50 mg SC thereafter. Statistically significant proportions of etanercept treated subjects achieved a 75 % or

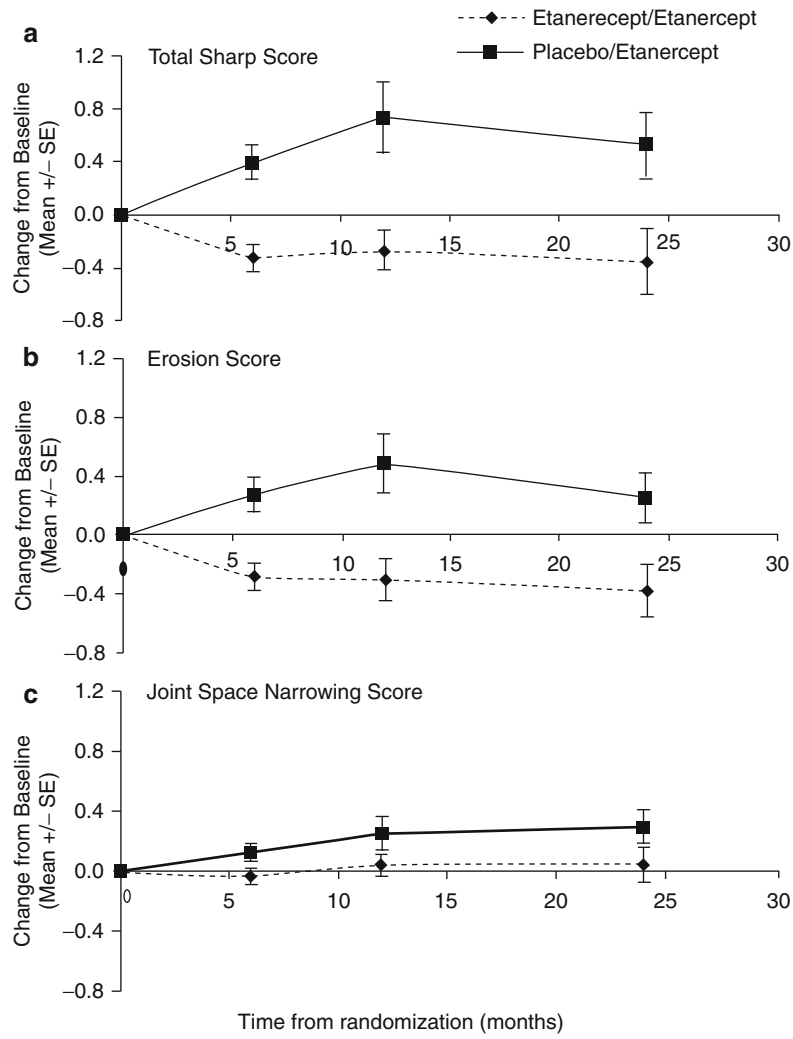


**Fig. 12.2** The TSS (**a**), erosion (**b**), and joint space narrowing (JSN) (**c**) changes from baseline to 6, 12, and 24 months [7] (Used with permission from Springer Publishing)

greater reduction in Psoriasis Area and Severity Index (PASI 75) scores compared to placebo (Table 12.1) [6, 7]. Clinically meaningful improvements in the quality of life have also been demonstrated in psoriasis patients treated with etanercept (Fig. 12.3) [6].

After discontinuation of therapy, a gradual onset of disease recurrence is observed. In one study, median time to disease relapse (measured as ≥50 % loss of PASI improvement achieved from baseline after 24 weeks of therapy) was 3 and 2 months, in PASI 50 and PASI 75 responders, respectively [8]. Successful discontinuation and re-treatment with etanercept has also been shown [8, 9].

Therapeutic efficacy after dosage reduction at 12 weeks from 50 mg SC twice weekly to 50 mg once weekly is maintained by a majority of patients as demonstrated by the percentage of subjects maintaining a PASI 50 or greater after "step-down" therapy (see Figs. 12.4 and 12.5) [8]. In addition, approximately 30 % of the non-responders (those not achieving a PASI 75) after 12 weeks of dose- reduction were shown to achieve a PASI 75 by week 24, despite continued reduced-dose therapy [8].

The long-term safety and efficacy of etanercept 50 mg twice weekly in patients with psoriasis has been investigated in a 96 week open-label extension trial [11].

**Table 12.1** The US and Global Phase III psoriasis clinical trials; study design, baseline characteristics, and clinical outcomes [6, 7]

| | US Phase III clinical trial [6] | Global Phase III clinical trial [7] |
|---|---|---|
| Study design | Multicenter (47 sites), randomized, double-blinded, placebo-controlled, parallel-group | Multicenter (50 sites), randomized, double-blinded, placebo-controlled, parallel-group |
| Number of patients | 672 patients were randomized, 652 participated in study treatment | 611 patients were randomized, 583 participated in study treatment |
| Duration | 24 weeks | 24 weeks |
| Drug regimen | 1. Placebo (n = 166) for 12 weeks, then etanercept 25 mg BIW for 12 more weeks<br>2. Low dose (25 mg QIW) (n = 160)<br>3. Medium dose (25 mg BIW) (n = 162)<br>4. High dose (50 mg BIW) (n = 164) | 1. Placebo (n = 193) for 12 weeks, then etanercept 25 mg BIW for 12 more weeks<br>2. Etanercept 25 mg BIW (n = 196) for 24 weeks<br>3. Etanercept 50 mg BIW (n = 194) for 12 weeks, then etanercept 25 mg BIW for 12 more weeks |
| Efficacy endpoints | *Primary endpoint:* PASI 75 at week 12<br>*Secondary endpoints:*<br>1. PASI 50 and 90 at week 12<br>2. Physician Global Assessment<br>3. Patient Global Assessment<br>4. Dermatology Life Quality Index | *Primary endpoint:* PASI 75 at 12 weeks<br>*Secondary endpoints:*<br>1. PASI 50 and 90 at 12 weeks<br>2. Patient Global Assessment |

| Demographics and baseline clinical characteristics | Placebo group (mean) | Low dose group (mean) | Medium dose group (mean) | High dose group (mean) | Placebo group (median) | Etanercept 25 mg BIW group (median) | Etanercept 50 mg BIW group (median) |
|---|---|---|---|---|---|---|---|
| Duration of psoriasis (years) | 18.4 ± 0.9 | 19.3 ± 0.9 | 18.5 ± 0.9 | 18.6 ± 0.9 | 17.5 (range 1.4–51.2) | 21.5 (range 0.8–64.6) | 18.1 (range 0.8–60.5) |
| PASI score | 18.3 ± 0.6 | 18.2 ± 0.7 | 18.5 ± 0.7 | 18.4 ± 0.7 | 16.0 (range 7.0–62.4) | 16.9 (range 4.0–51.2) | 16.1 (range 7.0–57.3) |
| Affected body surface area (%) | 28.8 ± 1.4 | 27.7 ± 1.5 | 28.5 ± 1.6 | 29.9 ± 1.6 | 20.0 (range 10.0–95.0) | 23.0 (range 7.8–95.0) | 25.0 (range 10.0–80.0) |

| Efficacy | Placebo group | Low dose group | Medium dose group | High dose group | Placebo group | Etanercept 25 mg BIW group | Etanercept 50 mg BIW group |
|---|---|---|---|---|---|---|---|
| Results | 12 weeks | | | | 12 weeks | | |
| PASI 50 | 14 % | 41 %[a] | 58 %[a] | 74 %[a] | 9 % | 64 %[b] | 77 %[b] |
| PASI 75 | 4 % | 14 %[a] | 34 %[a] | 49 %[a] | 3 % | 34 %[b] | 49 %[b] |
| PASI 90 | 1 % | 3 %[a] | 12 %[a] | 22 %[a] | 1 % | 11 %[b] | 21 %[b] |
| Mean PASI improvement | 14.0 ± 2.6 | 40.9 ± 2.4[a] | 52.6 ± 2.7[a] | 64.2 ± 2.4[a] | NA | NA | NA |
| Results | 24 weeks | | | | 24 weeks | | |
| PASI 50 | NA | 58 % | 70 % | 77 % | NA | NA | NA |
| PASI 75 | 33 % | 25 % | 44 % | 59 % | 28 % | 45 % | 54 % |
| PASI 90 | NA | 6 % | 20 % | 30 % | NA | NA | NA |
| Mean PASI improvement | NA | 50.3 ± 2.5 | 62.1 ± 2.5 | 71.1 ± 2.2 | NA | NA | NA |

[a]$P < 0.001$ for comparison with placebo at week 12
[b]$P < 0.0001$ for comparison with placebo at week 12

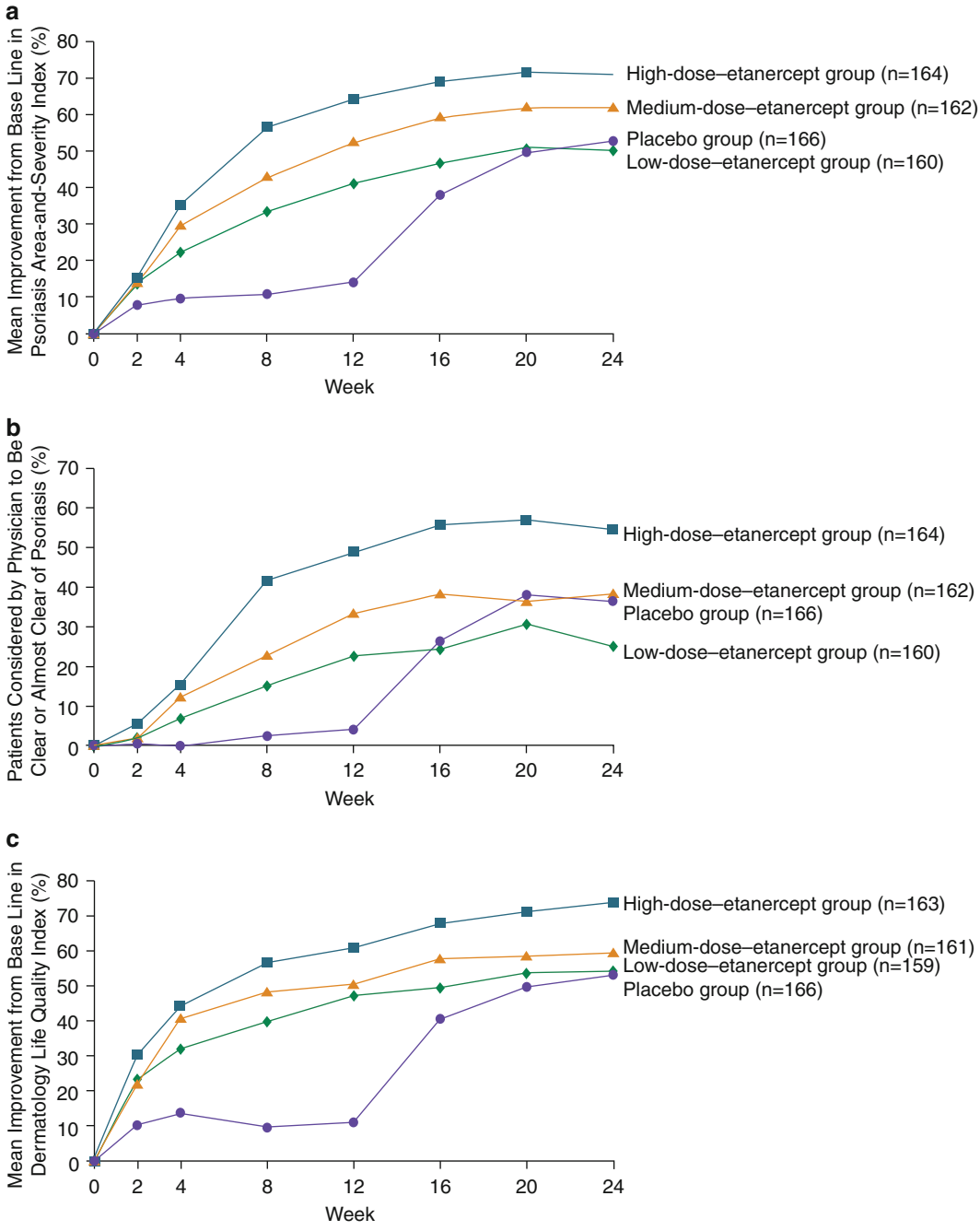


**Fig. 12.3** Clinical response to etanercept therapy measured by the Psoriasis Area-and-Severity Index (panel **a**), the Physician's Static Global Assessment (panel **b**), and the Patient-Reported Dermatology Life Quality Index (panel **c**). After week 12, the original placebo group received etanercept treatment [9] (Used with permission from the Massachusetts Medical Society Publishing)

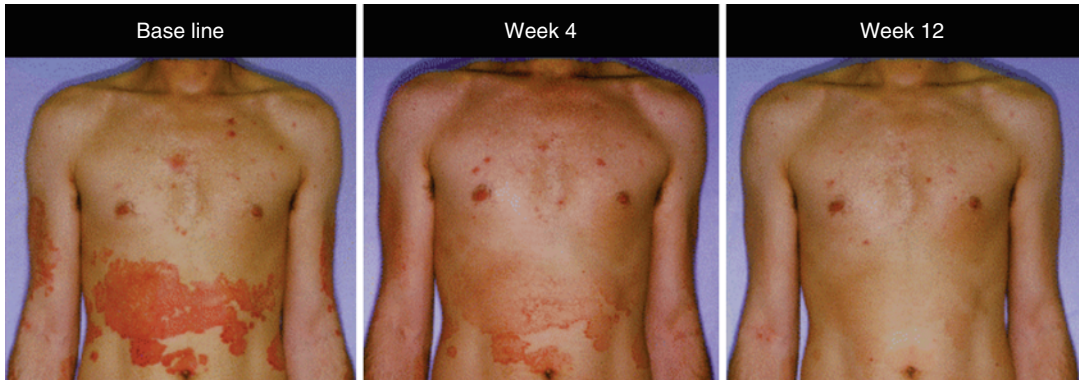


**Fig. 12.4** Etanercept provided improvement in psoriasis: photographs of a patient in the etanercept 50 mg twice weekly group at baseline, week 4, and week 12 [8] (Used with permission from John Wiley and Sons Publishing)

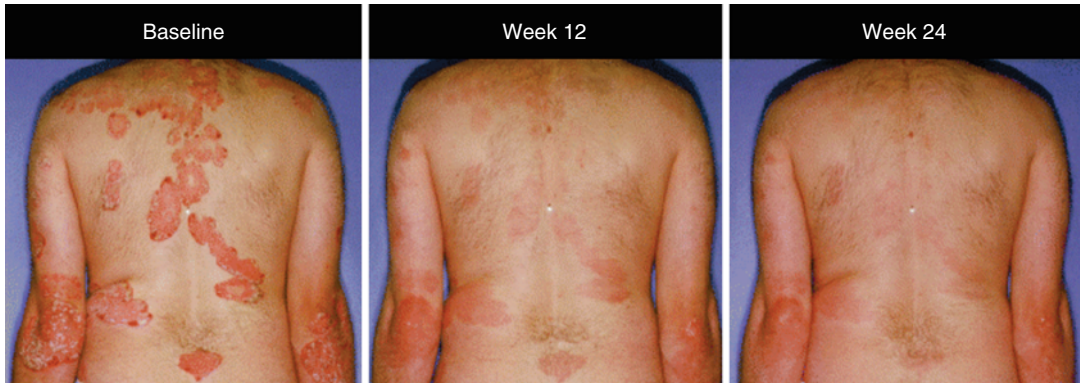


**Fig. 12.5** Psoriasis improvement was maintained after dose reduction: photographs of a patient in the etanercept 50 mg twice weekly (BIW) group at baseline and week 12, and at week 24 (after 12 weeks of etanercept 25 mg BIW) [8] (Used with permission from John Wiley and Sons Publishing)

Significant improvement in psoriasis associated depression in patients treated with etanercept (compared to placebo) was demonstrated in a study that included assessment of the Beck depression inventory (BDI) and Hamilton rating scale for depression (HAM-D) [12].

A recent retrospective study investigating potential racial and ethnic differences found no differences in safety and efficacy variables (including adverse event rates and improvements in body surface area of involvement) between Caucasians, African-Americans, and Hispanics [13].

## Combination Therapy

Etanercept has been used safely in combination with other agents to enhance or maintain efficacy. Adjunctive topical calcipotriene 0.005 % and betamethasone dipropionate 0.064 % ointment [14], narrow-band UVB phototherapy [15], or methotrexate [16, 17], has been reported in published trials. The above adjunctive therapies can be considered in cases of waning or insufficient efficacy with etancercept monotherapy. However, potential risks and benefits must be considered

and appropriate monitoring is advised when combining therapies (especially those with potential immunosuppressive and/or malignancy risks).

## Safety

A general outline recommending risk assessment prior to commencing etanercept therapy, as well as recommendations for specific monitoring of symptoms and routine laboratory tests when initiating and maintaining etanercept therapy, is provided (Table 12.2) [4, 5, 18, 19].

As with other anti-TNF therapies, serious and opportunistic infections, (including bacterial, mycobacterial, fungal, viral, parasitic) have been observed in patients receiving etanercept. Reactivation of latent tuberculosis (TB) is a risk for this class of biologics and therefore screening for TB is required at baseline and annually [4, 5, 18, 19]. Fatal cases of reactivation of hepatitis B virus have also been reported and as such, baseline screening for viral hepatitis is required before initiation of treatment with etanercept [4, 5, 18, 19].

Other non-infectious considerations include congestive heart failure (CHF) and demyelinating disorders. Worsening of CHF and rare new onset cases of CHF have been reported in patients taking etanercept [3–5, 19, 20]. In addition, there are rare reports of exacerbation or new onset of demyelinating disorders among etanercept patients [4, 5, 19]. Therefore, TNF inhibitors, including etanercept should be considered with caution in patients with pre-existing CHF or demyelinating disorders [4, 5, 19].

## Malignancies

Malignancies have been reported in patients using etanercept and other anti-TNF agents. Rates of malignancies among patients with anti-TNF therapy have been analyzed using clinical trial data and large rheumatologic disease and biologic therapy databases [21–25]. Reported malignancies include lymphomas, non-melanoma skin cancers (NMSC), leukemia, and rare cases of Merkel Cell carcinoma (see Fig. 12.6) [26].

Among adult psoriasis patients treated with etanercept in clinical trials (n=4,410) up to 36 months, the observed rate of lymphoma was comparable to that in the general population [5]. No cases were observed in the etanercept- or placebo-treated patients during the controlled portions of these trials. However, in the controlled portions of etanercept trials in adult rheumatology patients - with rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) – two lymphomas were observed among etanercept treated patients versus 0 among control patients [5]. In combined data of controlled and uncontrolled portions of clinical trials of etanercept for adult rheumatology patients (RA, AS, and PsA) representing 12,845 patient years of therapy, the rate of lymphoma observed (0.10 per 100 patient-years) was threefold higher than that expected in the general US population based on the Surveillance, Epidemiology, and End Results (SEER) Database [5]. However, higher rates of lymphoma (up to several-fold) have been reported in the RA patient population compared to the general population [5].

Higher rates of non-melanoma skin cancer have been observed among psoriasis patients treated with etanercept. In controlled clinical trials of adult psoriasis patients (n=1,245), the rate of NMSC observed was 3.54 cases per 100 patient-years among those treated with etanercept versus 1.28 cases per 100 patient-years among control patients [5]. Rare cases of Merkel cell carcinoma have been reported in the post-marketing period [5]. For all etanercept patients at risk for skin cancer, full body skin examinations are recommended [5].

Excluding lymphoma and NMSC, no difference in exposure-adjusted rates of malignancies between etanercept and placebo-treated patients have been observed in the controlled portions of etanercept clinical trials (across all indications) [5, 27].

In the pediatric population, malignancies including lymphoma and leukemia have been reported, particularly among children or adolescents taking concomitant immunosuppressive agents [5].

**Table 12.2** Recommended risk assessment prior to introduction etanercept therapy (a) and recommended symptom and laboratory monitoring prior to initiating and while maintaining etanercept therapy (b) [4, 5, 18, 19]

| (a) |
|---|
| *Contraindications* |
| Concurrent live vaccination |
| History of etanercept-induced hypersensitivity reactions |
| Use in those with Wegener's granulomatosis receiving immunotherapy (associated with higher incidence of solid malignancies and does not improve clinical outcome if compared to standard therapy alone) |
| Septicemia, or active infection |
| *Relative contraindications/cautions* |
| Pregnancy (pregnancy category B), inadequate data for risk assessment for breast feeding, caution advised |
| Caution if CHF, especially CHF grade III–IV New York Heart Association (NYHA) |
| Caution in patients with or at risk for demyelinating disorders |
| Caution if HBV carrier |
| Personal history of frequent or recurrent infections, including history of chronic open wounds. Caution if TB risk, history of latent TB, or if patient travels or resides to regions with endemic TB or mycoses |
| Caution if moderate to severe alcoholic hepatitis |
| Personal history of uncontrolled diabetes mellitus |
| History of malignancy within the past 5 years or in patients with increased malignancy risk |
| History of blood disorders or myelosuppression |
| Caution in patient >65 years of age |
| Caution use in patients with concurrent immunosuppressants- anakinra or abatacept is not recommended with etanercept therapy |
| In patients with a significant exposure to varicella virus, etanercept therapy should be temporarily discontinued and considered for prophylactic treatment with varicella zoster immune globulin |
| Caution in patients with latex allergy- the needle cover of prefilled syringes and needle cover within needle cap contain latex-derived components |
| (b) |
| *Baseline monitoring* |
| PPD (baseline and annually) or Quantiferon Gold (for latent TB) is required, along with CXR for exclusion of active TB |
| Liver Function Test (baseline and every 2–6 months), Hepatitis B and C testing, Complete Blood Count (baseline and every 2–6 months), Basic Chemistry (baseline and every 2–6 months), and optional baseline Antinuclear Antibodies (ANA) |
| *Monitoring of signs and symptoms* |
| Discontinue etanercept therapy during active infection. Consider empiric anti-fungal treatment for those at risk for invasive fungal infections or for patients residing or travelling to regions where mycoses are endemic |
| Discontinue etanercept 1–2 weeks prior to surgery, and reinitiation of etanercept therapy 2 weeks after uncomplicated surgical procedures |
| Discontinue etanercept therapy 4 weeks prior to and reinitiate 4 weeks after vaccination (to prevent decreased vaccination efficacy) |
| Discontinue etanercept therapy if malignancy detected, with the exception of cutaneous basal cell carcinoma |
| Periodic evaluation of signs and symptoms of opportunistic infections |
| Yearly examination for skin cancer detection |
| If pregnancy occurs, discuss risks versus benefits (pregnancy category B drug) |
| Consider risks versus benefits in patients with cardiovascular co-morbidities |
| Provide annual inactivated Influenza vaccination, preferably prior to biologic therapy initiation |
| Monitor hepatitis B carriers for reactivation during and several months after initiating etanercept therapy. If reactivation occurs, consider discontinuing etanercept and beginning anti-viral therapy |

*CHF* congestive heart failure, *PPD* purified protein derivation, *CXR* chest X-ray

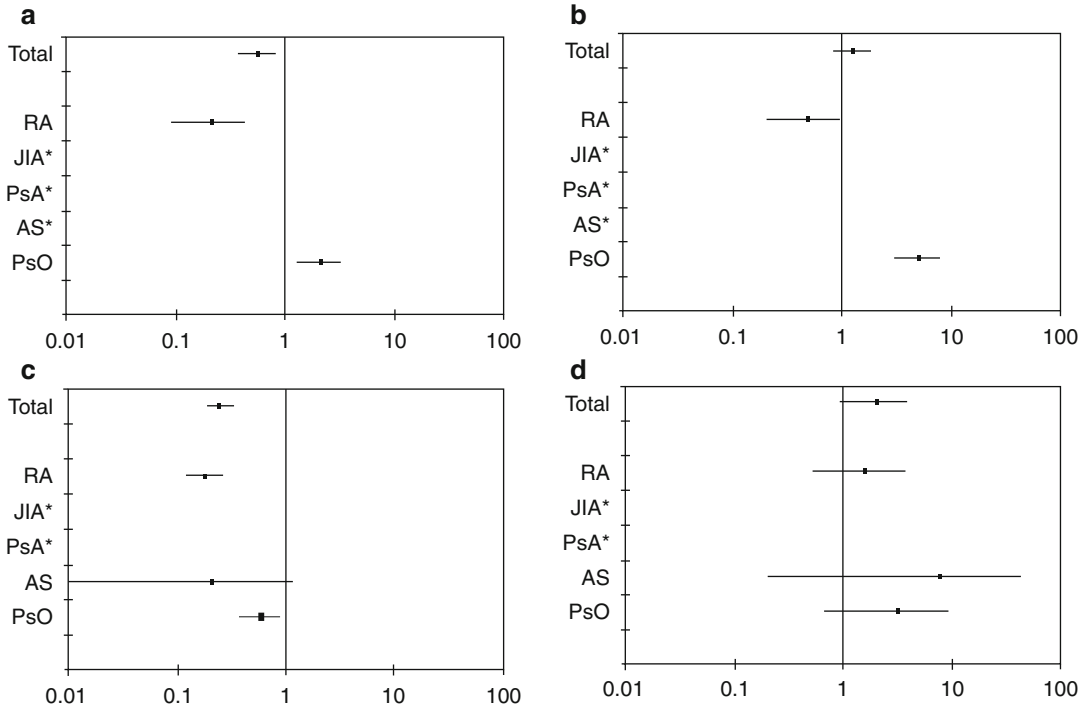


**Fig. 12.6** SIRs with 95 % CIs for dermatologic malignancies in patients receiving etanercept in clinical trials. Data are presented for (**a**) cutaneous SCCs-high-sun-exposure comparison, (**b**) cutaneous SCCs-low-sun-exposure comparison, (**c**) BCCs-high-sun-exposure comparison, and (**d**) melanomas. *AS* ankylosing sondylitis, *BCCs* basal cell carcinomas, *JIA* juvenile idiopathic arthritis, *PSA* psoriatic arthritis, *PsO* psoriasis, *RA* rheumatoid arthritis, *SCCs* squamous cell carcinomas, *SIR* standardized incidence ratio. *SIR not available (no observed cases) [26] (Used with permission from *Journal of Drugs in Dermatology*)

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# Adalimumab

# 13

Elizabeth J. Horn and Jennifer C. Cather

**Abstract**

Psoriasis is common, chronic, disease of the immune system, affecting 2–3 % of the population worldwide. Characterized by scaling, erythema, and thickened plaques on the skin, some also develop psoriatic arthritis, a painful and potentially debilitating inflammatory arthritis. Psoriasis is associated with a number of comorbidities, and psoriasis patients often report poor health-related quality of life. Adalimumab is a fully humanized monoclonal antibody that blocks tumor necrosis factor alpha (TNF-α), a cytokine elevated during inflammation. Adalimumab is approved for psoriasis and psoriatic arthritis, among other indications for immune diseases. Clinical trials have shown adalimumab to be efficacious and well tolerated, with a safety profile similar to other TNF-inhibitors in the class. As with any immunosuppressive therapy, appropriate screening and monitoring of patients receiving adalimumab is required. Here, we review adalimumab, an important addition to the psoriasis treatment armamentarium.

**Keywords**

Psoriasis • Psoriatic arthritis • Adalimumab • TNF-α • TNF inhibitor • TNF-blocker • Clinical trials • Health related quality of life

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## Introduction

Psoriasis is an immune-mediated inflammatory disease that affects 2–3 % of the population worldwide [1]. Psoriasis patients experience episodic flares with few spontaneous remissions. Psoriasis is characterized by scaling, erythema, and thickened plaques on the skin (Fig. 13.1). In addition to physical symptoms, psoriasis patients often experience psychosocial issues and have poor health related quality of life (HRQoL) [2].

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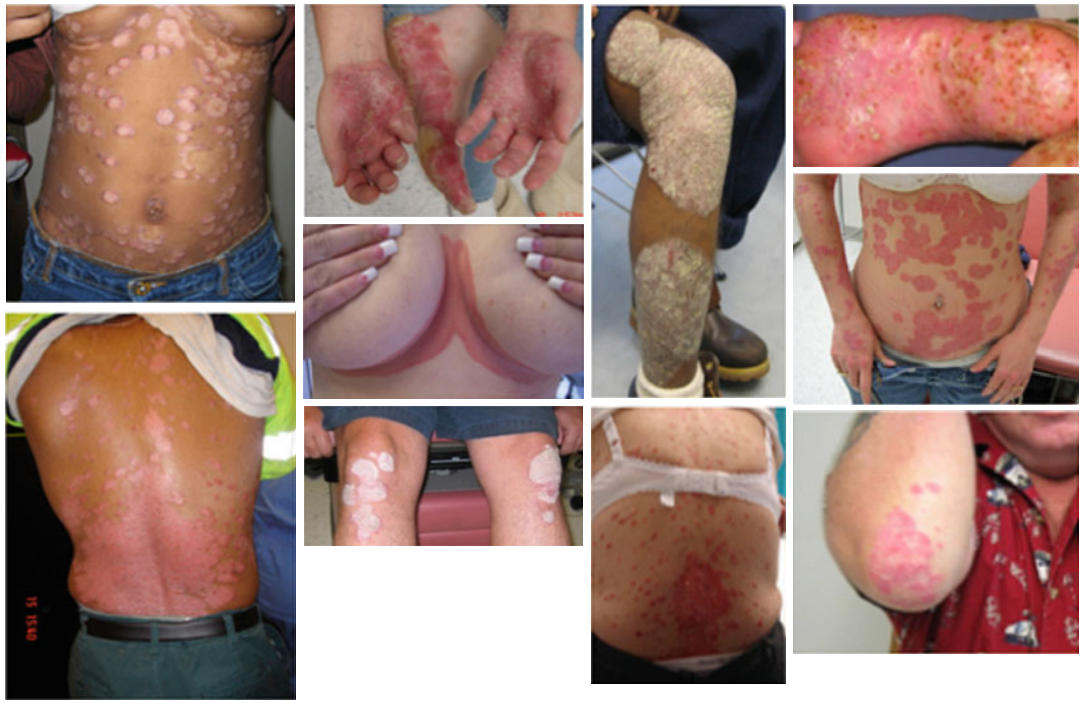

**Fig. 13.1** The many forms of psoriasis

Psoriasis is a complex disease, and onset results from a combination of genes and environment [3]. Some patients with psoriasis also develop psoriatic arthritis, a painful and potentially debilitating inflammatory arthritis (6–42 % depending on the population studied) [4]. Psoriasis is also associated with a number of comorbidities, including obesity, cardiovascular disease, diabetes (Type II), and metabolic syndrome [5–7]. Individuals with psoriasis may also be at risk for other autoimmune diseases, such as Crohn's disease [8]. A variety of treatment options are available, and patients with moderate to severe psoriasis are candidates for systemic therapy [9, 10]. Fortunately a number of biologic agents have been approved for psoriasis, and additional molecules are currently being studied in clinical trials [11]. Here we review adalimumab, (brand name Humira), a fully humanized monoclonal IgG1 antibody that blocks tumor necrosis factor alpha (TNF-α), a cytokine elevated in inflammation [12]. Adalimumab binds both soluble and membrane-bound TNF-α, and blocks TNF-α interactions at the p55 and p75 TNF receptors.

## Adalimumab

Adalimumab was first approved in 2002 for rheumatoid arthritis. Today, it is approved for ankylosing spondylitis, Crohn's disease, juvenile idiopathic arthritis, plaque psoriasis, psoriatic arthritis, and rheumatoid arthritis. Adalimumab is also being studied in hidradenitis suppurativa [13]. Adalimumab is given by subcutaneous injection, with dosing dependent on indication (Table 13.1). Adalimumab is available as a single-use prefilled pen (40 mg/0.8 mL) or a single-use prefilled glass syringe (40 mg/0.8 mL or 20 mg/0.4 mL). Adalimumab was the third TNF-inhibitor approved for psoriatic arthritis and psoriasis, and other approved TNF-inhibitors include etanercept (brand name Enbrel), infliximab (brand name Remicade), and golimumab (brand name Simponi, only approved for psoriatic arthritis) (Table 13.2).

A number of guidelines of care for psoriasis have been published, including American Academy of Dermatology guidelines [4, 10, 14–16], German

guidelines [17, 18], Canadian guidelines [19], European guidelines [20, 21], and British guidelines [22]. Consensus statements have also explored monitoring and vaccinations with biologics [23] and monitoring comorbidities [24], while others have examined psoriasis treatment in a case-based manner [16, 25].

Here we provide an overview of adalimumab in psoriasis and psoriatic arthritis. We review the pivotal phase III clinical trials for psoriasis and psoriatic arthritis, and ongoing safety and monitoring considerations. We also provide insight into treatment of special populations with adalimumab.

**Table 13.1** Adalimumab indications and dosing

| Indication | Approval date | Dose |
|---|---|---|
| Ankylosing spondylitis | July 2006 | 40 mg eow |
| Crohn's disease | February 2007 | 160 mg on day 1 (4–40 mg injections or 2–40 mg injections over 2 consecutive days), followed by 80 mg on day 15, followed by a maintenance dose of 40 mg eow starting day 29 |
| Juvenile idiopathic arthritis | February 2008 | 20 mg eow [(15 kg (33 lbs) to <30 kg (66 lbs)]; 40 mg eow [≥30 kg (66 lbs)] |
| Plaque psoriasis | January 2008 | 80 mg initial dose; 40 mg eow starting 1 week after initial dose |
| Psoriatic arthritis | October 2005 | 40 mg eow |
| Rheumatoid arthritis | December 2002 | 40 mg eow |

*eow* every other week

## Adalimumab in Clinical Trials for Psoriasis and Psoriatic Arthritis

A number of clinical trials have been conducted for psoriasis and psoriatic arthritis. REVEAL (Randomized controlled evaluation of adalimumab every other week dosing in moderate to severe psoriasis trial), CHAMPION (Comparative study of adalimumab versus methotrexate versus placebo in psoriasis patients), and ADEPT (Adalimumab effectiveness in psoriatic arthritis trial) are explained in detail below.

### Reveal

The pivotal phase III psoriasis trial, REVEAL, was a 52-week, prospective multicenter, randomized, double-blind placebo controlled trial of 1,212 moderate to severe psoriasis patients, designed to examine efficacy, safety, and tolerability [12]. The criteria for enrollment was similar to many biologics trials, where individuals were at least 18 years old, had been diagnosed with moderate to severe psoriasis for at least 6 months, and had stable psoriasis for at least the past 2 months. Here, moderate to severe psoriasis was defined as 10 % or more body surface area affected, a psoriasis area severity index (PASI) of 12 or greater, or a physician's global assessment (PGA) of at least moderate severity at the baseline visit. Treatment washout periods were

**Table 13.2** Biologics approved for psoriasis and psoriatic arthritis

| Biologic | Target | Approval psoriasis | Approval psoriatic arthritis |
|---|---|---|---|
| Adalimumab | TNF-alpha | 2008 | 2005 |
| Alefacept[a] | LFA-3 | 2003; discontinued 2011 | Not applicable |
| Efalizumab[b] | CD11a | 2003; withdrawn 2009 | |
| Etanercept | TNF-alpha | 2004 | 2002 |
| Golimumab | TNF-alpha | Not applicable | 2009 |
| Infliximab | TNF-alpha | 2006 | 2005 |
| Ustekinumab | IL12/IL23 | 2009 | 2013 |

[a]Alefacept voluntarily discontinued in 2011
[b]Efalizumab withdrawn due to safety concerns in 2009

**Table 13.3** Baseline demographics and disease characteristics

| Characteristic | Placebo (n = 398) | Adalimumab (n = 814) |
|---|---|---|
| Age, mean (SD), y | 45.4 (13.4) | 44.1 (13.2) |
| Male, n (%) | 257 (64.6) | 546 (67.1) |
| Caucasian, n (%) | 359 (90.2) | 742 (91.2) |
| Weight, mean (SD), kg | 94.1 (23.0) | 92.3 (23.0) |
| Duration of psoriasis, mean (SD), y | 18.4 (11.94) | 18.1 (11.91) |
| History of PsA, n (%) | 113 (28.4) | 224 (27.5) |
| BSA affected, mean (SD), % | 25.6 (14.76) | 25.8 (15.51) |
| PASI score, mean (SD) | 18.8 (7.09) | 19.0 (7.08) |
| PGA, n (%) | | |
| Moderate | 220 (55.3) | 417 (51.2) |
| Severe | 155 (38.9) | 346 (42.5) |
| Very severe | 23 (5.8) | 51 (6.3) |
| Previous psoriasis treatment[a], n % | | |
| Topical therapy | 290 (72.9) | 618 (75.9) |
| Phototherapy | 59 (14.8) | 138 (17.0) |
| Systemic nonbiologic | 88 (22.1) | 188 (23.1) |
| Systemic biologic | 53 (13.3) | 97 (11.9) |
| Laser | 0 | 1 (0.1) |

Reprinted with permission from Menter et al. [12]
All data shown are for patients in period A. Differences in baseline characteristics for patients in periods B and C vs. period A were minimal
*BSA* body surface area, *PASI* psoriasis area and severity index, *PGA* physician's global assessment, *PsA* psoriatic arthritis
[a]Within 12 months before study treatment

**Table 13.4** Adalimumab efficacy in REVEAL trial at week 16

| Group | PASI 75 (%) | PASI 90 (%) | PASI 100 (%) |
|---|---|---|---|
| Placebo | 7 | 2 | 1 |
| Adalimumab | 71 | 45 | 20 |

required: topical therapy (2 weeks), phototherapy (2 weeks for UVB phototherapy and 4 weeks for PUVA), systemic therapies (4 weeks), and biologic therapies (12 weeks, or 6 weeks for efalizumab). Low to mid-potency topical corticosteroids were permitted on the palms, soles, face, and intertriginous areas. All potential participants were screened for latent tuberculosis, and if latent disease was present, individuals could enroll as soon as appropriate chemoprophylaxis for tuberculosis was started. Patients with a history of chronic recurrent infections, demyelinating disease, cancer, or lymphoproliferative disease were excluded (Table 13.3). Patients were randomized 2:1, adalimumab to placebo. The first 16 weeks were placebo controlled, with one group receiving 80 mg adalimumab at week 0 followed by 40 mg adalimumab at week 1 and then every other week thereafter for 15 weeks, while the other group received placebo. At week 16, patients in the placebo arm received 80 mg adalimumab, followed by 40 mg adalimumab every other week beginning in week 17. Also at week 16, all patients achieving a 75 % or greater response rate were entered into a 17-week open label extension, receiving 40-mg adalimumab every other week. Those who did not achieve PASI 75 were entered into another open label extension, receiving 40 mg every other week. At week 33, loss of adequate response was examined with patients who had achieved PASI 75 at weeks 16 and 33, and they were re-randomized 1:1 to adalimumab or placebo.

At week 16, the primary endpoint, 71 % of patients in the adalimumab group had achieved at least a 75 % improvement in PASI score, compared to 7 % of placebo using intent to treat (ITT) analysis (Table 13.4). In ITT, those lost to follow-up are considered non-responders in the analysis. PASI 90 and PASI 100 were achieved by 45 and 20 %, respectively, in the adalimumab group at 16 weeks. At week 24, 70 % of all patients had achieved PASI 75. At week 33, the loss of adequate response phase was initiated. Patients randomized to placebo lost response more frequently (28 % compared to 5 % in the adalimumab group), and time to loss of adequate response was shorter in the placebo group.

Adalimumab was well-tolerated in this study. The majority of adverse effects (AEs) were mild to moderate. Less than 2 % of patients discontinued use due to adverse events, and there were no deaths. Infections included upper respiratory tract infections, nasopharyngitis, and sinusitis. Injection site reactions were more common in the adalimumab group, occurring in 3.2 % of the adalimumab group compared to 1.8 % of the placebo group. Serious adverse events (SAEs) were

**Table 13.5** Adverse events in REVEAL at 16 weeks

| Adverse event, n (%) | Placebo (n=398) | Adalimumab (n=814) |
|---|---|---|
| Any AE | 221 (55.5) | 506 (62.2) |
| Mild or moderate AE | 211 (53.0) | 484 (59.5) |
| Serious AE | 7 (1.8) | 15 (1.8) |
| Serious infectious AE | 4 (1.0) | 5 (0.6) |
| Infectious AE | 89 (22.4) | 235 (28.9)* |
| AE leading to withdrawal | 8 (2.0) | 14 (1.7) |
| Malignancies, excluding NMSC | 1 (0.3) | 2 (0.2) |
| NMSC | 1 (0.3) | 4 (0.5) |
| Upper respiratory tract infection | 14 (3.5) | 59 (7.2)† |
| Nasopharyngitis | 26 (6.5) | 43 (5.3) |
| Headache | 15 (3.8) | 40 (4.9) |

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Events shown include AEs that occurres in ≥5 % of patients in any treatment group and AEs of particular interest
*AE* adverse event, *NMSC* nonmelanoma skin cancer
*$p=0.19$ vs. placebo by Fisher's exact test
†$p=.01$ vs. placebo

**Table 13.6** Adalimumab efficacy in REVEAL during open label extension

| Weeks | PASI 75 (%) | PASI 90 (%) | PASI 100 (%) |
|---|---|---|---|
| 100 | 83 | 59 | 33 |
| 160 | 75 | 50 | 31 |

comparable in both groups at 16 weeks (Table 13.5). The REVEAL trial had an open label extension period that enabled participants to receive adalimumab therapy for approximately 3 years [26]. For those who achieved PASI 75, efficacy was well maintained over the 3-year period, using a last observation carried forward (LOCF) analysis (Table 13.6). A subanalysis examined consequences of when therapy was stopped and restarted with adalimumab [27]. Efficacy was slightly higher for those who received continuous adalimumab therapy compared to the retreatment group (75 % compared to 73 % at week 108 using LOCF). Retreatment response was greatest in patients who had experienced PASI 50 or greater at the time retreatment was started.

Because 16 weeks is not sufficient for identifying AEs, a 3-year extension provides more insight into potential safety concerns. During the 3-year open label extension, adalimumab was well tolerated [26]. There were two cases of tuberculosis, five candidiasis infections, and two deaths (coronary artery disease in a 75-year old mean and unknown cause of death in a 47-year old man). There were no cases of lymphoma, lupus-like syndrome, or demyelinating disorders during this period (Table 13.7). One of the limitations of the open label extension is that individuals whose dose escalated to 40-mg every week were considered off protocol, and LOCF prior to dose escalation was used in the analysis, although they were still receiving adalimumab.

In addition to the physical symptoms of psoriasis, psoriasis can also impact an individual's ability to work [28]. The effect of adalimumab on work productivity was examined using the Work Productivity and Activity Impairment (WPAI) questionnaire during the REVEAL trial [29]. At 16 weeks, adalimumab decreased psoriasis related work productivity and activity impairment, and improvements in WPAI were seen in the adalimumab treated group compared to the placebo group, 15.5 and 11.1 %, respectively. Individuals who were unemployed and had high scores of total work productivity impairment and total activity impairment also had measurably more severe psoriasis. When psoriasis symptoms worsened, patients described increases in pain, increased WPAI scores, and greater impairment in mental and physical component summaries, respectively [30].

A number of subanalyses were also conducted from the REVEAL trial. One analysis examined if there were any differences in adalimumab efficacy or safety between different patient subgroups during the initial 16 weeks of the trial [31]. While improvement in psoriasis was seen consistently across most subgroups, decreased response to adalimumab occurred in patients with greater weight or body mass index. This was most apparent in obese individuals (BMI ≥30), where 65 % achieved PASI 75, compared to 75 % of overweight individuals (BMI ≥25 but <30), and 79 % of individuals with a normal BMI (BMI

**Table 13.7** Adverse events in REVEAL during open label extension. Numbers and rates (as events per 100 PY) of adverse events over more than 3 years of adalimumab exposure

| | All adalimumab exposure | Year 1 | Year 2 | Year ≥3 |
|---|---|---|---|---|
| | N = 1,159 | N = 1,159 | N = 621 | N = 443 |
| | 2,043.8 PY | 1,009.5 PY | 504.8 PY | 529.5 PY |
| Any adverse event | 5,009 (245.1) | 3,174 (314.4) | 978 (193.7) | 857 (161.9) |
| Serious adverse events | 149 (7.3) | 60 (5.9) | 40 (7.9) | 49 (9.3) |
| Serious infections | 30 (1.5) | 18 (1.8) | 3 (0.6) | 9 (1.7) |
| Adverse events leading to discontinuation | 96 (4.7) | 61 (6.0) | 14 (2.8) | 21 (4.0) |
| Adverse events of interest | | | | |
| Tuberculosis | 2 (<0.1) | 1 (<0.1) | 0 | 1 (0.2) |
| Opportunistic infection excluding tuberculosis | 5 (0.2)[a] | 2 (0.2) | 2 (0.4) | 1 (0.2) |
| Allergic reactions | 12 (0.6) | 8 (0.8) | 2 (0.4) | 2 (0.4) |
| Congestive heart failure | 6 (0.3) | 1 (<0.1) | 1 (0.2) | 4 (0.8) |
| Malignancies, excluding NMSC and lymphoma | 15 (0.7)[b] | 5 (0.5) | 5 (1.0) | 5 (0.9) |
| NMSC | 17 (0.8)[c] | 9 (0.9) | 3 (0.6) | 5 (0.9) |
| Lymphoma | 0 | 0 | 0 | 0 |
| Lupus-like syndrome | 0 | 0 | 0 | 0 |
| Demyelinating disorder | 0 | 0 | 0 | 0 |

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Exposure includes treatment with adalimumab at 40 mg every other week (eow) in REVEAL and the open-label extension study, as described in the Methods section. Years 1, 2, and ≥3 are nonoverlapping intervals from the start of adalimumab treatment, by patient; maximal continuous exposure to adalimumab 40 mg eow was 3.92 years
*N* number of patients, *NMSC* nonmelanoma skin cancer, *PY* patient-years of drug exposure
[a]All were events of candidiasis, including two oral and one oropharyngeal; none were serious adverse events
[b]Seven prostate cancer and one each of: breast cancer, malignant melanoma in situ, neoplasm prostate, neuroendocrine tumor, renal cell carcinoma, throat cancer, thyroid cancer, and tongue neoplasm malignant stage unspecified
[c]Thirteen basal cell carcinomas, three squamous cell carcinomas (all year 1), and one skin neoplasm (year 1)

18.5 < 25). There were no significant differences in SAEs between adalimumab and placebo across subgroups. Subgroups examined included age, sex, race, baseline weight intervals, baseline body mass index, disease duration, baseline severity, prior treatments and comorbidities.

Another subanalysis explored the effects of comorbidities (e.g. hypertension, psoriatic arthritis, hyperlipidemia, obesity, depression, arthritis, diabetes mellitus, and cardiovascular disease) on patient reported outcomes [32]. Comorbidities were associated with greater impairment in HRQoL and work productivity, measured by the Dermatology Life Quality Index (DLQI), Short Form 36 (SF-36) health survey, and WPAI questionnaire. There were consistent improvements in DLQI, SF-36 physical component summary score, SF-36 mental components summary score, and WPAI in the group receiving adalimumab at 16 weeks. In an analysis of a phase II study, patients receiving adalimumab also experienced a reduction of symptoms of depression compared to the placebo group, measured by the Zung Self-rating Depression score [33].

## Champion

Another psoriasis trial of interest, CHAMPION, was conducted in Europe and Canada, and included a comparator arm of methotrexate as well as a traditional placebo arm [34]. Patient inclusion criteria and washout periods were similar to the REVEAL trial (described in detail above) except patients were required to be methotrexate and TNF-inhibitor naïve. CHAMPION

was a randomized, double blind, double dummy placebo controlled trial, and 217 patients were randomized 2:2:1 to adalimumab (40 mg every other week after an 80 mg loading dose), methotrexate (7.5–25 mg weekly), or placebo.

The primary endpoint was patients achieving a 75 % improvement in PASI score at 16 weeks. At week 16, 79.6 % of the adalimumab group achieved PASI 75, compared to 35.5 % of the methotrexate group and 18.9 % of the placebo group. In addition, 16.7 % of the adalimumab group and 7.3 % of the methotrexate group achieved PASI 100. This study has been acknowledged for using the traditional systemic therapy methotrexate as an active comparator. It has also been criticized, because the methotrexate arm was conducted for such a short time period, and a successful methotrexate regimen typically takes a longer period of time and has additional dose modifications.

Many patients reported adverse events, including 73.8 % of the adalimumab group, 80.9 % of the methotrexate group and 79.2 % of the placebo group. Most adverse events were mild. Some (5 % or 15 patients) withdrew from the study, and eight of the withdrawals were for adverse events, including one from the adalimumab group, six from the methotrexate group, and one from the placebo group. Elevated liver enzymes were more common in the methotrexate group compared to the adalimumab or placebo groups, 9.1, 1.9, and 7.5 % respectively. An additional analysis of the CHAMPION trial examined adverse event free days during the comparator arm of the trial [35]. Those in the adalimumab group experienced more adverse-event free days (36.9 days) compared to those in the methotrexate (8.3 days) or placebo (6.7) groups over the 16-week period. While these data are encouraging, a limitation is the short duration of the comparator arm, allowing only those adverse events occurring within the first 16 weeks to be captured.

## ADEPT

Adalimumab has also been studied in psoriatic arthritis. ADEPT was a phase III randomized, double-blind, parallel-group, placebo controlled trial examining adalimumab efficacy and safety in psoriatic arthritis patients [36]. Like other psoriatic arthritis trials, patients who had moderately to severely active psoriatic arthritis and a history of inadequate response to non-steroidal anti-inflammatory drugs (NSAIDS) were eligible to participate. Patients were stratified by methotrexate use and psoriasis skin involvement (≥3 % BSA or <3 %). Approximately half of patients were taking methotrexate at baseline. Patients in the adalimumab arm received 40 mg adalimumab subcutaneously every other week for 48 weeks. If improvement was not seen at week 12 (defined as at least a 20 % decrease in both swollen and tender joint counts on two consecutive visits), participants could receive corticosteroids or disease modifying anti-rheumatic drugs (DMARDS). Primary endpoints were the American College of Rheumatology 20 % improvement (ACR20) response at week 12 and changes in modified total Sharp score (mTSS) of structural damage at week 24. In addition, HRQoL was measured in all patients. For those patients who also had 3 % or more body surface area of psoriasis, skin improvement was also measured.

At 12 weeks, 58 % of the adalimumab group achieved ACR20, compared to 14 % of the placebo group (Table 13.8). Patients in the adalimumab group had a modified Psoriatic Arthritis Response Criteria (PsARC) response rate of 62 % at week 12, and 60 % at week 24, compared to placebo rates of 26 % at week 12 and 23 % at week 24. Adalimumab also inhibited joint destruction, as is seen with the TNF-inhibitors etanercept and infliximab [37]. Radiographs were taken at baseline and at week 24. The mean change in mTSS was −0.2 for patient receiving adalimumab compared to 1.0 for those receiving placebo. Erosion scores were examined, and there was improvement in those receiving adalimumab (mean change 0) compared to placebo (mean change 0.6). When joint space narrowing scores were examined, there was a mean change of −2 in the adalimumab group compared to 0.4 in those receiving placebo. Skin symptoms also improved in those patients who also had psoriasis (see Table 13.8). Improvements in health related quality of life, fatigue, and disability, measured using the DLQI, SF-36, Functional

**Table 13.8** Adalimumab efficacy in ADEPT at weeks 12 and 24

| Group | Week 12 | | | Week 24 | | |
|---|---|---|---|---|---|---|
| | **ACR20** (%) | **ACR50** (%) | **ACR70** (%) | **ACR20** (%) | **ACR50** (%) | **ACR70** (%) |
| Placebo (n = 161) | 14 | 4 | 1 | 15 | 6 | 1 |
| Adalimumab (n = 151) | 58 | 36 | 20 | 57 | 39 | 23 |
| | **PASI 50** (%) | **PASI 75** (%) | **PASI 90** (%) | **PASI 50** (%) | **PASI 75** (%) | **PASI 90** (%) |
| Placebo (n = 69) | 15 | 4 | 0 | 12 | 1 | 0 |
| Adalimumab (n = 69) | 72 | 49 | 30 | 75 | 59 | 42 |

Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Scale and HAQ DI were also seen [38]. HAQ DI scores improved significantly in patients receiving adalimumab compared to the control group.

Regarding safety data from the ADEPT trial, adverse events were similar between the adalimumab and placebo groups at 24 weeks [36]. There were 12 serious adverse events, 7 in the adalimumab group and 5 in the placebo group. Treatment was discontinued by four individuals because of adverse events, three in the adalimumab group and one in the placebo group. Alanine aminotransferase levels (ALT) were elevated more frequently in patients in receiving adalimumab, and in most cases ALT elevations were transient, resolving without discontinuing adalimumab. Elevated ALT levels were observed in individuals taking concomitant methotrexate, isoniazid, or alcohol.

At the end of the 24-week trial, participants could continue into a 24-week open-label extension [39]. Adalimumab was given 40 mg subcutaneously every other week after week 24 for 24 weeks. Radiographs were taken at week 48, and safety data was collected. Many (n = 285) enrolled in the open-label extension, including 138 from the adalimumab arm and 147 from the placebo arm. ACR responses were maintained at 48 weeks. Those on continuous adalimumab therapy had ACR20, ACR50, and ACR 0 rates of 48, 24, and 20 %, respectively at week 48. For those in the placebo group at week-24 crossing over to the adalimumab group, 48, 24, and 20 % achieved ACR20, ACR50, and ACR70, respectively, after 24 weeks of adalimumab treatment. ACR scores were obtained using an ITT analysis in the open label extension.

Skin improvement was also maintained at 48 weeks in the adalimumab group, with response rates of 67, 58, 46, and 33 % for PASI 50, PASI 75, PASI 90, and PASI 100, respectively. In the group receiving placebo until week 24, improvement was seen at week 48, with response rates of 61, 54, 33, and 31 % achieving PASI 50, PASI 75, PASI 90, and PASI 100. Improvements in disability measurements were also maintained at 48 weeks. When considering joint progression, patients receiving adalimumab the entire time had a mean mTSS of −0.1 at week 24, and −0.1 at week 48, indicating sustained control of progression. For those in the placebo group until week 24 that then received adalimumab until week 48, mTSS were 0.9 and 1.0, respectively, indicating potential halting of progression at week 48. Improvements were also seen in joint erosion scores and joint progression scores through 48 weeks.

Adalimumab was well tolerated during weeks 24–48, with the most common adverse events being upper respiratory tract infections, nasopharyngitis, and injection site reactions. One serious infection was reported (gastroenteritis) and ten other SAEs were reported. Elevated serum transaminase levels were also reported in nine patients. During the first 48 weeks there were no deaths and no reports of tuberculosis or granulomatous infections, demyelination, lymphoma or carcinoma, new antinuclear antibody formation, drug-induced lupus, or congestive heart failure.

Two-year data has also been published from the ADEPT trial, providing a better understanding of efficacy and safety in patients with psoriatic arthritis [38]. The open-label extension of the ADEPT trial was continued for 120 weeks, and data were available for 144 weeks after the

beginning of the ADEPT trial. ACR20, ACR50, and ACR70 scores at week 104 were 57.3, 27.8, and 29.9 % respectively. PsARC response rates were 65.9 % at week 48 and 63.5 % at week 104. All analyses used LOCF. Improvements in HRQoL and disability were also maintained. Inhibition of radiographic progression was also seen throughout the 144 weeks. From baseline to week 48, 102 patients had no progression, and 84.3 % of these had no radiographic progression at week 144, as evaluated with mTSS. From week 48 to 144, mean changes in mTSS were 0.1 for the placebo/adalimumab group and 0.4 for the adalimumab only group. A subanalysis of the ADEPT trial examined risk factors that predict radiographic progression [40]. Elevated baseline C-reactive protein (CRP) (≥1.0 mg/dl: odds ratio = 3.28) was a strong independent risk factor for joint progression, and treatment with adalimumab reduced the risk of progression fivefold. Individuals taking adalimumab also experienced lowering of CRP levels compared to controls.

Over the 2 years, adalimumab was well tolerated, and adverse events were similar to what is expected in rheumatoid arthritis patients. Throughout 2 years of exposure, there were five opportunistic infections, one patient had peritoneal tuberculosis and four patients experienced oral candidiasis. Additionally, there was one case of non-Hodgkin's B-cell lymphoma, two basal cell carcinomas, and one neuroendocrine carcinoma of the skin. There were no reports of central nervous system demyelinating disease, lupus-like syndrome, congestive heart failure, or adalimumab-related allergic reactions (Table 13.9).

## Practical Considerations for TNF-Inhibitors

There are a number of safety and practical considerations for all TNF-inhibitors, including adalimumab [10]. TNF-inhibitors are contraindicated in patients with active, serious infections. Testing for tuberculosis should be performed on all patients who will be treated with TNF-inhibitors. The Centers for Disease Control (CDC) has released guidelines regarding testing for tuberculosis [41]. Additionally, live vaccines should not be used in patients receiving TNF-inhibitors (Table 13.10). Demyelinating events, new onset or exacerbation of symptoms, may also occur under TNF-blockade. Anti-TNF therapy should not be used in patients with a history of demyelinating disease (e.g. multiple sclerosis, optic neuritis, and peripheral demyelinating disease such as Guillain-Barre syndrome). Caution should be used in patients with congestive heart failure. Patients should also be screened for hepatitis B prior to receiving therapy, as TNF-blockers may reactive hepatitis B in patients who are carriers of the disease. Many individuals experience injection site reactions, although most are minor. Malignancies, hepatotoxicity, and new onset psoriasis with anti-TNF therapy are also considerations.

Prior to initiating systemic therapy, including adalimumab, a physical examination should be performed and a full medical history taken. It is important to ask about age appropriate cancer screening (pap smears, mammograms and colonoscopies), cancer history, infection history, and vaccination history. A total body skin examination should also be performed. Clinicians should also inquire about social and lifestyle history, and family planning if relevant. A number of labs can also be requested, including a complete blood count (CBC) and comprehensive metabolic panel (CMP), Hepatitis screen (B and C), a human immunodeficiency virus (HIV) screen if warranted, and a tuberculosis test upon initiation and yearly. C-reactive protein (Hs-CRP) levels may also be valuable to measure at baseline and during treatment. Once systemic therapy is initiated, monitoring patients on therapy is vital. Patients should have periodic physical examinations. Patients must have a yearly PPD for tuberculosis and periodic CBC and liver function tests (LFT) are recommended. Initial screening and recommended monitoring for all TNF-inhibitors are reviewed in Table 13.11 [10].

## Adalimumab Safety Across Indications

A recent analysis explored adalimumab safety in 23,457 participants across 71 global trials,

**Table 13.9** Adverse events in ADEPT over 2 years. Summary of safety during 24-week double-blind, randomised controlled trial (ADEPT) and throughout 2 years of open-label adalimumab exposure

| AE | 24-week randomized, controlled trial | | | | 2 years of adalimumab exposure | |
|---|---|---|---|---|---|---|
| | Placebo | | Adalimumab | | | |
| | (N = 162) n (%) | (PY 71.1) Events (events/100 PY) | (N = 151) n (%) | (PY 66.8) Events (events/100 PY) | (N = 298) n (%) | (PY 676.5) Events (events/100 PY) |
| Any AE | 130 (80.2) | 487 (684.8) | 122 (80.8) | 430 (644.1) | 273 (91.6) | 1,977 (292.2) |
| Any AE least possibly related to study drug | 47 (29.0) | 138 (194.0) | 64 (42.4) | 156 (233.7) | 160 (53.7) | 556 (82.2) |
| Any severe AE | 11 (6.8) | 13 (18.3) | 5 (3.3) | 5 (7.5) | 54 (18.1) | 71 (10.5) |
| Any serious AE | 7 (4.3) | 11 (15.5) | 5 (3.3) | 5 (7.5) | 50 (16.8) | 62 (9.2) |
| Any AE leading to discontinuation of study drug | 5 (3.1) | 6 (8.4) | 6 (4.0) | 6 (9.0) | 20 (6.7) | 22 (3.3) |
| Infections | 64 (39.5) | 109 (153.3) | 68 (45.0) | 88 (131.8) | 207 (69.5) | 521 (77.0) |
| Serious infection | 1 (0.6) | 1 (1.4) | 1 (0.7) | 1 (1.5) | 15 (5.0) | 16 (2.4) |
| Malignancies | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (1.3) | 4 (0.6) |
| Lymphoma | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.3) | 1 (0.1) |
| Non-melanoma skin cancers | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.7) | 2 (0.3) |
| Other malignancies | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.3) | 1 (0.1) |
| Demyelinating disease | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Injection-site reaction | 5 (3.1) | 36 (50.6) | 10 (6.6) | 39 (58.4) | 43 (14.4) | 221 (32.7) |
| Opportunistic infection excluding tuberculosis[a] | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (1.3) | 4 (0.6) |
| Tuberculosis (peritoneal) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.3) | 1 (0.1) |
| Lupus and lupus-like syndrome | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Congestive heart failure | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Death[b] | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (1.0) | 3 (0.4) |

Reprinted with permission from Mease et al. [38]

*ADEPT* adalimumab effectiveness in psoriatic arthritis trial, *PY* patient-years

[a]All four patients had oral candidiasis

[b]One death occurred outside of the adverse event (AE) reporting period that extends 70 days (equivalent to five adalimumab half-lives) beyond the last adalimumab injection

rheumatoid arthritis (36 trials, n = 14,109), juvenile idiopathic arthritis (3 trials, n = 212) ankylosing spondylitis (4 trials, n = 1,684), psoriatic arthritis (4 trials, n = 837), psoriasis (13 trials, n = 3,010), and Crohn's disease (11 trials, n = 3,606) [42]. This analysis represented 12 years of adalimumab exposure, with 52.5 and 48.7 % of patients receiving concomitant immunosuppressant agents or concomitant systemic steroids, respectively. The majority of patients (60 %) were rheumatoid arthritis patients, and approximately two-thirds received concomitant therapy. The most frequently reported serious adverse events were infections, and these were most often seen in the rheumatoid arthritis and Crohn's disease trials. Malignancy rates, of concern during immunosuppression, were as expected in adalimumab-treated patients compared the general population. There was an increase in lymphoma incidence in patients with rheumatoid arthritis, but this increase was in the expected range of rheumatoid arthritis patients not on anti-TNF-therapy. Non-melanoma skin cancer rates were elevated in rheumatoid arthritis

**Table 13.10** Live vaccines

| Name | Trade name | Sponsor |
|---|---|---|
| Adenovirus Type 4 and Type 7 Vaccine, Live, Oral | No trade name | Barr Labs, Inc. |
| BCG Live | BCG Vaccine | Organon Teknika Corp LLC |
| BCG Live | TICE BCG | Organon Teknika Corp LLC |
| Influenza Vaccine, Live, Intranasal (Trivalent, Types A and B) | FluMist | MedImmune, LLC |
| Influenza Vaccine, Live, Intranasal (Quadrivalent, Types A and B) | FluMist Quadrivalent | MedImmune, LLC |
| Measles Virus Vaccine, Live | Attenuvax | Merck & Co, Inc |
| Measles and Mumps Virus Vaccine, Live | M-M-Vax | Merck & Co, Inc (not available) |
| Measles, Mumps, and Rubella Virus Vaccine, Live | M-M-R II | Merck & Co, Inc |
| Measles, Mumps, Rubella and Varicella Virus Vaccine Live | ProQuad | Merck & Co, Inc |
| Mumps Virus Vaccine Live | Mumpsvax | Merck & Co, Inc |
| Rotavirus Vaccine, Live, Oral | ROTARIX | GlaxoSmithKline Biologicals |
| Rotavirus Vaccine, Live, Oral, Pentavalent | RotaTeq | Merck & Co., Inc. |
| Rubella Virus Vaccine Live | Meruvax II | Merck & Co, Inc |
| Smallpox (Vaccinia) Vaccine, Live | ACAM2000 | Acambis, Inc |
| Typhoid Vaccine Live Oral Ty21a | Vivotif | Berna Biotech, Ltd |
| Varicella Virus Vaccine Live | Varivax | Merck & Co, Inc |
| Yellow Fever Vaccine | YF-Vax | Sanofi Pasteur, Inc |
| Zoster Vaccine, Live, (Oka/Merck) | Zostavax | Merck & Co., Inc. |

http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm. Accessed 31 Aug 2012

**Table 13.11** Recommended monitoring of TNF-inhibitors

| | Adalimumab [1] | Etanercept [1] | Infliximab [1] |
|---|---|---|---|
| Dosing | 80 mg the first week, 40 mg the second week, followed by 40 mg every other week given subcutaneously | 50 mg twice/week given subcutaneously for 3 months followed by 50 mg once/week | 5 mg/kg dose infusion schedule at week 0, 2, and 6 and then every 6–8 weeks; dose and interval of infusions may be adjusted as needed |
| Toxicity | Moderately painful injection site reactions are noted; Rare reports of serious infections (i.e., tuberculosis and opportunistic infections) and malignancies; There are rare reports of drug-induced, reversible side effects including lupus without renal or CNS complications cytopenia, MS, and exacerbation of and new onset of CHF | Mildly pruritic injection site reactions may occur; Rare cases of serious infections (i.e., tuberculosis) and malignancies; There are also rare cases of drug-induced, reversible side effects including lupus without renal or CNS complications, cytopenia, MS, and exacerbation and new onset of CHF | Infusion reactions and serum sickness can occur more commonly in patients who have developed antibodies; The incidence of infusion reactions may be reduced by concurrent administration of methotrexate; Rare cases of serious infections (i.e., tuberculosis) and malignancies including hepatosplenic T-cell lymphoma (in children); There are rare reports of drug-induced, reversible side effects including lupus without renal or CNS complications, cytopenia, MS, and exacerbation of and new onset of CHF |
| Baseline monitoring | PPD is required; LFT, CBC, and hepatitis profile | PPD is required; LFT and CBC | PPD is required; LFT, CBC, and hepatitis profile |
| Ongoing monitoring | Periodic history and physical examination are recommended while on treatment; Consider a yearly PPD, and periodic CBC and LFT | Periodic history and physical examination are recommended while on treatment; Consider a yearly PPD, and periodic CBC and LFT | Periodic history and physical examination are recommended while on treatment; Consider a yearly PPD, and periodic CBC and LFT |

patients, psoriasis patients, and Crohn's disease patients. While there may be some distinct differences in patient populations, no new safety signals were revealed.

## Black Box Warnings: Infection and Malignancy

A series of warnings are detailed on the prescribing information of adalimumab, including boxed warnings for serious infections and malignancies [43]. Patients taking adalimumab are at increased risk of serious infection, and many who developed serious infections while taking adalimumab were also taking concomitant immunosuppressants (e.g. methotrexate or corticosteroids). Tuberculosis is a concern, including active tuberculosis and reactivation of latent tuberculosis. All patients should be screened for latent tuberculosis prior to initiating therapy. A positive test for latent tuberculosis is induration of 5 mm or greater with tuberculin skin testing, even for patients with a previous BCG vaccination. If latent tuberculosis is present, anti-TB therapy should be initiated prior to beginning adalimumab or any TNF-inhibitor. Because, anti-TB therapy can increase liver function tests, and in rare cases adalimumab can, too, it is appropriate to wait a month after beginning anti-TB therapy before starting adalimumab. Compliance with tuberculosis prophylaxis is key. Consultation with an infectious disease clinician for managing patients with latent tuberculosis is recommended. Invasive fungal infections (e.g. histoplasmosis, coccidioidomycosis, candidiasis, spergillosis, blastomycosis, and pneumocystosis) and opportunistic bacterial (e.g. legionaella, listeria) or viral infections have been reported. Patients presenting with a serious infection should discontinue adalimumab.

Malignancies have been reported in patients taking TNF-inhibitors. Hepatosplenic T-cell lymphoma (HSTCL), a rare and usually fatal T-cell lymphoma, has been reported almost exclusively in adalimumab-treated males with Crohn's disease taking concomitant azathioprine or 6-mercaptopurine. In the controlled phase of adalimumab trials, more malignancies were seen in the adalimumab group compared to the control group, 0.6 per 100 patient years among adalimumab treated patients, and 0.5 per 100 patient years among 2,749 control treated patients (usually 4 months for most adalimumab trials). There was an increased rate of non-melanoma skin cancer, and it was more prevalent in those patients with previous immunosuppressant therapy and psoriasis patients previously treated with PUVA. When considering lymphoma, more cases of lymphoma were observed in the TNF-blocker patients compared to controls. In adalimumab trials, three lymphomas occurred in 6,693 adalimumab treated patients compared to 1 in 3,749 patients in the control group, across 32 global trials. In 45 trials, the rate of lymphoma was 0.11 per 100 patient years, approximately 3-fold higher than that of the general population. Patients with chronic inflammatory disease may also be at a higher risk than the general population, even in the absence of therapies. Post-marketing cases of acute and chronic leukemia have also been observed. Most patients who developed malignancies were also receiving concomitant immunosuppressants.

It has been challenging to determine the relationship between infection and malignancy and TNF-inhibitors. A meta-analysis examined 20 randomized, placebo-controlled psoriasis trials of TNF-inhibitors, etanercept, infliximab, adalimumab, golimumab and certolizumab, with 6,810 patients total [44]. There was a small increased risk of infection (odds ratio 1.18) but no increased risk of serious infection (odds ratio 0.7). There was an increased risk of malignancy in the TNF-inhibitor group compared to the control group (odds ratio 1.48 for all malignancies and 1.26 when nonmelanoma skin cancer was excluded).

## Post-marketing Safety Information

A number of additional safety signals have been observed in post-marketing surveillance of adalimumab [43]. Hypersensitivity reactions may occur, and anaphylaxis or angioneurotic edema

may be rare events. Allergic reactions were seen in ~1 % of patients taking adalimumab. There have also been rare reports of hematologic reactions, including cytopenia, with TNF-therapy. Adalimumab treatment may result in autoantibody formation, and in rare cases, the development of a lupus-like syndrome. Demyelinating disease, reactivation of hepatitis B infections, and worsening of congestive heart failure have been reported, underscoring the importance of appropriate screening. Elevations in liver enzymes were also reported.

A number of adverse events have also been reported in post-marketing surveillance [43]. These include gastrointestinal disorders (diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis), liver failure, sarcoidosis, nervous system disorders (demyelinating disorders and cerebrovascular accident), respiratory disorders (interstitial lung disease, including pulmonary fibrosis, pulmonary embolism), skin reactions (Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), alopecia, and vascular disorders (systemic vasculitis and deep vein thrombosis).

## Special Populations

Most clinical trials are conducted in adults, and there is limited data about TNF-inhibitor use in women of childbearing potential during pregnancy, in children, and in the elderly. Use of adalimumab in these special populations is reviewed below.

Pregnancy can affect the severity of psoriasis, as one-third of women experience improvement, one-third experience worsening of disease, and the remaining third see no change in their psoriasis [45]. Adalimumab, like other TNF-inhibitors, is classified as pregnancy category B. Experts recommend using adalimumab with caution during pregnancy [46]. Women who become pregnant while on adalimumab, or any biologic, are encouraged to enroll in a pregnancy registry. Additionally, TNF-inhibitors are not typically used during lactation [47]. Interestingly, adalimumab has been studied during in vitro fertilization (IVF). Women with lower levels of TNF-α had better success rates with IVF, and there were no increases in birth defects due to adalimumab treatment, although the study was small (100 pregnant women, 136 babies) [48, 49].

Psoriasis in children can be challenging to treat, as few treatments have been studied in children. Etanercept has been studied in a pediatric psoriasis population, and is reviewed here [50]. Adalimumab has not been studied in children with psoriasis. However, adalimumab is approved for children with juvenile idiopathic arthritis, and this the only population where adalimumab efficacy and safety in children has been assessed in clinical trials [51].

Elderly psoriasis patients also pose additional management challenges. In the elderly, adalimumab can be used as a first line therapy in patients with more extensive disease [52]. It is important that elderly patients are properly monitored, due to the higher incidence of infections and malignancies, generally, in this population.

## Adalimumab Pearls

TNF-inhibitors are the treatment of choice for individuals with both psoriasis and psoriatic arthritis [4]. TNF-inhibitors are also the treatment of choice for patients with Hepatitis C [53]. TNF-inhibitors show synergy with methotrexate, and patients with higher BMIs tend to do better on the monoclonals, including adalimumab [54, 55]. Rotation within the class is possible, but there may be diminishing returns after trying two different TNF-inhibitors.

A number of small studies have examined rotation within the class. In one study, 30 patients who failed etanercept were transitioned to adalimumab [56]. Efficacy was examined at weeks 12, 24, and 48, and 27, 36, and 54 % achieved PASI 75. Adalimumab was well tolerated, and there was no increase in adverse events for patients receiving adalimumab who had previously

received etanercept. Another study examined 14 patients with inadequate responses to etanercept who were transitioned to adalimumab [57]. At 16 weeks, 9/14 (64 %) achieved PASI 50, (of these four achieved PASI 75 and one achieved PASI 90). No serious adverse events were reported.

A subanalysis of BELIEVE was also conducted to examine efficacy of adalimumab in patients treated previously with anti-TNF agents [58]. BELIEVE was a double-blind, randomized, controlled trial where patients received 80 mg at week 0 and 40 mg every other week of adalimumab with topical vehicle or topical calcipotriol/betamethasone dipropionate once daily for 4 weeks and then as needed [59]. The trial enrolled 703 patients, with 38.6 % having prior anti-TNF therapy compared to 61.4 % who were naïve to anti-TNF therapy. Nearly two-thirds (61.7 %) of patients with prior anti-TNF therapy achieved PASI 75 at week 16 compared to 71.17 % of anti-TNF naïve patients. Adalimumab was well tolerated, and adverse events were similar between those with previous anti-TNF therapy and those without.

Another open-label phase IIIb trial, PRIDE (an open-label access program to evaluate the safety and effectiveness of adalimumab when added to inadequate therapy for the treatment of psoriasis), was conducted in Canada, and examined adalimumab response in patients who had not responded previously to other psoriasis therapies [60]. The trial enrolled 203 patients in the 24-week trial. Patients received 80 mg loading dose at week 0 and 40 mg every other week beginning at week 1, for 23 weeks. At week 16, 70.9 % achieved PASI 75. Adalimumab was well tolerated, and 9 experienced serious adverse events.

As with all psoriasis therapies, it is important to understand real-world patient experiences. A recent study examined patient reported reasons for discontinuing treatment [61]. Patients (n = 1,095) with moderate to severe psoriasis who received systemic treatment were interviewed. Of these, 200 patients received adalimumab in the past and were asked why they discontinued it. The top three reasons for discontinuing adalimumab were because it did not work well enough (34 %), worked well at first but stopped working well (22 %), or non-life threatening side effects (14.5 %).

## Complications of Not Treating Psoriasis

Not all moderate to severe psoriasis patients are being treated as suggested by guidelines. A National Psoriasis Foundation survey showed that nearly 40 % of patients surveyed were not in treatment for their psoriasis [62]. Of those who were in treatment, 57 % of patients with severe psoriasis were on topical therapy alone, and only 3 % of these patients had ever tried phototherapy, a systemic therapy, or a biologic. In a chart review of dermatologists treating ten or more psoriasis patients per month, 40 % of patients with severe disease received topical therapy alone [63]. There are complications of not treating psoriasis. Extensive psoriasis leaves an unresolved inflammatory burden in skin. In addition, there is an elevated systemic inflammatory burden that impacts comorbidities. New data suggests that treatment with TNF-inhibitors can reduce the risk of myocardial infarction [64]. In addition to physical complications, there are also psychosocial implications. Untreated or inadequately controlled psoriasis can impact quality of life and physical functioning. In addition, untreated psoriasis may have an economic impact through time lost from work and reduced productivity while at work. There are a number of appropriate treatments for individuals with moderate to severe psoriasis. Adalimumab is one of these treatments, and is a viable option for some.

## Final Thoughts

Adalimumab, a member of the anti-TNF class of biologics, is an appropriate treatment for individuals with psoriasis, with or without psoriatic arthritis. Numerous clinical trials (e.g. REVEAL, CHAMPION, ADEPT, and others) have shown adalimumab to be efficacious and well tolerated

with a safety profile similar to others in the class. Adalimumab treatment also improved HRQoL. As with all immunosuppressive therapies, appropriate screening and monitoring of patients on adalimumab is required. Adalimumab is an important option within the psoriasis treatment armamentarium.

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# Infliximab and Golimumab

14

Cerrene N. Giordano and Robert E. Kalb

**Abstract**

Psoriasis and psoriatic arthritis are common chronic inflammatory disorders with substantial physical, financial and psychosocial burdens for patients. Biologic therapy for these conditions has been a major improvement in the therapeutic armamentarium. These drugs can maintain control of the disease, restore physical function and significantly improve the quality of life. This chapter provides a comprehensive review of the safety and efficacy of two of the monoclonal antibody tumor necrosis factor alpha (TNFα) blocking drugs. Infliximab was the first such agent approved for use in the United States in 1998. Golimumab is one of the more recent additions to this family of drugs. There has now been over 15 years of clinical experience with TNFα inhibitors. This experience has allowed physicians to utilize these agents in a manner to maximize efficacy while decreasing the risks of the potential side effect. We will summarize the published data and experience with these two specific agents.

**Keywords**

Infliximab • Golimumab • Psoriasis • Psoriatic arthritis • Drug therapy Monoclonal antibodies

## Introduction

The treatment of psoriasis and psoriatic arthritis has undergone a revolution with the advent of biologic therapy providing patients with more treatment choices and greater hope for sustained symptomatic relief [1, 2]. Infliximab (Remicade) is one of the more widely used tumor necrosis factor (TNF)-alpha inhibitors, and has extensive clinical experience in various immunologic conditions. It is a chimeric human-murine monoclonal antibody, consisting of human constant and murine variable regions and binds to both soluble and membranous forms of TNF-alpha, thereby neutralizing the cytokine's effect [3–6]. It was first approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate to severe

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Crohn's disease in August of 1998. Its use was later expanded to include the following indications: rheumatoid arthritis (11/1999), ankylosing spondylitis (12/2004), psoriatic arthritis (05/2005), ulcerative colitis (09/2005), pediatric Crohn's disease (05/2006), psoriasis (09/2006), and pediatric ulcerative colitis (09/2011) [7, 8]. In dermatology the drug is usually administered intravenously over 2 h, at a dosage of 5 mg/kg on weeks 0, 2, and 6, followed by maintenance infusions every 8 weeks thereafter [3, 9]. While the intravenous administration can be inconvenient, it is administered infrequently and has the benefit of rapidly achieving high serum concentrations, therefore offering the potential for rapid and sustained improvement [4, 6, 10, 11].

Golimumab (Simponi) is a newer member of the TNF antagonist family. It functions as a fully human IgG1k monoclonal antibody that targets both transmembrane and soluble forms of TNF-alpha with high affinity and specificity [12, 13]. In 2009, golimumab was FDA approved for use in numerous inflammatory diseases, including moderate-severe rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis either alone or in combination with conventional agents [13, 14]. Golimumab is self-administered as a 50 mg or 100 mg subcutaneous injection once each month.

## Mechanism of Action

Infliximab and golimumab exert their anti-inflammatory effects by binding to the soluble and transmembrane forms of TNF-alpha, thereby inhibiting the induction of the inflammatory cascade and ultimately resulting in the rapid reduction in the number of cells at the site of inflammation [15]. However, no definitive mode of action has been established despite numerous theories. Numerous in vitro and in vivo studies have contributed to the knowledge base behind TNF-alpha inhibitors, and it has been proposed that apoptosis, reduction of proinflammatory cytokines, down-regulation of adhesion molecules, and increases in circulating T regulatory cells are the main mechanisms of action behind the efficacy of TNF-alpha inhibition [3, 13]. Recently, the literature has been focused on the newly discovered TH17/IL-17 pathway as another possible pathway in the induction and maintenance of various autoimmune diseases [16]. IL-17+ T cells [17] and IL-23p19 gene expression [18] are found to be increased in lesional psoriatic skin. Moreover, injection of IL-23 into mice induces a TNF-dependent psoriatic-like disorder [18], not surprisingly as IL-23 has previously been shown to stimulate macrophage TNF production [19]. Although the exact pathogenesis remains largely unknown, it is possible that TNF-alpha's role is more closely linked to the TH17 pathway than previously thought.

## Efficacy for Psoriasis and Psoriatic Arthritis

### Infliximab

The first documented treatment response with infliximab was published in a case report of a patient with a long-standing history of Crohn's disease with concomitant severe psoriasis [20]. The patient received a single infusion of infliximab (5 mg/kg) and 4 weeks later there was a dramatic improvement in the severity of the psoriasis.

Based on this report, a double-blind, randomized trial was conducted and published in 2001 (Fig. 14.1) [21]. This was a trial of 33 patients with clinically-defined moderate-severe plaque psoriasis who were randomized to receive either intravenous placebo or intravenous infliximab in either 5 mg/kg or 10 mg/kg dosages at weeks 0, 2, and 6. Three patients withdrew from the study, one from each treatment group. At week 10, 9 of the 11 (82 %) patients in the infliximab 5 mg/kg group and 10 of the 11 (91 %) patients in the infliximab 10 mg/kg group were considered responders (clear or almost clear rating according to the PGA) compared to only 2 of 11 (18 %) receiving placebo ($p < 0.01$). Additionally, 9 of 11 (82 %) in the infliximab 5 mg/kg group and 8

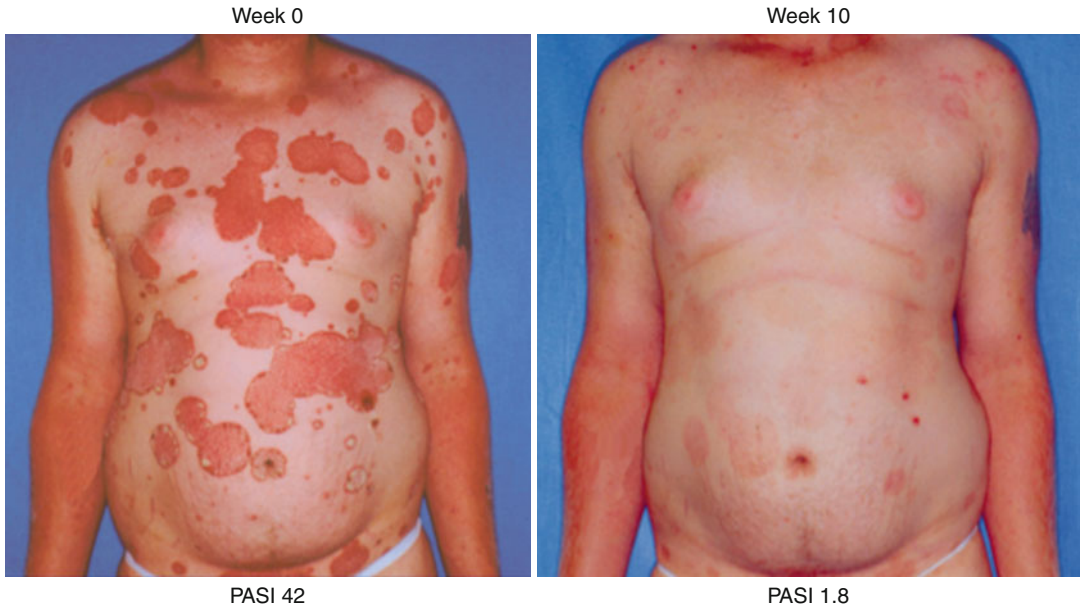


**Fig. 14.1** Infliximab therapy: psoriasis at baseline and at week 10 (With permission from Chaudhari et al. [21])

of 11 (73 %) in the infliximab 10 mg/kg group achieved at least a PASI 75 compared with only 2 of 11 (18 %) in the placebo group ($p<0.05$). In both infliximab-treated groups, the median time to response was only 4 weeks. This was the first controlled trial documenting the high degree of clinical benefit and rapid time to response in the treatment of moderate-severe plaque psoriasis. Numerous randomized controlled trials followed to confirm this initial success.

In the multicenter, double-blind phase II SPIRIT trial by Gottlieb et al. in 2004, 249 patients with severe-type plaque psoriasis were randomly assigned to receive infusions of either 3 mg/kg, 5 mg/kg, or placebo administered at weeks 0, 2, and 6 [22]. At week 10, 72 % and 88 % of the patients treated with 3 and 5 mg/kg of infliximab, respectively, achieved a 75 % or greater improvement using the PASI evaluating system. This was in comparison to only 6 % of patients in the placebo group ($p<0.001$). Furthermore, 46 % of patients treated with 3 mg/kg and 58 % treated with 5 mg/kg reached a 90 % improvement in PASI score compared to only 2 % of the patients in the placebo group ($p<0.001$). Quality of life scores were also improved with the use of infliximab. This study demonstrated a rapid and significant improvement in the signs and symptoms of psoriasis with the use of infliximab, with clinical improvement noted in the treatment groups after only 2 weeks.

In 2005 and 2007, two large phase III multicenter, randomized, double-blind placebo-controlled studies were conducted called the EXPRESS I and II trials (Fig. 14.2) [23, 24]. These studies also demonstrated the dramatic effectiveness of infliximab in patients suffering from moderate-severe plaque psoriasis. In EXPRESS I, 378 patients were allocated to receive infusions of either 5 mg/kg of infliximab or placebo at weeks 0, 2, and 6, and then every 8 weeks thereafter to week 46 [23]. Beginning at week 24, the patients in the placebo group crossed over to receive infliximab treatments. Although remarkable clinical improvements were noted at week 6 (after only two infusions), by the end of the induction period (week 10) 80 % of patients treated with infliximab achieved PASI 75, with 57 % reaching at least a 90 % improvement (PASI 90), and 26 % of patients achieving complete clearing of the skin (a score of 0 in PASI). This is in comparison to 3, 1, and 0 % in the placebo

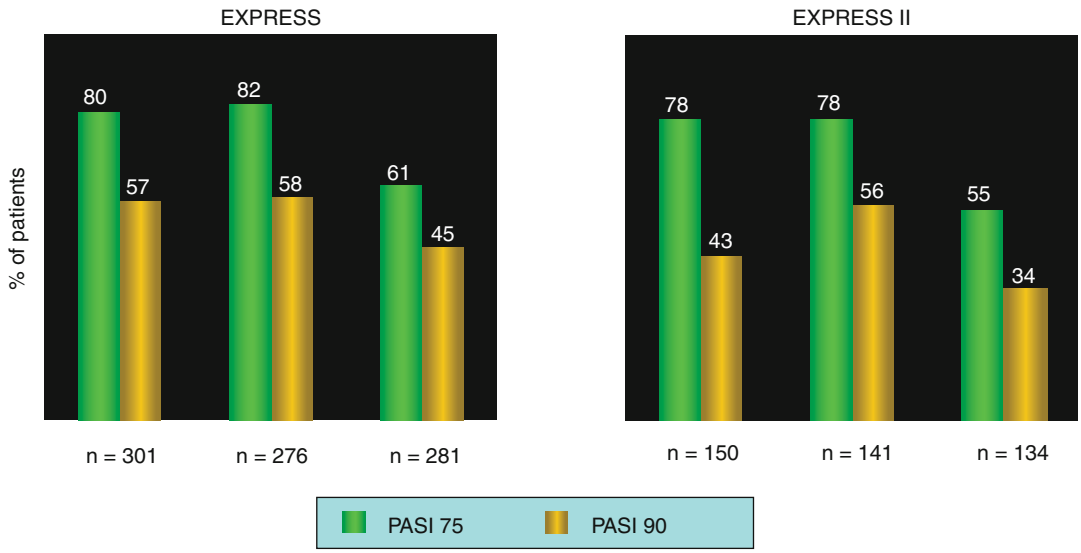


**Fig. 14.2** Infliximab phase III study efficacy (With permission from Reich et al. [23] and Menter et al. [24])

group, respectively ($p<0.0001$). Of significant importance, the PASI 75 and PASI 90 responses were maintained through week 50, with 82 and 61 % of patients attaining a PASI 75 at weeks 24 and 50 (Figs. 14.3 and 14.4) [23]. Also of importance are the effects observed for patients suffering from nail psoriasis, a traditionally treatment-resistant disease. Nail Psoriasis Severity Index (NAPSI) improvements were noted as early as week 10 in infliximab-treated patients. At week 24, there was a 56 % mean decrease of the NAPSI in the infliximab group, and this response was also maintained through week 50 ($p<0.0001$ for week 24) (Fig. 14.5) [23].

The EXPRESS II trial also documented the efficacy of infliximab in a placebo-controlled protocol [24]. In addition, this trial compared the efficacy of continuous therapy (every 8 weeks) versus intermittent (as needed) maintenance regimens. Eight hundred and thirty five patients were randomized to induction therapy at weeks 0, 2, and 6 with infliximab 3 mg/kg, 5 mg/kg, or placebo. At week 14, the infliximab group was then further randomized to continuous or maintenance regimens at their originally designated dose. Not surprisingly, at week 10, 75.5 % and 70.3 % of patients in the 5 and 3 mg/kg groups achieved a PASI 75, and 45.2 and 37.1 % achieved a PASI 90, compared to 1.9 and 0.5 % of placebo patients ($p<0.001$). Through week 50, this study demonstrated that the clinical response to treatment was best maintained using continuous infliximab therapy compared to an as-needed basis in both dosage groups. The median of the average percent improvement in PASI from week 16 through week 50 was 89.6 % in the 5 mg/kg every-8 week group compared to 76.4 % in the as-needed group ($p<0.001$). Similar results were obtained for the 3 mg/kg group as well, with 80.6 % improvement in the continuous group versus 72.4 % in the as-needed group ($p<0.001$). Furthermore, the authors showed that a 5 mg/kg dosage regimen achieved superior induction and maintenance scores compared to the lower dosage. Patient assessments across treatment groups were consistent with the PASI scores, as the continuous infusion of 5 mg/kg group reported the greatest improvements in their DLQI quality of life scores.

Separate trials were conducted for patients suffering from psoriatic arthritis with similar demonstrations of efficacy for infliximab. In 2005 and 2007, the IMPACT I and II trials were conducted as randomized, double-blind

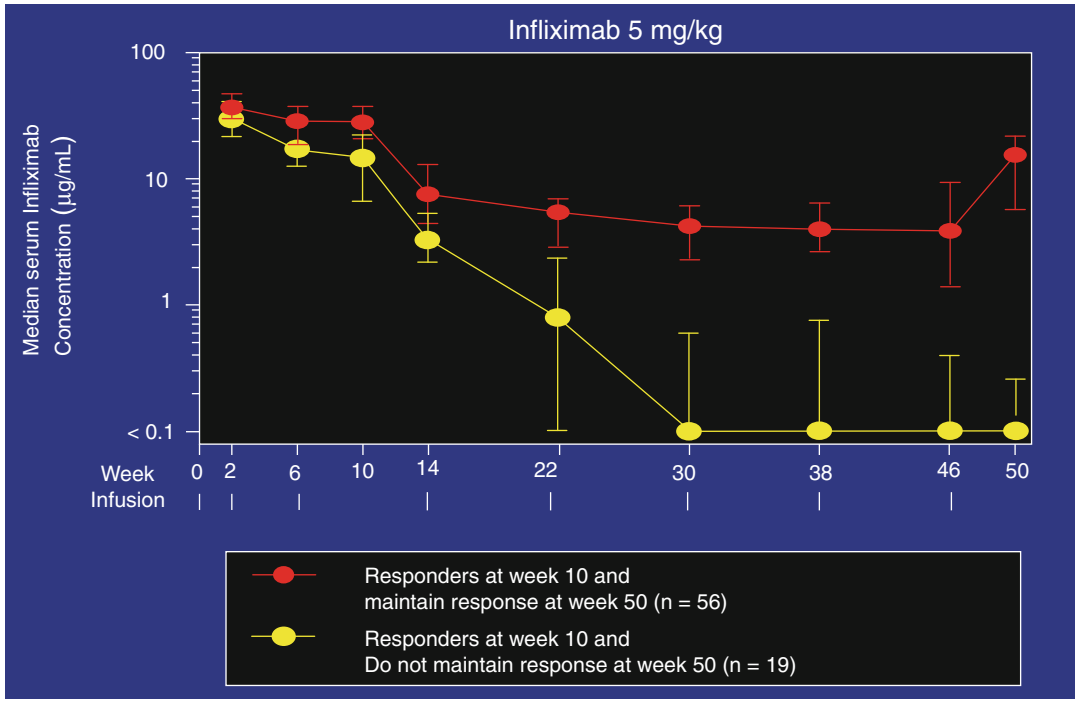


**Fig. 14.3** Median serum concentration of infliximab through week 50 in week 10 responders (With permission from Reich et al. [23])

placebo-controlled studies enrolling patients with psoriatic arthritis in whom prior therapy with at least one disease-modifying anti-rheumatic drug (DMARD) had previously failed [25, 26]. In IMPACT I, 104 Patients were assigned to receive infusions of either 5 mg/kg of infliximab or placebo at weeks 0, 2, 6, and 14. After week 16, patients initially assigned to receive placebo were crossed over to receive infliximab, and all groups received 5 mg/kg of infliximab every 8 weeks through week 50. At week 16, 65 % of patients treated with infliximab attained an ACR20 response, compared to only 10 % of placebo-treated patients ($p < 0.001$). In addition, 46 % of the infliximab group produced an ACR 50 response and 29 % an ACR 70 response, where no placebo-treated patients achieved either of these end points ($p < 0.001$). Furthermore, at the 16-week evaluation 75 % of infliximab-treated patients were improved according to the PsARC, compared to only 21 % of placebo-controlled patients ($p < 0.001$). Also of note, the infliximab group showed substantial improvements in the percentages of patients suffering from the common complications of psoriatic arthritis, namely dactylitis and enthesitis. The IMPACT I trial evaluated changes in psoriatic skin disease as well. Among patients with baseline PASI scores of ≥2.5, 100, 68, and 36 % achieved at least a PASI score of 50, 75, and 100 from baseline to week 16. None of the placebo-controlled patients achieved any of these endpoints in the same time frame ($p < 0.001$). At week 50, 86 %, 59 %, and 41 % of patients in the infliximab only group and 69, 50, and 38 % of patients in the placebo/infliximab crossover group achieved PASI scores of at least 50, 75, and 100 respectively (p value not reported). The PASI improvement in psoriasis index is usually assessed as a secondary endpoint in psoriatic arthritis trials such as the IMPACT I and II studies. The psoriasis response in these trials should not be directly compared to the results in the larger phase III psoriasis trials because of the significantly dif-

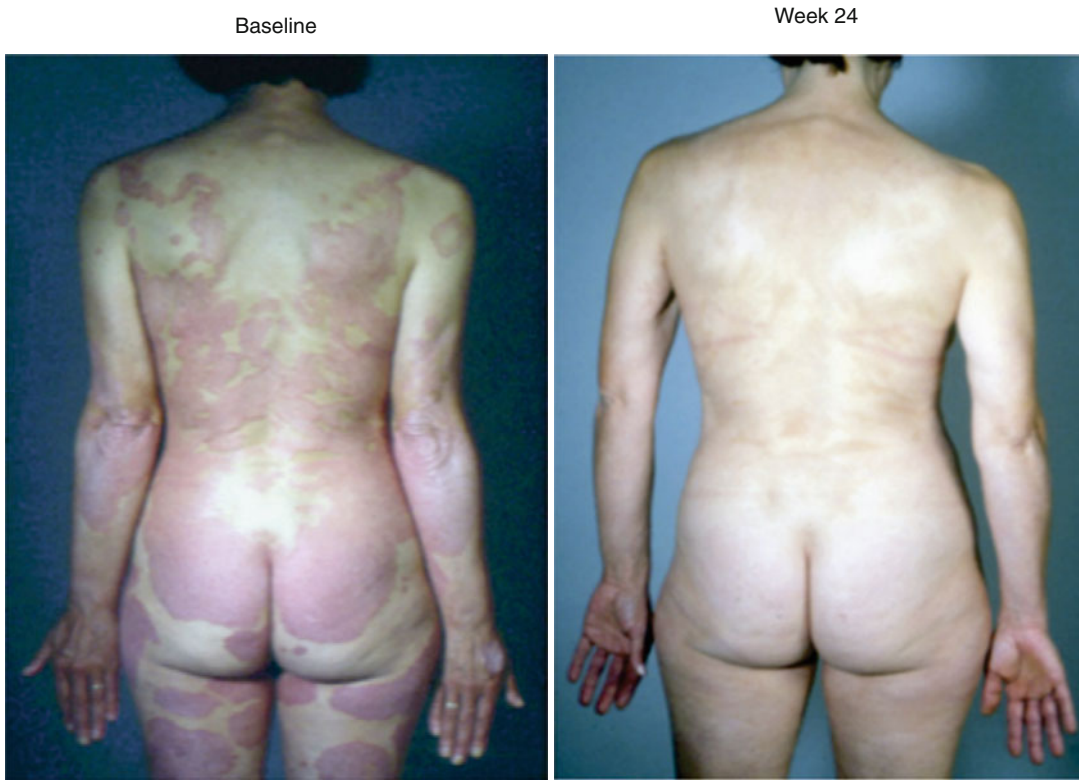


**Fig. 14.4** Infliximab therapy: psoriasis at baseline and at week 24 (With permission from Reich et al. [23])

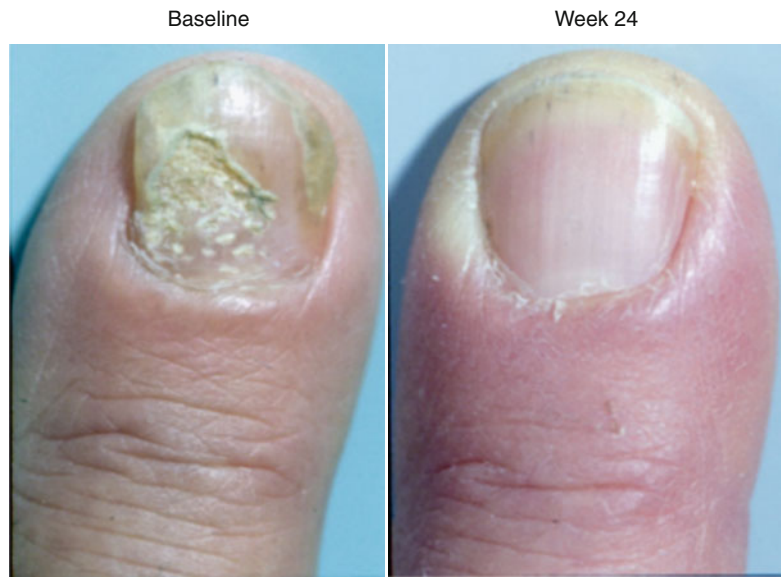


**Fig. 14.5** Infliximab Therapy: target nail at baseline and at week 24 (With permission from Reich et al. [23])

ferent baseline patient characteristics and the degree and severity of the psoriasis.

The IMPACT II was a 54 week multicenter study designed to expand the published clinical response data from the initial, 24 week, double blind placebo-controlled period [27], and expanding the number of enrolled patients to 200 [26]. As previously reported, these results demonstrated significant improvements in the signs and symptoms of psoriasis and psoriatic arthritis, as well as quality of life and physical functioning in patients through 1 year of treatment. These authors also demonstrated that 5 mg/kg is a sufficient dose for a majority of patients, as dose escalation from 5 to 10 mg/kg was assessed in 15 non-responders (patients who did not achieve ACR 20). Interestingly, in the patients requiring dose escalation, patients who had not achieved an ACR 20 score before escalation were unable to achieve the response despite doubling of the drug dosage. Furthermore, dose escalation did not appear to significantly improve PASI responses either. Out of the 15 patients who received dose escalations, only 12 had a baseline BSA of 3 % or greater and were therefore included in the PASI analysis. Of these 12 patients, five achieved a PASI 75 at week 38 and all five maintained that response through week 54. Conversely, the seven patients who did not achieve a PASI 75 response at week 38 were unable to achieve the response after dose escalation. This study also assessed attainment of a "major clinical response," a criteria previously used to assess rheumatoid arthritis and defined as ACR 70 improvement for 24 consecutive weeks. At week 54, major clinical response was achieved by 12.1 % of the infliximab-treated group. Overall, these studies showed that infliximab therapy significantly reduces the signs and symptoms of psoriatic arthritis in patients resistant to other treatment modalities. Moreover, these benefits were sustained through 1 year of therapy.

While all biologics have performed well in short-term clinical trials, very limited direct comparisons between agents are available, particularly for psoriasis. However, since most studies used similar designs and end points, limited comparisons from randomized controlled trials are possible. Adalimumab and infliximab appear to have similar efficacy, with 70–80 % of patients achieving a PASI 75 score at 12 weeks [9]. According to a systematic review by Rodgers et al., infliximab is associated with the highest probability of response on joint (ACR and PsARC) and skin (PASI) outcomes from 12 to 14 weeks [28]. Etanercept appears to be slightly less efficacious than its counterparts, demonstrating 50 % of patients attaining a PASI of 75 at 12 weeks. Of course, head-to-head trials are necessary to obtain more accurate data. Also of note, an unsatisfactory response with one TNF antagonist does not rule out a clinical response to another agent with the same mechanism of action [9]. There is limited data on selecting the alternative drug or predicting its effectiveness and safety in a patient who has already failed one agent, and additional trials are necessary. This will be further discussed later in the chapter.

In August 2011, the first documented head-to-head, randomized trial (RESTORE 1) comparing the efficacy and safety of infliximab versus methotrexate was published (Fig. 14.6) [29]. 868 methotrexate-naïve patients were randomized to receive 5 mg/kg of infliximab at weeks 0, 2, 6, 14, and 22 or 15 mg weekly methotrexate with a dose increase to 20 mg weekly at week 6 if the PASI response was <25 %. Patients with less than a PASI 50 response were allowed to switch treatment groups at week 16. At week 16, a PASI 75 response was achieved by 508/653 (78 %) of infliximab-treated patients compared to 90/215 (42 %) of patients receiving methotrexate, and this response was maintained throughout the 26-week study ($p<0.001$). Key secondary endpoints, including PGA, DLQI, and PASI 90 were likewise achieved by a greater proportion of infliximab-treated patients. More impressively, 46/63 (73 %) patients who switched from methotrexate to infliximab at week 16 demonstrated a PASI 75 at week 26. Although the incidence of severe adverse events was slightly higher in the infliximab group (7 % vs. 3 %), a majority of the

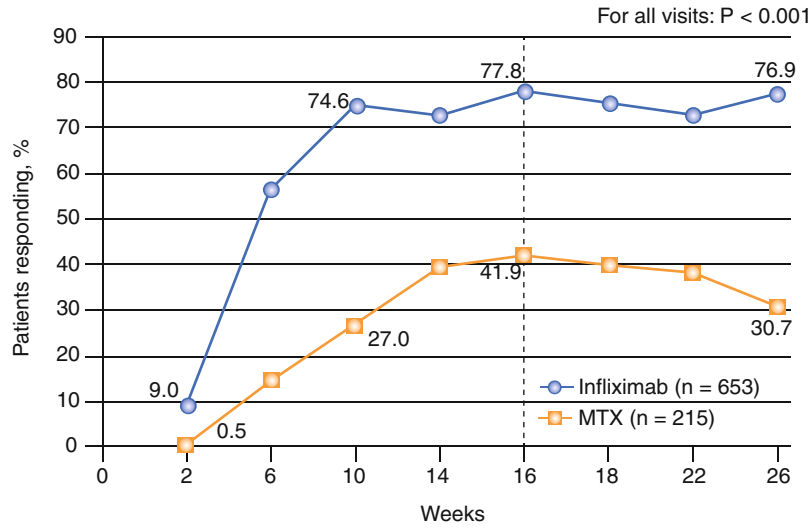


**Fig. 14.6** Efficacy of infliximab versus methotrexate (Adapted from Barker et al. [29])

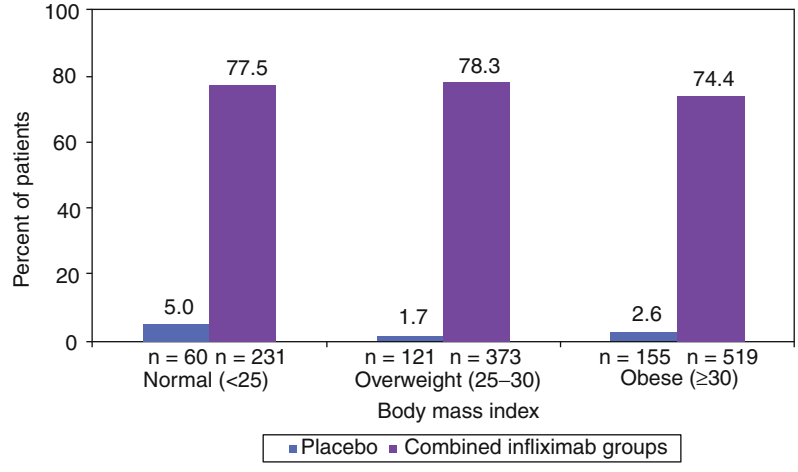


**Fig. 14.7** Infliximab: BMI and efficacy (With permission from Reich et al. [32])

serious adverse events were infusion-related reactions, and the overall adverse event incidence was comparable between groups. The study demonstrated that infliximab was both well tolerated and more efficacious than methotrexate in patients with moderate-severe plaque psoriasis. Moreover, infliximab was proven to be a successful alternative agent in patients who had previously failed methotrexate therapy.

One of the major advantages of infliximab is that it has a weight-based dosing on a milligram per kilogram basis unlike a majority of the TNF antagonists used to treat psoriasis [30, 31]. This allows for a more individualized patient-tailored therapy, which is particularly important as patients with psoriasis are typically above average weight [30, 31]. Additionally, a few studies have demonstrated the continued efficacy of infliximab regardless of body mass index, whereas the efficacy of fixed-dose TNF antagonists may be compromised [30–32]. In one study (Fig. 14.7), there was no significant difference between the number of patients who achieved an efficacious response with a BMI greater than or equal to 30 (74.4 %) compared to those of normal body weight (77.5 %) [32].

## Combination Therapy

Currently, there is anecdotal evidence to suggest that patients with psoriasis may obtain an improved response from combination therapy with infliximab and a more conventional therapeutic agent such as methotrexate, cyclosporine, acitretin, or narrow-band UVB (nb-UVB) phototherapy [33–36]. While controlled trials are lacking for combination therapy in psoriasis, studies exist comparing combination therapies in other autoimmune diseases. Recently, an open-label study (RESPOND study) was conducted comparing the efficacy and safety of methotrexate alone versus methotrexate in combination with infliximab in patients suffering from psoriatic arthritis [37]. One-hundred fifteen methotrexate-naïve patients were randomly assigned to receive either 15 mg/week of methotrexate plus infliximab 5 mg/kg at weeks 0, 2, 6, and 14, or methotrexate therapy alone (15 mg/week). At week 16, 86.3 %, 72.5 %, and 49.0 % of patients receiving combination therapy compared to 66.7, 39.6, and 18.8 % of patients receiving methotrexate alone achieved ACR 20 ($p=0.021$), 50 ($p=0.0009$), and 70 ($p=0.0015$) responses, respectively. Improvements in skin disease were noted as well. Of the patients whose baseline PASI was 2.5 or greater, 97.1 % of those on combination therapy and 54.3 % of those on methotrexate alone experienced a 75 % or greater improvement in PASI scores ($p<0.0001$). Additionally, combination therapy was determined to be generally well-tolerated by the patient population. In the infliximab plus methotrexate group, 46 % had treatment-related adverse events (2 serious AEs) while the methotrexate alone group experienced 24 % AEs (no serious AEs). While the overall incidence of adverse events was higher in the combination therapy group, a majority of the events were mild to moderate. Overall, the use of infliximab plus methotrexate in patients with psoriatic arthritis achieved greater improvements in all clinical outcomes with a rapid response to treatment and profound disease suppression with relative safety in comparison to methotrexate alone.

In 2010, the results of a randomized, double-blind trial comparing the efficacy of infliximab monotherapy, azathioprine monotherapy, and the combination of the two drugs in patients with Crohn's disease were published [38]. Five-hundred eight patients with moderate to severe Crohn's disease were randomized to receive either 5 mg/kg infliximab at weeks 0, 2, 6, and then every 8 weeks thereafter, 2.5 mg/kg oral azathioprine daily, or combination therapy with the two medications (with the monotherapy groups also receiving either oral or infusion placebos). At week 26, 56.8 % of the patients receiving combination therapy were in steroid-free clinical remission compared to 44.4 % of those receiving infliximab alone ($p=0.02$) and 30.0 % receiving azathioprine alone ($p=0.006$ for comparison with infliximab and $p<0.001$ for comparison with combination therapy). At week 50, a similar trend was obtained with 46.2 % of patients on combination therapy, 34.9 % on infliximab alone ($p=0.04$), and 24.1 % on azathioprine alone ($p=0.03$ for comparison with infliximab and $p<0.001$ for comparison with combination therapy) maintaining clinical remission status. Safety data was generally similar among groups with serious infections occurring in 3.9 % of the combination group compared to 4.9 % in the infliximab group and 5.6 % in the azathioprine group. While this study documented the incremental benefit of combination therapy for Crohn's disease, controlled data are lacking in psoriasis. Whether combination therapy with all TNF antagonists, including infliximab, will be more effective in improving or maintaining response are important questions to be answered for patients with psoriasis.

Maintaining the high initial response with infliximab therapy for a chronic disease such as psoriasis remains a challenge as noted in the previous paragraph. The mechanisms for loss of response include antibodies to infliximab, tolerance to the drug, and drug metabolism for individual patients [39–41]. The highest predictor of continued response is serum levels of infliximab at the time of infusion (Fig. 14.3) [23]. For patients with rheumatoid arthritis who lose response,

increasing the infliximab dose or decreasing the frequency of infusions are frequently used strategies. There is less experience in psoriasis but in the case series published in etanercept non-responders, the majority of patients received infliximab every 6 weeks [41, 42]. Many physicians either start with methotrexate in combination with infliximab or add methotrexate to maintain response. Methotrexate may alter drug pharmacokinetics or prevent autoantibody production.

## Golimumab

Although a relatively new medication, golimumab has shown impressive results in the few studies conducted thus far concerning its efficacy. It was involved in the largest randomized controlled trial of a biologic agent in psoriatic arthritis and was shown, overall, to significantly improve signs and symptoms associated with psoriatic arthritis. Although one may expect that the effects of golimumab in the treatment of psoriasis are comparable to other TNF antagonists with a similar benefit in psoriatic arthritis, there are no published trials directly assessing the effects of this medication in psoriasis. Therefore, it is not known how golimumab compares to other TNF inhibitors in the treatment of moderate to severe psoriasis.

In a randomized, placebo-controlled, multicenter clinical study (GO-REVEAL), 405 patients with active psoriatic arthritis were enrolled and randomly assigned to receive subcutaneous injections of placebo, golimumab 50 mg, or golimumab 100 mg every 4 weeks through week 20 [43]. At week 14, 51 % and 45 % of patients receiving golimumab 50 and 100 mg respectively, achieved an ACR 20 response, compared with only 9 % of patients receiving placebo therapy ($p<0.001$). At week 24, an ACR 20 response was observed in 52 % of patients in the 50 mg group and 61 % in the 100 mg group, versus 12 % of patients receiving placebo ($p<0.001$). More impressively, data presented at the 2009 Annual Meeting of the European Rheumatologists in Copenhagen revealed an ACR 20 of 91.4 % and 73.1 % in the 50 and 100 mg groups respectively [12].

In this same trial, golimumab also showed improvements in psoriatic plaque disease as well. In patients who were also suffering from at least 3 % BSA involvement of skin psoriatic disease, 40 % in the 50 mg golimumab group and 58 % in the 100 mg golimumab group had at least 75 % improvement in their skin disease (PASI 75) by week 14 [43]. This was compared to only a 3 % PASI 75 response in placebo-treated patients ($p<0.001$). This beneficial response was maintained through week 24 in both golimumab groups (56 and 66 % for 50 and 100 mg) whereas only 1 % of patients in the placebo group reached a PASI 75 at this time marker ($p<0.001$). At week 104, data revealed a PASI 75 of 68.8 % of patients in the 50 mg group and 76 % in the 100 mg golimumab group [12]. Again, it is important to realize that baseline characteristics in psoriasis severity are significantly different in psoriatic arthritis trials than the large phase III psoriasis studies.

Additionally, major improvements were observed in secondary end-points, including the NASPI for nail disease, the physician's global assessment of psoriatic nail disease, and health assessment questionnaire compared with placebo [43]. Psoriatic nail disease is commonly associated with psoriatic arthropathy, but rarely studied and often times refractory to treatment. In the GO-REVEAL trial, assessment of a single target fingernail using the aforementioned methods of analysis revealed significantly greater improvement from baseline to weeks 14 and 24 was observed in each golimumab dose group versus placebo. Similarly, patients in both golimumab treatment groups had significantly improved HAQ scores at week 24 compared to the placebo group. Therefore, in this study, golimumab improved significantly the clinical signs and symptoms of psoriatic arthritis, along with associated skin and nail disease, as well as physical functioning and quality of life [12].

## Safety Considerations

With 12 years of clinical use, the safety profile of TNF-inhibitors is well characterized [2]. In clinical trials, infliximab and golimumab have been

proven to be generally well tolerated, however, due to their down-regulatory effects on the immune system, all TNF antagonists have labeled warnings about the potential development of bacterial, viral, and fungal infections during treatment [9, 44–46]. While the most common adverse events are mild, consisting of nausea, headache, upper respiratory tract infections, abdominal pain, fatigue, and fever, serious and sometimes fatal events have been reported [7, 47, 48]. Kavanaugh et al. reported that only 8.6 % of patients treated with golimumab experienced a serious adverse event up to 104 weeks [12]. Infusion-related reactions are also possible and were reported in about 20 % of patients receiving infliximab compared to only 10 % in placebo groups [22, 49]. These reactions included hypertension, hypotension, bronchospasm, chest pain, dyspnea, pruritus and fever [50, 51]. Infusion-related reactions may occur with all intravenously-administered biologic agents, but because infliximab is a human-mouse antibody, anaphylaxis is possible, although uncommon [2]. For golimumab, injection site reactions occurred in 8.9 % of golimumab treated patients, but only with 0.7 % of all golimumab injections over 104 weeks of treatment [12]. Malignancy, autoimmune disease, demyelinating disease, and congestive heart failure [13] serve as additional concerns with the use of these agents, however with appropriate screening and selection of patients, the potential for development of these more serious conditions declines. Also of important note, the adverse event data of many of the biologics are derived primarily from patients with rheumatoid arthritis (RA) or inflammatory bowel disease (IBD) as they have the most long-term and extensive data available [1, 28]. The generalizability of these findings in patients suffering from psoriasis and psoriatic arthritis remains unclear. More recent data suggests the side effect profile may be more favorable in patients with psoriatic diseases [1, 52, 53].

## Infusion-Reactions

Infusion-related reactions are unique to infliximab as this is currently the only TNF antagonist that is administered intravenously. Infliximab infusions can be administered within a hospital or a community setting [52]. Typically, infliximab is administered over a 2 h time span, however, a recent prospective cohort study demonstrated that infliximab infusion can be safely administered over 1 h in patients with no past history of significant infusion reaction [54]. A majority of the reactions are mild, consisting of flushing, dizziness, nausea, sweating, and increase in temperature, typically occurring within the first 2 h after treatment [22, 55–57]. However, since infliximab contains foreign protein-derived agents, more serious reactions, although rare, are possible and include shortness of breath, hypo/hypertension, chest tightness, symptoms of anaphylaxis such as urticaria, and bronchospasms. Delayed reactions have also been reported, occurring up to 2 weeks after therapy. These are typically arthralgias, myalgias, headache, fatigue, and influenza-like symptoms [23, 55, 58]. It has been estimated that infusion reactions occur in 3–22 % of patients receiving treatment for psoriasis [56]. Typically, symptoms can be monitored and will resolve with minor analgesics or antihistamines, however if a severe reaction develops, infliximab should be discontinued immediately with commencement of appropriate treatment [57]. Generally, infliximab treatment can be continued after a mild or moderate reaction. Attempts have been made to reduce the probability of infusion-related reactions. Various agents have been administered as premedications, including intravenous steroids and antihistamines, however most trials have failed to demonstrate a protective effect of premedications and lead to doubt on whether their risk of potential side effects is justifiable [54, 59–61]. Comedication with disease-modifying therapies [54, 62–64] and ensuring a reliable maintenance schedule (opposed to an as-needed schedule) [57] have been shown to reduce the risk.

## Infection

Infections are serious complications that can result from the use of TNF antagonists. While the most common types reported are upper respiratory

tract infections and urinary tract infections, more serious infections such as cellulitis, pneumonia, abscesses, skin ulceration, pyelonephritis, cholecystitis, and sepsis have occurred [12, 43, 48, 49]. Although observational studies and meta-analyses of rheumatoid arthritis and inflammatory bowel disease randomized controlled trials have indicated an increased risk of serious and non-serious infections [65–71], clinical safety data specific for psoriasis and psoriatic arthritis demonstrated only a very small increased risk of overall infection with the short-term use of biologics, without an increased risk in the development of more serious infections [1]. Furthermore, the authors even suggested that the increased risk of overall infection may be attributable to variations in follow-up time between the treatment and placebo groups. Rheumatoid arthritis and IBD patient populations are typically treated with the concomitant use of additional immunosuppressants and have a higher background incidence of infection. These factors are the likely explanations for an increased infection rate in these groups [65, 66]. By design, patients with psoriasis receive monotherapy in clinical trials [72–76]. Although the overall risk for infection reached statistical significance, it may have limited clinical implications as 97.6 % of the reported infections were non-serious, with a large majority represented by upper respiratory infections [1]. More surprisingly, Dommasch et al. found a marginally statistically significant decreased risk of serious infection [1]. There were three reported cases of cellulitis in the placebo group, versus only one in the treatment group. It is postulated that an improvement in skin disease and a decreased amount of excoriations and breaks in the skin barrier are possible explanations for this unexpected finding.

A significant concern of health practitioners is the potential for the reactivation of tuberculosis [7, 49, 77]. The risk of reactivation of latent TB is, of course, dependent on the incidence of latent infection [4]. From January 1998 to September 2002, the reported cumulative incidence for patients in the USA was estimated at 54/100,000 for infliximab [78]. However, the reality of this serious risk has lead to the introduction of pre-treatment screening procedures, which have successfully reduced the number of cases [67, 79]. It has been reported that reactivation occurs at the greatest frequency within the first 12 weeks of treatment [80, 81]. The mechanism by which TB reactivation occurs is unclear, although infliximab has been hypothesized to reduce the activity of cytotoxic CD8+ T cells [3]. As these cells, along with the cytokine TNF-alpha, are crucial for the maintenance of granulomas and the lysis of host cells harboring intracellular invaders, such as *Mycobacterium tuberculosis*, these data provide an insight into the mechanism whereby this infection remains a potent concern for those undergoing therapy with anti-TNF agents [3]. Screening should include a full history and physical exam, and a purified protein derivative skin test in all patients, with chest radiography and interferon-gamma-based TB tests as considerations in patients where there is suspicion of a compromised skin test [13, 82, 83]. In the case of latent TB, it is imperative that post-exposure prophylaxis treatment be initiated prior to biologic therapy. Recent CDC guidelines (Dec 2011 MMWR) suggest that 3 months of isoniazid with or without/rifapentine (or rifampin) is the treatment of choice in countries such as the USA with low to moderate levels of latent infection [84]. In the setting of active TB, anti-TNF agents should be discontinued immediately. It remains controversial whether these agents can be resumed upon completion of anti-tuberculous therapy.

Additional rare severe, opportunistic infections have also been reported, such as listeriosis, coccidioidomycosis, and histoplasmosis along with infections caused by *Cryptococcus*, *Aspergillus*, and *Pneumocystis* [2, 48]. Although the incidence of fungal infections were not significantly increased in clinical trials, based on case reports and post-marketing surveillance data, a fungal infection should be suspected if a patient on biologic therapy develops a fever [13]. Whether these types of rare infections are more common with infliximab compared to other TNF antagonists is not known but this may be the case [2, 13, 48].

Viral infections are an additional concern, as there have been reports of reactivated hepatitis

B, and worsening of hepatitis C [2]. It is therefore prudent to screen patients for HBV and HCV before initiating therapy. All anti-TNF agents carry a boxed warning regarding the reactivation of hepatitis B. In the case of a positive result, anti-TNF therapy should be initiated only in combination with hepatitis treatment and close monitoring of liver enzymes and viral DNA levels under the supervision of a specialist. It is interesting to note that, in some individuals with hepatitis C, TNF inhibitors have been reported to demonstrate safety and sometimes actually improve hepatic disease [85–88]. There is currently limited evidence on the safety of infliximab treatment in HIV positive individuals [13]. Caution is therefore advised when considering anti-TNF therapy in these high-risk individuals [89].

In addition to the aforementioned screening measures, no live vaccinations should be administered to a patient undergoing TNF antagonist therapy, and these agents should be withheld if patients are given antibiotics and completely discontinued in the presence of severe infections, as these patients have a higher propensity to develop serious bacterial complications [44–46].

Despite the risk of infectious complications, the overwhelming majority of these infections are minor, consisting mainly of upper respiratory infections [1]. Recently, *JAMA* published a multicenter, retrospective study examining whether the use of biologic agents was associated with an increased risk of serious infections requiring hospitalization in comparison to non-biologic agents [90]. They determined that TNF-antagonists were not associated with an increased risk of hospitalization for serious infections across multiple autoimmune diseases, including psoriasis and psoriatic arthritis. However, it was noted that within rheumatoid arthritis patients, infliximab was associated with a higher rate of serious infection when compared alone to non-biologics (adjusted hazard ratio: 1.25, 95 % confidence interval: 1.07–1.48) and when compared to the other TNF agents, etanercept (aHR: 1.26; 95 % CI: 1.07–1.47) and adalimumab (aHR: 1.23; 95 % CI: 1.02–1.48). Subgrouping of the TNF antagonists was not performed for psoriasis specifically, however the rate of serious infections for the biologics as a group compared to the non-biologics was not significantly different. Baseline use of glucocorticoids, however, was associated with a significantly increased risk of serious infection and hospitalization compared to no baseline use of steroids.

An additional concern surrounding the increased risk of infections is whether or not this risk will further increase perioperatively, and whether or not infliximab infusions should be held for a certain period of time before a major or minor surgery. Recently, a retrospective study was conducted to assess the safety of preoperative infliximab use before restorative proctocolectomy and ileal pouch-anal anastomosis (IPAA) in patients suffering from ulcerative colitis (UC) [91]. Although controversy exists surrounding the risks of preoperative infliximab [92–95], it was determined that short-term postoperative and infectious complications were similar between the group that had received infliximab within 12 weeks of the surgery (44.8 %), and those who had not (44.2 %) [91]. In fact, a trend toward lower rates of wound infection was observed for the infliximab group (3.5 %) compared to controls (19.2 %). While these results are promising, there is a need for prospective studies.

## Malignancy

Although there is conflicting evidence meta-analyses and observational studies with TNF antagonists in the RA population demonstrated an increased risk of malignancy [65, 66, 96–105]. Again, the same argument holds true as above where the different disease states and the combination of immunosuppressants in this population may have a synergistic effect resulting in an increased risk of infection and malignancy that may not be applicable to the psoriatic patient population [72–76]. In fact, in a recent meta-analysis the authors concluded that there was no statistically significant increased risk of malignancy in patients with psoriatic disease on short-term biologic therapy [1].

Overall, in the malignancies observed, 70.6 % were non-melanoma skin cancers [1]. Whether this was an artifact of increased recognition as the psoriatic lesions healed is uncertain. Additionally, it has been proposed that a patient's psoriasis may inherently increase their risk for developing lymphoma, further complicating the analysis of biological agents [105, 106]. In the golimumab trials, non-melanoma skin cancers were also the most common, however colon cancer, prostate cancer, and small cell lung carcinoma were also observed, although infrequently [12]. Furthermore, the results of randomized controlled trials show that 26 % of malignancies occur within 12 weeks from enrollment in patients receiving TNF inhibitors, suggesting pre-existence of the cancers before initiation of biologic therapy [107]. Therefore, it is prudent that patients undergo age and risk adequate screening before initiation of treatment.

Overall, the short-term risk-benefit profile of biologics in patients with psoriatic disease is favorable. However, long-term studies with larger patient populations are necessary in order to adequately assess the risk of cancer and serious infection with chronic use of infliximab and golimumab.

## Laboratory Data/Autoimmune Disease

Some studies have reported abnormalities in laboratory data associated with the use of infliximab. In a randomized study by Reich et al., a significant increase in liver enzymes, aspartate and alanine aminotransferases was observed [23]. Patients remained asymptomatic, however there is currently not enough data to reach a definitive conclusion on the clinical significance of this finding. Hematological disturbances have also been noted, such as rare cases of aplastic anemia and pancytopenia, which can further predispose the patient to serious infections [2].

Additionally, due to its chimeric nature, infliximab has been shown to result in the formation of antibodies [48]. Most commonly, antinuclear antibodies (ANA), antibodies to double-stranded DNA, and anti-cardiolipin antibodies have been reported [108–110]. Studies of Crohn's disease show that 44 % develop ANAs at some point during the course of their treatment with infliximab [7, 49]. While the development of systemic lupus erythematosus (SLE) in patients undergoing biologic treatment is rare, it is postulated that the important role TNF plays in autoregulation may be linked with new signs of autoimmune disease in patients receiving anti-TNF agents [13, 111, 112]. It is also noted that withdrawal of therapy typically results in resolution of symptoms. Several demyelinating and neurologic events, including exacerbations of pre-existing multiple sclerosis (MS), have also been reported with the use of TNF antagonists [9, 13]. Because of this increased risk, patients with MS along with their first-degree relatives have been cautioned against the use of the drugs [44, 45].

In addition to autoimmune antibodies, it has been reported that anti-infliximab antibodies may develop over time with regular use of the drug [7, 113]. The primary concern is that these antibodies are speculated to result in decreased efficacy of the medication, in regard to both initial response as well as long-term efficacy [9]. Approximately 10 % of patients with Crohn's disease and rheumatoid disease in clinical trials have developed antibodies [49], and reports of up to one-third of patients with psoriatic disease [24, 77]. The exact significance of elevated antibody levels relative to drug efficacy remains uncertain at this time, however studies have established relationships among antibody formation and low serum drug levels or failure and loss of response in patients with rheumatic and inflammatory bowel disease [114–118]. In psoriasis, elevated levels of antibodies were discovered in non-responders, and authors concluded that they appeared to play a role in the lack or regression of response [24, 119, 120]. In one trial in particular, patients with an initial response to infliximab positive for antibodies to the drug at week 10 were less likely to maintain a good response at 1 year than their antibody-negative counterparts [24]. Moreover, these same authors proposed that the presence of antibodies is associated with increased rates of infusion reactions to infliximab [24]. Therefore, loss or initial lack of response to infliximab warrants testing the patients for antibodies. Unfortunately, these tests are not readily

available in most clinical settings and various methodologies have been used in trials without extensive comparative testing [24, 114, 115, 117, 118, 120, 121]. According to a few studies, the use of methotrexate in combination with TNF inhibitors appears to reduce the incidence of antibody formation [4, 113, 116]. Finally, it has also been suggested that the presence of autoimmune antibodies can predict treatment failures, although additional research is necessary [114].

## Dermatologic

Various skin complications have been reported with the use of anti-TNF agents, some of which include, delayed hypersensitivity type reactions, lupus-like syndrome, bullous skin lesions, eczematide-like purpura, annular lichenoid eruption, and leucocytoclastic vasculitis [48]. In addition, several eczematous eruptions have occurred with the use of infliximab, however most reactions resolve with discontinuation of the offending agent [122].

Interestingly, there are an increasing number of cases documenting the paradoxical formation of psoriasis during treatment with TNF inhibitors [3, 123–127], primarily in patients treated for other autoimmune diseases, such as Crohn's disease and rheumatoid arthritis [128, 129]. The mechanism of this paradoxical phenomenon, considering the proven benefits of TNF inhibition in psoriatic disease, remains elusive [13]. It has been speculated that the pathophysiology involves the disequilibrium of cytokines caused by the inhibition of TNF-alpha. One review suggests that this disruption in cytokine balance results in the up-regulation of plasmacytoid dendritic cells resulting in the unopposed production of interferon-alpha and the formation of skin disease in predisposed individuals [130], while another study suggests the involvement of activated autoreactive T cells and damage via autoimmune mechanisms [127]. Various treatments have been reported to be useful in this situation although this is anecdotal data (aggressive topical therapy, the addition of methotrexate, acitretin, cyclosporine, phototherapy, or switching the TNF agent) [131]. Complete discontinuation of all biologics is often unnecessary, and a change in the TNF antagonist used should be considered if conventional treatment fails [130].

## Treatment Switches

There is evidence that a gradual decline in therapeutic efficacy occurs in some patients with TNF antagonists, whether through decreased bioavailability of the drug or as a biological adaptation to chronic blockade, such as the development of anti-drug antibodies [7, 42, 113]. Surprisingly, switching to a different biologic agent has proven effective in treatment-refractory patients, although the underlying mechanism remains elusive at this time. In 2007, JAAD published a retrospective study involving the efficacy of infliximab in patients who previously failed treatment with etanercept [42]. Infliximab was initiated at 5 mg/kg and administered on weeks 0, 2, 6, 14, and every 8 weeks thereafter. After only 12–14 weeks of infliximab therapy, 17 of 19 (89 %) patients showed improvements in their PGA and BSA. Fifteen (79 %) still maintained adequate control on infliximab at the time of study publication, although 10 patients required infliximab dose escalation, with a majority of patients requiring infusions every 6 weeks to maintain continued response. In addition, safety data was obtained and compared between the two TNF-antagonists. The use of infliximab was associated with a possible increased incidence in adverse events compared to etanercept (16 versus 5 events, respectively). However, a majority of these events were considered minor.

More recently, a multicenter, open-label prospective study (PSUNRISE) was conducted to evaluate the clinical response of an etanercept-to-infliximab switch in patients with psoriasis unresponsive to, or with a loss of response to, etanercept therapy [41]. Two-hundred fifteen patients were included who had a PGA score of at least 2 despite 4 or more months of treatment with etanercept. Patients received intravenous infusions of infliximab 5 mg/kg at weeks 0, 2, 6, 14, and 22. At week 10, 65.4 % of patients achieved a PGA score of 0 (clear) or 1 (minimal) and 61.3 % of patients maintained this response

throughout the 26 weeks. Moreover, there were no unexpected side effects or safety concerns experienced during this study. This trial demonstrates that patients with an inadequate response to etanercept can achieve substantial benefit after switching to infliximab.

### Conclusion

Infliximab has been clinically available for over a decade and a large body of data exists proving its generally increased efficacy and fewer adverse events over traditional agents in numerous inflammatory disorders, including psoriasis and psoriatic arthritis. Research has proven the effectiveness of infliximab and golimumab in treating signs and symptoms of psoriasis, and demonstrated their rapid and prolonged suppression of inflammation preventing long-term disease progression, especially in debilitating disease such as psoriatic arthritis. Although questions remain regarding the long-term safety of these drugs, no new or unexpected safety issues have emerged over the years, and infliximab and golimumab have been shown to be well-tolerated when clinicians appropriately select patients and adhere to adequate screening and monitoring guidelines. However, long-term studies and continued surveillance of patients is warranted. As for long-term efficacy, there is a great need for the development of predictive biomarkers to predict response to biologic therapy, and more data is needed in order to fully characterize the role of neutralizing anti-drug antibodies. Overall, the benefit:risk profile of these medications is favorable, and at this time, cost appears to be the main barrier to the more widespread and extensive use of these biological agents.

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# Ustekinumab

# 15

Caitriona Ryan and Craig L. Leonardi

**Abstract**

Ustekinumab is a fully human IgG antibody to the common p40 subunit of interleukin-12 (IL-12) and IL-23, which has shown considerable efficacy in the treatment of psoriasis and psoriatic arthritis. This review examines the efficacy and safety of ustekinumab for the treatment of psoriasis in clinical studies to date. Ustekinumab was shown to be highly effective in the treatment of moderate-to-severe psoriasis with sustained response for up to 5 years in the majority of patients. Adverse events in clinical studies to date have been for the most part, mild and similar to that in placebo-treated patients. Controversial meta-analyses, however, have generated concern regarding the cardiovascular safety of this class of drugs and some have advised caution when using ustekinumab in patients with cardiovascular risk factors until more robust, long-term safety data is available.

**Keywords**

Ustekinumab • Psoriasis • Psoriatic arthritis (or arthritis) • IL12 • IL23 Cardiovascular • Efficacy • Safety

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**Conflicts of Interest**

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## Introduction

Ustekinumab (Janssen Pharmaceuticals, Inc., Philadelphia, PA) is a fully human immunoglobulin G1 (IgG1) kappa monoclonal antibody to the p40 subunit common to interleukin-12 (IL-12) and IL-23, which has shown significant efficacy in the treatment of moderate-to-severe psoriasis [1]. It is licensed for the treatment of chronic plaque psoriasis and psoriatic arthritis in adults in the United States, Europe and multiple other countries and studies for the treatment of palmo-plantar psoriasis have recently been completed [2]. IL-12 and IL-23 are heterodimeric cytokines which possess a common p40 subunit linked by a disulphide bond to a unique chain, IL-12p35 and IL-23p19, respectively [3, 4]. The p40 subunit binds to the IL-12 receptor-beta1 (IL-12Rb1) on the surface of T lymphocytes and natural killer cells. Interleukin-12 is a potent inducer of interferon-gamma (IFN-g), which promotes T-cell differentiation toward a Th1 lineage, while interleukin-23 is the major regulator of Th17 CD4 cells, a subset of T helper cells distinct from Th1 and Th2 cells, defined by their ability to produce IL-17 [5]. Interleukin-23 stimulates IL-17A, IL-17F and IL-22 production from Th17 cells and mediates its effects through Janus kinase-2 (JAK2) and STAT3, leading to hyperproliferation of keratinocytes and production of chemokines, angiogenic factors (VEGF) and pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-a), nitric oxide and IL-1b [6, 7]. As psoriasis was originally thought to predominately be a Th1-cell mediated disease, and the critical role of Th17 cells only a recent finding, ustekinumab was specifically developed to target IL-12. The concomitant inhibition of IL-23 was thus, a fortuitous result of targeting the p40 subunit [8, 9]. A similar monoclonal antibody targeting the p40 subunit, briakinumab, also, highly efficacious in the treatment of psoriasis, however, was recently withdrawn from clinical trials due to safety concerns relating to adverse cardiovascular risk, infection and malignancy and has thus raised concerns regarding the safety of ustekinumab [10].

## Pharmacokinetics

In phase I studies in psoriasis, ustekinumab showed linear pharmacokinetics with both ascending single intravenous doses and ascending single subcutaneous doses of the drug [11]. After a single subcutaneous dose, ustekinumab was slowly absorbed, reaching maximum concentration ($t_{max}$) between 7 and 14 days [12]. The absolute bioavailability (F) of ustekinumab was estimated to be 57.2 % after a single subcutaneous dose, with an apparent volume of distribution of 79-161 ml/kg at the terminal phase [13]. Steady-state concentrations were achieved by week 28 in phase III studies in psoriasis, with trough steady-state serum concentrations ($c_{trough}$) showing dose proportionality. The median $c_{trough}$ in those taking 90 mg every 12 weeks was twice that of those taking 45 mg in two phase III psoriasis studies (0.47 vs 0.21 ug/ml in PHOENIX 1 and 0.49 vs 0.26 ug/ml in PHOENIX 2), with no evidence of accumulation with either dosage regimen. The metabolic pathway of ustekinumab has not yet been fully elucidated. As a human IgG monoclonal antibody, ustekinumab is most likely degraded into small peptides and amino acids by the reticuloendothelial system in the same manner as endogenous IgG. A combined analysis of phase III studies in psoriasis calculated the mean half-life to be 21.6 days [14]. A population based approach was used to further characterize the pharmacokinetic profile of ustekinumab based on two phase III studies [1, 14, 15]. Mean values for apparent clearance, apparent volume of distribution and absorption rate constant were 0.465 L/day, 15.7 L and 0.354/day, respectively. Based on the known bioavailability of ustekinumab, the volume of distribution of ustekinumab was calculated to be approximately 8.9 L in a 90 kg psoriasis patient, suggesting that ustekinumab is confined to the intravascular system, with limited tissue distribution. Factors influencing variation in apparent clearance and apparent volume of distribution included body weight, diabetes mellitus (independent of weight) and anti-drug antibodies to ustekinumab [14]. The most

significant effect was caused by body weight, with an apparent clearance and apparent volume of distribution approximately 55 and 37 % higher, respectively, in those with a bodyweight of greater than 100 kg compared with those of 100 kg or less. This emphasizes the importance of dose adjustment in those who have a higher bodyweight to achieve a similar efficacy. None of the 28 concomitant medications analyzed had a significant effect on the pharmacokinetic profile. 3.2 % of patients developed antibodies to ustekinumab, which was associated with a mean increase in apparent clearance of 35.5 % in these patients.

In the US, the current licensed dosage regimen is 45 mg of ustekinumab at baseline, 4 weeks and every 12 weeks in those less than 100 kg in weight, and 90 mg of ustekinumab at the same intervals for those heavier than 100 kg.

## Pharmacodynamics

Two phase I studies have examined the pharmacodynamics of ustekinumab in lesional psoriatic skin. The first examined the effect of intravenous ustekinumab in 18 patients. There was a significant reduction in the expression of IFN-gamma (γ), TNF α, IL-8, IL-10, IFN-γ-inducible protein-10 and monocyte chemotactic protein-1 (MCP-1) within 2 weeks of administration of the drug before clinical response and histological changes were evident [16]. A significant reduction in total CD3+ T cells was observed in responders (those achieving a PASI-75 response) but not in non-responders by week 2. Levels of TNF- α were significantly reduced in responders but not in poor responders, while levels of IL-12p40 and IL-23p19 were reduced in both populations, particularly in responders. When baseline genetic expression of responders was compared to that of non-responders, mRNA expression of TNF-a was significantly higher in responders and correlated with the percentage improvement in PASI, suggesting that this may be a predictor of treatment response. The second phase I study examined the effect of subcutaneous ustekinumab in 21 patients. Punch biopsies were obtained from lesional skin 24 h before, and 1 week after IL-12/23 antibody administration, and the mRNA expression of various cytokines, including TNF-a, IFN-g, IL-8, IL-18, IL-12/23p40 subunit, IL-23p19 subunit, IL-12p35 subunit, IL-10, IP-10, RANTES and CCL-2 was measured using real-time polymerase chain reaction. Although there was no significant change in the expression of these cytokines at week 1 compared to baseline, the mRNA expression of IL-8, IL-18 and IFN-g was significantly decreased in the lesional skin of those who had a sustained response of at least 70 % improvement in PASI at three separate time-points (week 8, 12 and 16), compared with those without sustained PASI improvement.

The effects of ustekinumab on lesional skin and peripheral blood in a subset of psoriasis patients were examined in a phase II psoriasis study [17]. At week 12, a significant decrease in median epidermal thickness correlated with a reduction in cellular proliferation (Ki67) and T-cell infiltration (CD3) by 84.3 and 70.7 %, respectively, in the combined ustekinumab group. Surprisingly, the level of IL-12p40, the target of ustekinumab, increased 13-fold from baseline to week 12, before slowly decreasing to near baseline levels by week 32. This was postulated to be due to decreased clearance of non-functional circulating complexes of ustekinumab-bound IL-12p40. The expression of cutaneous lymphocyte antigen (CLA), which facilitates homing of activated T cells to the skin, significantly decreased from baseline in ustekinumab-treated patients compared with placebo, while there was no change in expression of CD45RA, CD45RO, CXCR3, CD25 or HLA-DR on T cells. The systemic effects of ustekinumab were also investigated *in vitro* in healthy donors using isolated peripheral blood mononuclear cells in the absence or presence of recombinant IL-12 or IL-23 [17]. Ustekinumab inhibited up-regulation of IL-12R, IL-2R α (CD25) and the co-stimulatory receptor CD40L, while reducing IL-12 and IL-23-induced secretion of the pro-inflammatory cytokines IFN-g, TNF-a, IL-2 and IL-17A.

## Clinical Efficacy

Two large scale phase III, multicenter, randomized, double-blind, placebo-controlled, parallel studies, PHOENIX 1 and PHOENIX 2, were performed to evaluate the subcutaneous administration of ustekinumab in patients with moderate-to-severe psoriasis [1, 15]. In PHOENIX 1, 766 patients were randomized to receive 45 mg or 90 mg of ustekinumab at baseline, week 4, followed by every 12 weeks, or to receive placebo at week 0 and 4, with crossover to receive either 45 mg of ustekinumab or 90 mg of ustekinumab at week 12 [1]. Those in the initial ustekinumab group who achieved a sustained PASI-75 at both week 28 and 40 were re-randomized at week 40 to ongoing treatment or withdrawal from treatment for another 36 weeks until loss of response (weeks 40–76). These patients were retreated when they lost at least 50 % of PASI improvement. At week 12, PASI-75 was achieved in 67.1 % of those receiving 45 mg, and 66.4 % of those receiving 90 mg of ustekinumab compared with 3.1 % of those taking placebo, while PASI-90 was achieved in 41.6, 36.7 and 2 % of these groups, respectively. Those receiving placebo, achieved similar response rates after crossover to active treatment. Maximum efficacy was achieved at week 24, with PASI-75 responses of 76.1 and 85 % for the 45 and 90 mg ustekinumab groups, respectively. A significantly higher proportion of those receiving maintenance treatment maintained a PASI-75 response compared to those from whom treatment was withdrawn ($p<0.0001$). Response rates stayed stable up to 76 weeks in the maintenance group, whereas the median percentage improvement in PASI began to decrease by week 44 in the withdrawal group, with a median time to loss of PASI-75 of 15 weeks. No rebound flare was observed on discontinuation of ustekinumab (defined as a PASI greater than 125 % of baseline). Of the 195 patients who recommenced ustekinumab after losing response, 85.6 % reestablished a PASI-75 response within 12 weeks. Patient-determined quality of life, as determined by DLQI, showed a similar improvement to objective assessments of disease severity, with median changes in ustekinumab-treated patients significantly greater than placebo-treated patients at week 12. A recent analysis showed that at 3 years, 79.8 % of patients (601 of 753 patients) who received one or more dose of ustekinumab remained in the study and that 80.9 % (45 mg) and 82.7 % (90 mg) of week 40 responders continuing treatment every 12 weeks achieved a PASI-75 response [18].

In PHOENIX 2, a similar schedule was followed over 52 weeks, with a total of 1,230 patients randomized to receive 45 or 90 mg of ustekinumab or placebo at baseline, week 4, and then every 12 weeks or placebo at baseline and week 4, followed by a placebo crossover to receive 45 or 90 mg of ustekinumab (week 12–28) [15]. At week 28, partial responders (those who had achieved greater than PASI-50 but less than PASI-75), were randomized to escalate dosing to every 8 weeks at their originally assigned dose, or to continue receiving ustekinumab every 12 weeks (week 28–52). At week 12, 66.7 % of patients receiving 45 mg ustekinumab, and 75.7 % receiving 90 mg ustekinumab achieved PASI-75, compared with 3.7 % receiving placebo, while PASI-90 was achieved in 42.3, 50.9 and 0.7 % of these groups, respectively. There was also a highly significant improvement in DLQI in the ustekinumab treated patients compared with the placebo group at week 12 ($p<0.0001$). Maximum PASI-75 response rates were attained at week 20 (74.9 % of the 45 mg group and 83.5 % of the 90 mg group). At week 28, 22.7 % of patients in the 45 mg ustekinumab group were partial responders compared with 15.8 % in the 90 mg group. Independent predictors of partial response included increased bodyweight, a history of non-response to biologic agents, longer duration of psoriasis and the presence of psoriatic arthritis. Partial responders had a significantly higher incidence of antibodies to ustekinumab (12.7 %) compared to responders (2 %), and serum trough drug levels were two to three times lower than those of responders. Escalation from a 12 weekly to an 8 weekly dosing regime resulted in a four to five times increase in the mean trough serum concentrations in partial responders between week 28 and week 52. In partial responders who

received dosing intensification of ustekinumab 90 mg every 12 weeks to ustekinumab 90 mg every 8 weeks, there was a significant increase in those achieving PASI-75, compared to those who remained at a dose of ustekinumab 90 mg every 12 weeks, with response rates of 68.8 and 33.3 %, respectively. There was no significant difference in response, however, in those randomized to receive 45 mg of ustekinumab every 8 weeks, compared to those who continued to receive 45 mg every 12 weeks.

The first study to directly compare the efficacy of two biologic agents in psoriasis was the ACCEPT study, a single-blind randomized, parallel phase III study of 903 psoriasis patients comparing the safety and efficacy of ustekinumab with etanercept [19]. Patients were randomized to receive ustekinumab 45 mg or 90 mg at baseline and at week 4 or etanercept 50 g twice weekly for 12 weeks. There was no placebo arm in this study. At week 12 PASI-75 was achieved in 67.5 % of those receiving 45 mg ustekinumab, 73.8 % of those receiving 90 mg of ustekinumab and 56.8 % of those receiving etanercept, while PASI-90 was achieved in 36, 45 and 23 % of these groups, respectively. A PGA of cleared or minimal was achieved in 65.1, 70.6 and 49 % of the groups.

## Psoriatic Arthritis

A randomized, double-blind, placebo-controlled, crossover phase II study of ustekinumab was performed in 146 patients with psoriatic arthritis who had an inadequate response to disease-modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs) or anti-TNF agents [20]. Patients had at least one plaque of psoriasis greater than 2 cm and active arthritis of at least 6 months duration, defined as 3 or more swollen joints, 3 or more tender joints, with either morning stiffness for at least 45 min or a C-reactive protein (CRP) of 15 mg/L or higher. Concurrent treatment with stable doses of methotrexate, corticosteroids and NSAIDs was permitted. Patients received either 90 mg of subcutaneous ustekinumab per week for 4 weeks, followed by placebo at week 12 and 16; or placebo for 4 weeks, followed by 90 mg of subcutaneous ustekinumab at weeks 12 and 16 (Group 2). Forty-two percent of patients in group 1 (ustekinumab-treated patients) achieved the American College of Rheumatology Criteria (ACR-20) at week 12 compared with 14 % of those in group 2 (placebo-treated patients) ($p = 0.0002$). There were also significant improvements in group 1 compared to group 2 at week 12 in tender joint count, patients' assessment of pain, patients' and doctors' assessments of disease activity, disease activity index score 28 (DAS-28) rating, severity of dactylitis and presence of enthesopathy. There was a significant improvement in functional status, as evidenced by a median decrease in the disability index of the health assessment questionnaire (HAQ) of 0.25 in group 1 compared with no change in group 2 ($p = 0.0075$), while the median decrease from baseline in DLQI was significantly higher in group 1 ($p < 0.001$). At week 24, when group 2 were crossed over from placebo to receive two doses of ustekinumab, ACR-20 and DAS-28 responses were similar to group 1 at week 12. The study was not powered adequately to detect difference in response related to concomitant methotrexate treatment. In a phase III study of 615 patients, 49.5 % of patients treated with 90 mg ustekinumab and 42.4 % of patients treated with 45 mg ustekinumab achieved an ACR-20 response at week 24 compared with 22.8 % of patients in the placebo-treated ($p < 0.0001$ for both comparisons) and responses were maintained at week 52 [21]. Another phase III study to evaluate the safety and efficacy of ustekinumab in psoriatic arthritis in TNF- α-naive and TNF- α exposed patients has recently been completed and the results are pending.

## Adverse Effects

The most comprehensive ustekinumab safety data to date comes from a pooled longitudinal analysis of phase II and phase III clinical trials in moderate-to-severe psoriasis [22–24]. This was based on all safety data available from the Phase

2 study, PHOENIX 1 and 2 and the ACCEPT study. A total of 3,117 patients has been followed for up to 4 years (6,791 patient-years). During the combined 12 week placebo-controlled period of these studies, 50.4, 57.6 and 51.6 % of patients treated with placebo, 45 mg of ustekinumab and 90 mg of ustekinumab, respectively, experienced at least one adverse event, while 1.4, 1.6 and 1.4 % of patients in these groups experienced a serious side effect and 1.9, 1.1 and 1.4 % were withdrawn from the study due to adverse effects. The most common side effects were nasopharyngitis, upper respiratory tract infections, headache and arthralgias. Rates of adverse events, serious adverse events, infections or adverse events requiring discontinuation of treatment did not increase with increased duration of treatment and were comparable between ustekinumab doses.

## Serious Infections

Based on animal models of cytokine deficiency and patients with genetic mutations encoding IL-12 and IL-23 or their receptors, there was particular concern about a theoretical increase in the risk of serious infections or malignancy with the advent of these agents. In animal models, IL-12 has been shown to be important in prevention against mycobacteria, salmonellosis and toxoplasmosis and patients with a genetic deficiency of the IL-12 receptor or the IL-12p40 subunit have an increased risk of severe infections with intracellular pathogens such as mycobacteria and salmonella [25–29]. Experimental animal models of herpes viral infection, viral encephalitis, viral hepatitis and acquired immunodeficiency syndrome (AIDS), have also demonstrated a central role for IL-12 in protecting against viral infection [30–33]. Interleukin-12 also appears to be important in defense against opportunistic fungal infections, with increased susceptibility to *Cryptococcus neoformans* infection observed in p35−/− or p40−/− knockout mice and prevention of infection following the administration of IL-12 [34, 35]. Similarly, IL-12p40−/− knockout mice did not control fungal proliferation and dissemination and succumbed to infection following intravenous inoculation of yeast cells of paracoccidioidomycosis.

Interleukin-23 is also believed to contribute to immune protection in the skin, lung and gut. Interleukin-23 and IL-17, however, have been shown to be only marginally involved in primary infections with pathogens that require $T_H1$ immunity [36–40]. One study showed that blocking IL-23 alone does not increase bacterial burden in immunocompetent mice after BCG infection but that blocking TNF-α or the p40 subunit results in increased infectious burden [41, 42]. Interleukin-23p19 deficient mice showed significant mortality following a sub-lethal dose of intrapulmonary *Klebsiella pneumoniae*, however, while IL-12p40-deficient, IL-12p35- deficient and IL-17R-deficient mice also show increased susceptibility to infection following inoculation [43]. Administration of IL-17 restored the normal infectious response in IL-23p19-deficient mice, but not completely in p40-deficient mice, suggesting the additional role of IL-12-induced IFN-g production in the immune defense to Klebsiella infection. Another experimental study showed that IL-23 plays a critical role in the host defense to *Pneumocystis Carinii* [44]. Individuals with abnormalities of Th17 cell function, such as patients with hyper-IgE (Job's) syndrome and chronic mucocutaneous candidiasis, are more prone to infection with *Staphylococcus aureus* and *candida albicans*.

However, clinical studies to date have not shown an increase in serious infections with the use of ustekinumab [24]. In the pooled analysis, the frequency of infection during the placebo-controlled period of the studies in patients receiving placebo, 45 mg of ustekinumab or 90 mg of ustekinumab, was 23.2, 27 and 24.1 %, respectively, while the rates of serious infection were similar between the placebo (1.70/100PY) and 90 mg (1.97/100PY) groups but lower in the in the 45 mg group (0.49/100PY) [24]. The rates of overall infection, serious infection and infections requiring antibiotic treatment remained stable or decreased over the 4 years, with rates serious infection of 0.8/100 patient years (PY) and 1.32/100PY for patients treated with 45 and 90 mg of ustekinumab respectively and were consistent with expected rates in psoriasis patients

using the Marketscan Database. No cases of tuberculosis were reported in the pooled analysis, but one man who had a previously negative purified protein derivative and QuantiFERON-TB Gold screening tests, had a tuberculosis reactivation after two doses of ustekinumab in a RCT of Asian psoriasis patients [45].

## Malignancy

Animal studies have also suggested increased tumorigenicity following inhibition of IL-12 [46–48]. Interleukin-12 has shown anti-tumor and anti-metastatic activity in murine tumor models of melanoma, renal cell carcinoma and breast cancer, while IL-12 deficient mice have an increased incidence of UVB-induced skin tumors and malignant transformation of papillomas [46–48]. Patients with congenital deficiencies of IL-12p40 or IL-12R, however, do not appear to have an increased incidence of malignancy [28]. Interleukin-23, in contrast, appears to promote tumor growth, suggesting that inhibition of this cytokine may inhibit carcinogenesis [49].

There were no differences in the incidence of non-melanoma skin cancer (NMSC) or other malignancies during the placebo-controlled phases of usekinumab studies [24]. The rate of NMSC was 0.7/100PY in the 45 mg group and 0.53/100PY in the 90 mg group (34 BCC and 10 SCC) and higher among patients previously treated with psoralen-UVA [23, 24]. Long-term follow-up data showed rates of malignancies other than NMSC of 0.63/100PY in the 45 mg group and 0.61/100PY in the 90 mg group, with a total of 42 malignancies over the course of the studies [24]. These rates were consistent with age-, race- and gender-matched rates expected in the normal United States population according to the Surveillance, Epidemiology, and End Results (SEER) database.

## Major Adverse Cardiovascular Events

The withdrawal of briakinumab, another anti-IL-12p40 agent, from clinical studies in 2011 has generated considerable controversy regarding the association between the use of anti-IL-12p40 agents and major adverse cardiovascular events (MACE, a composite endpoint of myocardial infarction, cerebrovascular accident, or cardiovascular death) [10, 50–52]. Despite two meta-analyses examining the use of anti-IL12-p40 inhibitors in psoriasis, conclusive evidence is not yet available regarding the effect of ustekinumab on cardiovascular risk. The first compared the excess probability of MACE in 22 RCTs in 10,183 patients receiving active treatment of anti-IL12p40 agents (ustekinumab and briakinumab) and TNF-α inhibitors [10]. Double-blind, placebo-controlled RCTs of anti-IL12p40 agents (ustekinumab and briakinumab) and TNF-α inhibitors (infliximab, etanercept and adalimumab) were compared and absolute risk differences were used as an effect measure, measuring the excess probability of MACE in those receiving active treatment compared to those receiving placebo. During the placebo-controlled phases of the anti-IL-12p40 studies, 10 of the 3,179 patients treated with anti-IL-12p40 therapies had a MACE compared with zero events in 1,474 patients treated with placebo (risk difference 1.2 events/100PY, $p=0.12$). In anti-TNF-α trials, only one of 3,858 patients treated with anti-TNF- α treatments had a MACE compared with one of 1,812 treated with placebo (risk difference 0.05 events/100PY, $p=0.94$). Although the apparent increase in MACE observed with patients receiving anti-IL-12p40 antibodies was not statistically significant, the authors suggested that the short 12–24 week placebo-controlled period and relatively small patient numbers might not have had adequate power to detect a real difference. A subsequent meta-analysis examining the rate of MACE in patients in RCTs of IL-12/23 antibodies showed a significantly higher risk of MACE in patients treated with anti-IL-12/23 agents compared with placebo. [142] The discrepancy between these meta-analyses results from the use of different statistical methods to compare MACE rates [53].

A 5-year safety study conducted by the manufacturers of ustekinumab, however, has shown no increase in the rate of MACE over time [54]. A total of five MACE (0.3 %), including one cardiovascular death, were reported in 1582 ustekinumab-treated patients compared with no

events in 732 placebo recipients (0 %) during the placebo-controlled phases of the pooled analysis [55]. All of these events occurred in patients with three or more cardiovascular risk factors. All cardiovascular events were re-adjudicated externally at the 4-year follow-up safety analysis and a total of 34 MACE were identified, with four cardiovascular deaths [55]. The rate of MACE was 0.56/100PY and 0.46/100PY in the 45 mg and 90 mg groups, respectively. This was reported to be below the expected rate of heart attacks and strokes when compared with two large databases of patients, the Framingham Heart Study reflecting the general US population, and a cohort of moderate-to-severe psoriasis patients in the General Practice Research Database. It was thus concluded that there was no apparent change in cardiac risk with this agent. Furthermore, other studies examining the use of ustekinumab in psoriatic arthritis and Crohn's disease have not shown an increase in cardiovascular events [56]. Until further evidence is available, however, caution is recommended when commencing patients with cardiovascular risk factors on ustekinumab.

### Other Adverse Events

Although there was initial concern that IL-12 blockade could result in skewing towards a Th2 type cytokine profile, there was no evidence of exacerbation of any atopic disease in these studies. No cases of demyelination were reported apart from a possible case in a patient who was retrospectively diagnosed with human immunodeficiency virus and profoundly lymphopenic at the time. Another case of reversible posterior leukencephalopathy syndrome was reported in a 65 year old with a history of alcohol abuse who recovered fully from the episode.

## Laboratory Abnormalities

In phase I studies of ustekinumab in psoriasis, transient asymptomatic decreases in CD4+ T cells and CD16+/CD56+ natural killer cells were observed in some patients but this was not seen in phase II or III studies [11, 12]. In phase II and III studies in psoriasis and in psoriatic arthritis, the incidence of haematological and biochemical abnormalities was low and similar between ustekinumab-treated and placebo-treated patients. In the phase II study of psoriasis, however, there was a non-significant trend of elevated non-fasting glucose levels in ustekinumab-treated patients (10 %) compared with controls (4 %) (p=0.23) [57]. This was not observed in subsequent phase III studies in psoriasis and ustekinumab was shown to have no effect on haemoglobin A1c levels.

## Pregnancy and Lactation

Ustekinumab is pregnancy category B. The product prescribing information states that ustekinumab should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus [58]. Toxicology studies on cynomolgus monkeys revealed no maternal or fetal abnormalities following administration of intravenous and subcutaneous doses of up to 50 mg/kg during the period of organogenesis [58]. Pregnancy registries will be the most important data source to evaluate the safety of ustekinumab in pregnancy and as of December 2010, 31 maternal pregnancies had been reported with no reports of birth defects or fetal deaths. The product prescribing information for ustekinumab advises caution in administration of ustekinumab to nursing mothers, where the unknown risks to the infant from gastrointestinal exposure to ustekinumab should be weighed against the known benefits of breast-feeding [58]. Ustekinumab is excreted in the milk of lactating monkeys, and as endogenous IgG is excreted in human milk, it is expected that ustekinumab will be also be present. It is not known if ustekinumab would be absorbed systemically through the immature neonatal gastrointestinal tract after ingestion.

## Cautions for Patients Treated with Anti-IL-12p40 Agents

There are no absolute contraindications to treatment with ustekinumab [58]. Treatment should be deferred in patients with clinically important

active infections until the infection resolves or is appropriately treated [58]. No increase in serious infections has been observed with the use of ustekinumab, however, despite initial concerns regarding longer half-life of the drug [24]. Patients with evidence of active or latent tuberculosis should be treated with anti-tuberculosis treatment prior to initiating treatment [58]. Caution should also be exercised when initiating ustekinumab in patients with cardiovascular risk factors. Conclusive evidence is not yet available regarding the effect of ustekinumab on cardiovascular risk and no consensus has been reached regarding the use of this drug in patients with cardiovascular risk factors. A statistical analysis performed by the sponsors of briakinumab to identify a subset of patients who were at higher risk of MACE, showed an event rate of 0.13 events/PPY in patients with one or less risk factor compared with 2.15/PPY for those with two or more risk factors [59]. As a result, we do not recommend initiating ustekinumab in patients with more than one cardiovascular risk factor until more robust evidence is available regarding the effect of anti-IL-12p40 inhibition on cardiovascular risk. Ustekinumab has no currently known drug interactions. Patients should receive all age-appropriate immunizations recommended by current guidelines prior to commencing ustekinumab and live vaccines should not be administered during treatment. The Bacillus Calmette-Guérin (BCG) vaccine should not be administered for 1 year prior to or after discontinuation of treatment [58].

## Conclusions

The field of psoriasis research has been revolutionized by the increased understanding of the pivotal role of the Th-17/IL-23 axis in disease pathogenesis. The development of anti-IL-12p40 agents represents a significant milestone in the biologic therapeutic era of psoriasis treatment, marking the advent of a generation of newer, more selective, targeted biologic treatments. These agents have shown considerable clinical efficacy in clinical trials. Ustekinumab, the only licensed anti-IL-12p40 agent, plays an important role in the current therapeutic armamentarium for psoriasis. The infrequency of dosing afforded by the long half-life of the drug is particularly appealing to patients. Adverse events in clinical studies to date have been for the most part, mild and similar to that in placebo-treated patients. However, concern remains regarding the need for caution relating to rare or long-term side effects of anti-IL12p40 agents in general until more long-term safety data is available. The current ustekinumab studies leading to its approval for psoriasis have involved only 3,000 patients with just over 5 years of continuous therapy, making the continued collection of comprehensive safety data in post-marketing and observational pharmacoepidemiologic studies absolutely essential. Due to the frequent use of phototherapy in our psoriasis population and potentially long latent periods before the development of malignancy, long-term follow-up safety data and the use of registries will also be important in examining the incidence of cutaneous and non-cutaneous malignancy in ustekinumab-treated patients. Heightened vigilance should be exercised when initiating patients with known cardiovascular risk factors on ustekinumab until the effects of anti-IL-12p40 blockade on cardiovascular inflammation, short-term and long-term, are fully elucidated.

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# T-Cell Targeted Therapy: Alefacept and Efalizumab

16

Jerry Bagel

**Abstract**

The importance of T-cell activation, T-cell migration into the dermis, and the production of pro-inflammatory molecules has been shown to be key steps in the pathogenesis of psoriasis. Targeted immunosuppressive agents that interfere with initial T-cell activation were some of the initial biologic agents introduced for the treatment of moderate-to-severe psoriasis. Two such agents are alefacept and efalizumab. These agents demonstrated moderate efficacy in the treatment of psoriasis. In 2009 the manufacturer of efalizumab voluntarily withdrew efalizumab from the market due to its association with an increased risk of progressive multifocal leukoencephalopathy. In 2011 the manufacturer of alefacept also withdrew the drug from the market, although due to business needs not due to a re-assessment of safety or efficacy. The future of T-cell targeted therapy remains uncertain as new biological agents targeting other components of the immune response are being developed.

**Keywords**

Alefacept • Efalizumab • T-cell • Psoriasis • Progressive multifocal leukoencephalopathy

Psoriasis vulgaris is hypothesized to be a T-cell mediated disease [1]. The epidermis and dermis of psoriatic lesions exhibit hyperproliferation of keratinocytes and accumulation of activated T-cells [2–5]. The importance of T-cell activation, T-cell migration into the dermis, and the production of pro-inflammatory molecules has been shown to be key steps in the pathogenesis of psoriasis [6, 7]. Targeted immunosuppressive agents that interfere with initial T-cell activation have been developed and may form the basis of effective psoriasis therapy. Two such agents are alefacept and efalizumab.

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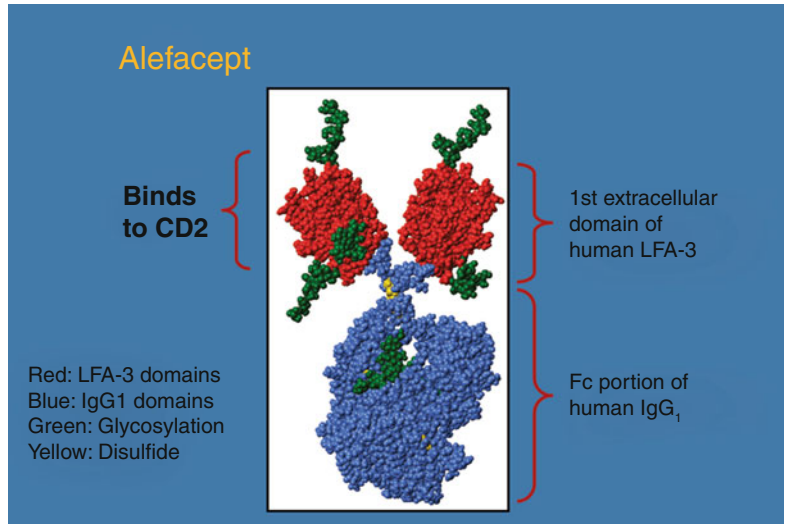


**Fig. 16.1** Structure of alefacept

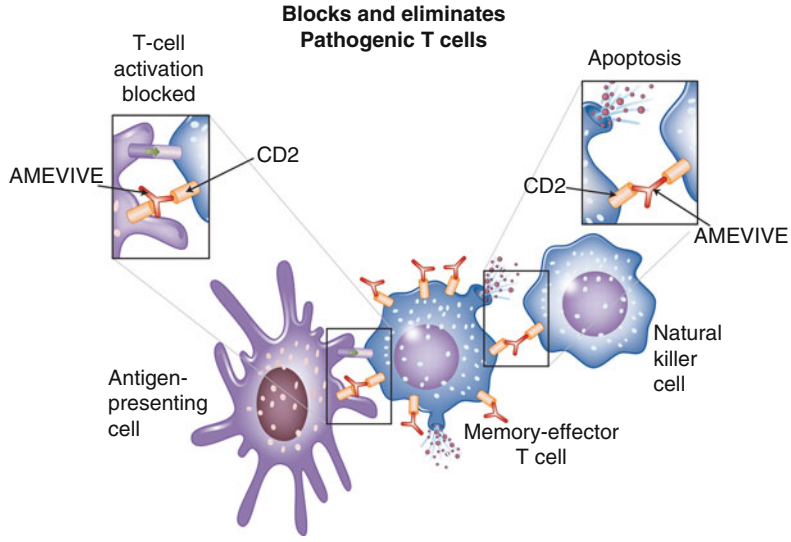


**Fig. 16.2** Mechanism of action of alefacept (Adapted with permission from: Krueger and Callis [58]. Concepts from: Gordon and West [59])

## Description and Mechanism of Action

Alefacept (Amevive, originally Biogen, Inc, currently Astellas Pharma US, Inc.) (Fig. 16.1) is an immunosuppressive dimeric fusion protein that consists of the extracellular CD2-binding portion of the human leukocyte function antigen-3 (LFA-3) linked to the Fc (hinge, CH2 and CH3 domains) portion of human IgG1. Alefacept is produced by recombinant DNA technology in a Chinese Hamster Ovary. Alefacept interferes with lymphocyte activation by specifically binding to the lymphocyte antigen, CD2, and inhibiting the LFA-3/CD2 interaction (Fig. 16.2), which plays a role in the pathophysiology of chronic plaque psoriasis. Alefacept also causes a reduction in subsets of CD2+ T lymphocytes (primarily CD45RO+), presumably by bridging between CD2 on target lymphocytes and immunoglobulin Fc receptors on cytotoxic cells such as natural killer cells. Treatment with alefacept results in a

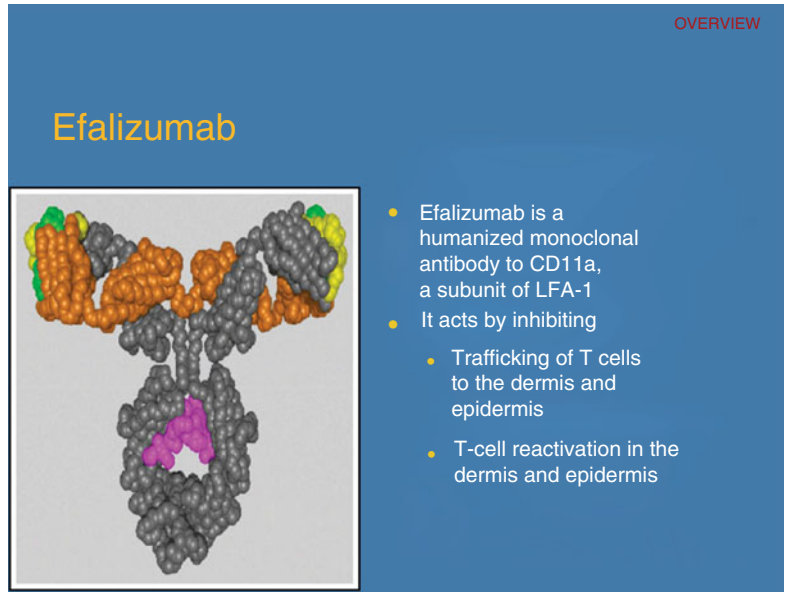


**Fig. 16.3** Structure of efalizumab

reduction of circulating total counts of memory effector CD4+ and CD8+ T lymphocytes, which stimulate the hyperproliferation of keratinocytes and are the predominant T-cells in psoriatic lesions and has been shown to improve the symptoms of psoriasis in clinical trials and in clinical practice [8].

Efalizumab (Raptiva, Genentech, Inc.) is an immunosuppressive recombinant humanized IgG1 monoclonal antibody that binds to human CD11a (Fig. 16.3) [9]. CD11a is a unique α(alpha) subunit of leukocyte function-associated antigen 1 (LFA-1), a member of the leukocyte β(beta)2-integrin family of adhesion molecules. LFA-1 contains CD11a and a β(beta) subunit CD18 and is expressed on all leukocytes [10]. Efalizumab decreases cell surface expression of CD11a and thus prevents the binding of LFA-1 to its ligand, intercellular adhesion molecule-1 (ICAM-1) [11]. ICAM-1 facilitates the binding of antigen-presenting cells [12] to T-cells and is thought to provide costimulatory signals necessary for T-cell activation [13]. LFA-1 is exclusively expressed on leukocytes and interacts with ICAM-1 to promote T-cell activation and migration of T-cells to target tissues during normal and pathologic function of immune system. Interactions among cellular adhesion molecules also facilitate the continuous recirculation of T-lymphocytes among lymph nodes, tissues, and blood [14]. LFA-1 is over expressed on memory T-cells, and ICAM-1 is expressed on vascular endothelial cells at sites of inflammation as well as on keratinocytes and is regarded as an inducer of inflammation and hyperkeratinization in psoriasis [15]. Efalizumab is believed to interfere with T-cell activation and migration by inhibiting the FLA-1/ICAM-1 adhesion interaction and has demonstrated a significant benefit in treating psoriasis in clinical trials and in clinical practice.

## Efficacy in Clinical Trials

### Alefacept

Initially alefacept was evaluated in a randomized, placebo-controlled, double-blind study of 229 patients with chronic plaque psoriasis who had least 10 % of body surface area (BSA) affected by chronic plaque psoriasis and were candidates for or previously received systemic therapy or phototherapy. Patients received intravenous alefacept (0.025, 0.075, or 0.150 mg/kg of body

weight) or placebo weekly for 12 weeks with follow-up for an additional 12 weeks. Disease severity was evaluated using the Psoriasis Area and Severity Index or PASI. PASI scores, which range from 0 (no psoriasis) to 72 (the most severe disease possible), combine assessments of the extent of the body surface area affected and the degree of erythema, induration, and desquamation [16]. Two weeks after completing treatment, alefacept groups achieved greater mean reductions in the baseline PASI score (38, 53, and 53 % in the groups receiving 0.025, 0.075, or 0.150 mg/kg, respectively) than the placebo group (21 %, $P<0.001$), and had higher proportions of patients with a mean reduction in baseline PASI score of at least 50 % (PASI-50) and of at least 75 % (PASI-75). Twelve weeks after completing treatment, 47, 63, and 42 % of the patients in the three alefacept groups respectively, achieved PASI-50 compared with 32 % in the placebo group ($P=0.02$), and 19, 31, and 33 % of the patients in respective alefacept groups achieved PASI-75 compared with 11 % of patients in the placebo group ($P=0.02$). A total of 118 patients completed alefacept therapy and required no additional treatment during the follow-up phase. Among them, 28 patients (24 %) were considered to be clear or almost clear of psoriasis 12 weeks after completing treatment. During treatment, there was a dose-dependent reduction in peripheral blood CD4+ and CD8+ memory effector T-cells, which was significantly correlated with clinical improvement in psoriasis. CD4+ and CD8+ naïve T-cells were not affected by alefacept treatment, indicating that alefacept therapy was targeting activated T-cells and not the immune system in general [17].

Alefacept received marketing approval from the US Food and Drug Administration (FDA) in 2003 based on the results from two pivotal phase III controlled clinical trials. The first trial evaluated the efficacy of two 12 week courses of alefacept against one 12-week course of alefacept and one 12-week course of placebo, and against one 12-week course of placebo and a 12-week course of alefacept in 553 patients with moderate to severe chronic plaque psoriasis. Patients received alefacept 7.5 mg or placebo once weekly administered by 30-s intravenous bolus. There was a 12-week treatment-free follow-up period in between and after the two courses of treatment. The results showed that only 28 % of patients treated with two courses of Alefacept achieved a 75 % reduction in their PASI (compared to 8 % of controls); however, 71 % of these patients kept at least a 50 % reduction of their PASI for a median of 7 months [18].

Since intravenous mode of delivery is inconvenient for a once weekly treatment, the second trial evaluated 507 patients with moderate to severe chronic plaque psoriasis during 12 weeks of once-weekly intramuscular injections of alefacept (0 mg (placebo), 10 mg, or 15 mg) and then for 12 additional weeks without treatment. The results showed dose-depended decreases in the baseline PASI scores with a maximum mean reductions of 46, 41, and 25 % in the 15-mg alefacept, 10-mg alefacept, and placebo groups, respectively, at 6 weeks post dosing. The clinical improvement was long lasting; mean PASI scores in the alefacept groups had not returned to baseline 12 weeks after completing treatment. Over the course of the study, the percentage of patients achieving at least a PASI-75 was higher ($P<0.001$) among patients receiving 15 mg of alefacept (33 %) or 10 mg of alefacept (28 %) than among patients receiving placebo (13 %) [19]. Both of these studies demonstrate good clinical efficacy of alefacept in patients with moderate to severe plaque psoriasis.

Unfortunately, Amevive was never marketed in Europe as the manufacturer withdrew the marketing application for its approval from the European Medicines Agency (EMEA) after a negative review by the European Union's Committee for Proprietary Medicinal Products [20].

## Efalizumab

Phase I/II studies confirmed the biological activity of efalizumab in patients with moderate to severe plaque psoriasis. In the first open label study, patients who had at least 10 % BSA affected by chronic plaque psoriasis and were candidates for or received systemic therapy or

phototherapy received a single dose (0.03–10 mg/kg) of intravenous efalizumab. Treatment with efalizumab 0.3 mg/kg or higher produced a dose-dependent reduction in baseline PASI scores and improvement in clinical severity of psoriasis, which was correlated with blocked CD11a staining in blood and in psoriatic plaques, decreased numbers of epidermal and dermal CD3(+) T cells, decreased keratinocyte and blood vessel expression of ICAM-1, and epidermal thinning [21]. In a second open-label dose-escalation study, patients with moderate to severe psoriasis received intravenous infusions of efalizumab for 7 weeks at doses of 0.1 mg/kg every other week, or 0.1 mg/kg weekly, 0.3 mg/kg weekly, and 0.3 increasing to 0.6 or 1.0 mg/kg weekly. Efalizumab dose of 0.3 mg/kg weekly was the lowest dose that produced detectable efalizumab levels, reduced CD11a availability on the surface of circulating CD3+ T-cells and cutaneous T-cells, consistently decreased T-lymphocyte counts in the dermis and epidermis of psoriatic lesions, downregulated ICAM-1 expression on keratinocytes, reduced epidermal thickness, and produced significant clinical improvement in psoriasis during the treatment period [22]. Intravenous infusion of 0.1 or 0.3 mg/kg or placebo was tested in 144 patients with moderate to severe plaque psoriasis for 8 weeks. One week after the final dose, patients who received efalizumab 0.3 mg/kg experienced significantly greater decreases in baseline epidermal thickness and PASI scores than patients who received placebo [23].

Due to inconvenience of intravenous drug delivery, subcutaneous administration of efalizumab was developed and tested in a series of studies. In a Phase I, open-label study, patients with moderate to severe psoriasis received a single dose of efalizumab (0.3 mg/kg/week) or escalating multiple doses of efalizumab (0.50–2.0 mg/kg/week) subcutaneously for 8 weeks and achieved 40–60 % improvement in signs and symptoms of plaque psoriasis and maintained the response over 6 weeks of post-treatment follow-up [24].

Subsequently, efalizumab was evaluated in two Phase III controlled clinical trials. In the first trial, 556 eligible patients with moderate to severe plaque psoriasis were randomized to receive subcutaneous injections of efalizumab 1.0 mg/kg or placebo weekly for 12 weeks. Efalizumab-treated patients experienced significantly better improvement than placebo-treated patients on all measures of psoriasis severity, including PASI (27 % of patients achieved PASI-75 with efalizumab vs. 4 % of patients with placebo) [25]. When efalizumab treatment was extended another 12 weeks up to 44 % of treated patients achieved PASI-75 at the end of therapy [26]. In the second trial, the patient population was modified during the trial to include high-need patients (patients who could not receive at least two of the currently available systemic therapies) at the request of the European regulatory authorities, but all 793 patients received 1 mg/kg/week efalizumab or placebo subcutaneously during the initial 12-week double-blind treatment period, which was followed by an observation period of up to 24 weeks and a 12-week open-label retreatment period for patients who relapsed. After 12 weeks of treatment, significantly more efalizumab-treated patients than placebo-treated patients achieved PASI-75 (31.4 % vs. 4.2 %, $P<0.0001$). Among high-need patients specifically, 29.5 % of efalizumab-treated patients achieved PASI-75 compared to 2.7 % of placebo-treated patients, also a significantly better improvement with efalizumab ($P<0.0001$) [27]. Based on results from the above studies, efalizumab received marketing approval from the US FDA and the European Medicines Agency in 2005 for the treatment of moderate to severe chronic plaque psoriasis in adults.

## Long-Term Therapy and Remission Rates

Psoriasis is a life-long recurring disease and often requires repetitive long-term therapy to keep the skin inflammation and hyperkeratinization under control. Alefacept was the only biologic agent that resulted in remission. Unfortunately only 20 % of those patients treated had a remission of greater than 7 months. There were no tests to help determine which patient would go into remission 28.

As for Efalizumab about 40 % of patients did very well on it long term, however about 10 % of

patients would flare while on the drug requiring therapeutic rescue usually with cyclosporine Thrombocytopenia was also an adverse event that was not uncommonly seen.

Three prospective open-label clinical trials [28–30] and one retrospective chart review [31] examined the effects of re-treatment with multiple courses of alefacept in patients who either did not achieve at least a PASI-50 response after the first course of treatment or regressed during follow-up. Also studies examined the effect of extended efalizumab therapy for 15 months [32] and 33 months [33]. The studies found that additional courses of alefacept or efalizumab provided an incremental increase in efficacy (the number of PASI-75 responders increased from around 30 % after one course of treatment to a little over 40 % after up to 21 months of alefacept treatment and 33 months of efalizumab treatment) and therefore offered more treatment-free, symptom-free periods to responding patients.

## Use in Combination Regimens

Due to the chronic and resistant nature of the disease, psoriasis is frequently treated using combination therapies in clinical practice. For patients with moderate to severe psoriasis, a biological agent may be supplemented with topical agents, methotrexate, cyclosporine, systemic retinoids such as acitretin, or ultraviolet B (UVB) phototherapy [34–36]. The combination of alefacept or efalizumab and narrowband UVB phototherapy was shown to be particularly successful, leading to a more rapid onset of response, a greater overall response to treatment, and to more patients achieving a PASI-75 response and having longer remissions than either biological agent alone in clinical studies [34, 37–41].

## Use in Scalp and Palmoplantar Psoriasis

Almost 50 % of patients with generalized chronic plaque psoriasis also have psoriasis on their scalp or hands and/or feet, locations that are particularly difficult to treat. An open-label study of 30 patients with scalp psoriasis found that 1–2 16-week courses of 15 mg of IM alefacept cleared or almost cleared scalp psoriasis in almost 30 % of treated patients [42]. Alefacept had also been successfully used in patients with plaque-type [43–45] and pustular [46–48] palmoplantar psoriasis, resulting in significant improvement or clearance in almost 30 % of patients and a reduction in pustules, pain, itching, and functional impairment. Although these findings are limited to small open-label studies and case reports, they demonstrate that alefacept has similar efficacy in localized and generalized forms of plaque psoriasis. Efalizumab therapy had also been studied patients with moderate to severe plaque psoriasis with concomitant scalp, palmoplantar, and nail psoriasis. Efalizumab had been shown to produce excellent (≥75 %) improvement in 42–63 % of patients with scalp and palmoplantar psoriasis and in 13–17 % of patients with nail psoriasis over 24 weeks of treatment [49, 50].

## Safety Considerations for T-Cell Targeted Therapy

The major safety concern during psoriasis treatment with agents that block T-cell activation and potentially downregulate the immune response is infection. Cold and flu-like symptoms are the most common adverse events associated with the use of alefacept or efalizumab in clinical trials. The incidence of malignancies and arthropathy were low, not significantly different from placebo, and did not increase with multiple courses of treatment with either biological agent [51–53]. No increased risk of opportunistic infections was detected during regulatory controlled clinical trials of alefacept or efalizumab. However, in clinical practice, three confirmed cases and one suspected case of progressive multifocal leukoencephalopathy (PML) resulting in death were reported in association with long-term efalizumab use. PML is a rare potentially fatal demyelinating disease believed to be caused by a re-activation of the John Cunningham virus (JVC) and occurs primarily in immunocompromised individuals [54, 55].

## Current and Future Status of T-Cell Targeted Therapy

In 2009 the manufacturer of efalizumab voluntarily withdrew efalizumab from the market due to its association with an increased risk of PML [56]. In 2011 the manufacturer of alefacept also withdrew the drug from the market, although due to business needs not due to a re-assessment of safety or efficacy [57]. The future of t-cell targeted therapy remains uncertain as new biological agents targeting other components of the immune response are being developed.

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# Research Pipeline I: Topical Therapies

17

Bassel Mahmoud and Linda Stein Gold

**Abstract**

Psoriasis is a common chronic inflammatory skin disease affected by both genetics and immune factors. This devastating disease has a huge impact on the quality of life of affected individuals and a pronounced economic burden on the society. Recent understanding of the immunopathogenesis of psoriasis has led to significant progress in its treatment. Many disease-related factors affect the choice of therapy. Mild psoriasis can generally be managed with topical medications, while moderate-to-severe psoriasis is conventionally treated with more aggressive systemic therapies. The ideal treatment should be cost-effective, provide long-term remission and exhibit few side effects. This chapter highlights topical therapies currently under development for psoriasis.

**Keywords**

Psoriasis • Topical • Pipeline • AN2728 • INCB18424 • JAK kinase inhibitor • Methotrexate

## Introduction

Psoriasis is a disease of the immune system gone array. As our understanding of the pathogenesis increases, we are able to develop drugs that specifically target the immunologic abnormalities. Exciting technology holds promise for developing topically applied treatments with selective mechanisms of action and minimal systemic risks.

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## Phases of Development of New Drugs [1]

A. Pre-clinical phase: Promising new agents first undergo pre-clinical testing in animals and are designated by the U.S. Food and Drug Administration (FDA) as an Investigational New Drug if the pre-clinical data is positive. Research then moves on to clinical testing in people through phase I, II and III clinical trials.
B. Phase I: This phase is concerned mainly with safety. It determines how the drug works in healthy study participants. Researchers

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examine the mechanism of action, safety and side effects, although the overall safety of the medication in patients is not established at this phase.

C. Phase II: This phase determines drug effectiveness by investigating the drug's clinical activity against a particular condition. A drug reaches phase II only after the FDA has reviewed the phase I data and concludes the drug is safe enough for patients to proceed with further testing. At this point, a larger group of patients is enrolled and rating scales specific to a condition or disease are used to evaluate efficacy.
D. Phase III: The medication at this stage is ready to be studied in a larger population, about 1,000 patients, with even more advanced rating scales and clinical measures such as how patients' activities of daily living are affected.
E. Phase IV: After the FDA has already granted approval, the study gathers more safety information from a larger group of patients, and provide information on how the drug may be best used or best combined with other treatments. Sometimes phase IV studies establish effectiveness in a subgroup of patients, such as patients over age 65 or pediatric patients.

## Immunopathogenesis of Psoriasis

Psoriasis is caused by an aberrant immune system and responds to drugs that suppress the body's immune response. In order to appreciate the treatments in the pipeline for psoriasis, one has to understand the immunopathogenesis of the disease.

Psoriasis is characterized by hyperproliferation and abnormal differentiation of epidermal keratinocytes, T lymphocytes infiltration, and vascular changes in the dermis such as angiogenesis, dilation, and high endothelial venule (HEV) formation [2]. The principal driver of lesion development and persistence is through the cytokines and chemokines released by T lymphocytes. Endothelial cells, neutrophils, and natural killer T cells may play an adjunctive role along with other cytokines and selectins such as intercellular adhesion molecule (ICAM)-1 [3].

The involvement of T lymphocytes in the pathogenesis of psoriasis can be described in terms of three events: the initial activation of T lymphocytes, the migration of T lymphocytes into the skin, and the various roles played by cytokines released from T lymphocytes and other cells [4].

A. T-lymphocyte activation: This step involves binding of unidentified antigens to the MHC on antigen-presenting cells (APCs) surface in the epidermis and dermis and the APC migrates to the lymph nodes, where the APC binds reversibly and briefly with naive or resting T cells through interactions between surface molecules located on both cells. Subsequently, the MHC presents the antigen to a T-lymphocyte receptor to begin activation of the T lymphocyte. The second signal for T-lymphocyte activation is a non-antigen/cell-cell interaction known as costimulation. If costimulation does not occur, the T lymphocyte will either undergo apoptosis or become unresponsive. Costimulation involves pairing of receptor with ligand on the T cell; these pairs include lymphocyte functional antigen (LFA)-3 interacting with CD2, B7 interacting with CD28, and ICAM-1 interacting with LFA-1 [5].
B. Migration into the skin: The activated T lymphocytes expand, which results in a proliferation of antigen-recognizing T lymphocytes, memory-effector cells. The T lymphocytes enter the circulatory system and, via cell-cell interactions with endothelial cells of the blood vessel, migrate to inflamed skin [5].
C. The role of cytokines: At the inflamed skin site, when the activated T lymphocytes encounter the initiating antigen, they release T-helper type 1 (TH1) cytokines, which play a central role in the phenotypic expression of psoriasis. Both CD4 and CD8 T lymphocytes produce TH1 cytokines. Key TH1-type cytokines involved in the pathogenesis of psoriasis are IFN-γ, interleukin (IL)-2, and TNF-α. IL-2 stimulates T-lymphocyte growth, and IL-2 treatment is associated

with psoriasis flares. IFN-γ may inhibit apoptosis of keratinocytes by stimulating expression of the anti-apoptotic protein Bcl-x leading to the hyperproliferation of keratinocytes observed in psoriatic lesions. TNF-α promotes psoriasis development in several ways. First it acts by increasing proliferation of keratinocytes. TNF-α augments the production of proinflammatory cytokines from T lymphocytes and macrophages, of chemokines from macrophages, and of adhesion molecules from vascular endothelial cells. In addition, TH1 cytokines cause the release of cytokines from other cells, producing a cascade of chemical messengers that largely produce the distinctive features of psoriatic lesions [3, 4]. Although initial research highlighted the role of T helper 1 (Th1) cells in psoriatic inflammation, recent studies increasingly indicate that immune responses by newly characterized Th17 cells are also involved [6]. IL-27 is involved in the priming of Th1 cells. Initial reports showed that IL-27 promotes Th1 differentiation from naive T cells through signal transduction and activation of transcription 1 (STAT1)-dependent pathways, inducing the production of IFN-γ [7]. However, subsequent studies have revealed an anti-inflammatory role of IL-27. IL-27 suppresses Th17 and Th2 differentiation and inhibits the production of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and IL-12p40 in macrophages, or IL-2, IL-6, and IL-17 in Th cells. Researchers concluded that topical application of IL-27 could be therapeutically beneficial to psoriatic lesions, by exerting anti-inflammatory effects both on keratinocytes and Th cells [8].

The role of cAMP-specific PDEs in psoriasis and atopic dermatitis has also been evaluated. The cAMP-specific PDE4 family has shown to have an important role in promoting inflammatory and immune cells. PDE4 inhibitors have been studied for the treatment of various skin disorders because of their broad anti-inflammatory actions and potent inhibition of cytokine release from T-helper cells (Th1 and Th2) [9].

Psoriasis remains a chronic, lifelong disease that often requires repetitive and lengthy treatments. The limitations of the traditional therapies for psoriasis have encouraged pharmaceutical companies to develop novel agents with the potential for reduced adverse effects and maximized patient benefits.

At our clinical research center, we have been doing cutting edge studies on psoriasis for over 20 years. The process of getting a drug approved is a journey of great time, effort and dedication from the research team, clinical investigators as well as the patients. We are entering a new era of topical therapy which is truly exciting. With our increased understanding of psoriasis we now have a host of new molecules which target specific immunologic abnormalities of the disease.

This chapter will highlight topical medications developed for psoriasis in the pipeline. The pipeline includes drugs that are in progress through phase II and phase III of clinical trials (Table 17.1).

## AN-2728: Cytokine Inhibitor (PDE4 Blocker); Anacor Pharmaceuticals Inc

AN-2728 is a PDE4 inhibitor formed from a phenoxy-2,1-benzoxaborole derivative, for the potential treatment of psoriasis and atopic dermatitis [10].

In initial in vitro studies, AN-2728 equally inhibited the activity of isoforms from all four PDE4 sub-families in human U937 cells; the compound also inhibited PDE7 activity, but the activity of PDE1 and PDE3 was not significantly affected. In addition, AN-2728 has been shown to inhibit the release of TNFα, IL-2, IFNγ, IL-5 and IL-10 [11].

AN-2728 is formulated as both a cream and an ointment. It inhibits the release of TNFα, IL-12 and IL-23. AN-2728 has displayed efficacy in three phase Ib clinical trials, a phase IIa trial and a phase IIb trial in patients with plaque-type psoriasis. A phase IIb dose-ranging trial was conducted to evaluate the safety and efficacy of AN2728 Ointment, 2.0 and 0.5 %, compared to Ointment Vehicle, applied once or twice daily for

**Table 17.1** Topical treatments of psoriasis in the pipeline

| Topical treatments in the pipeline | | | | |
|---|---|---|---|---|
| Name | Company | Mechanism of action | Phase | Indication |
| AN2728 | Anacor Pharmaceuticals Inc. | Anti-inflammatory (phosphodiesterase-4 inhibitor) | II | Psoriasis |
| AS101 | BioMAS Ltd. | Anti-inflammatory (integrin inhibitor) | II | Psoriasis |
| INCB18424 | Incyte | Anti-inflammatory (JAK kinase inhibitor) | II | Psoriasis |
| DPS-101, calcipotriol + niacinamide cream | Dermipsor Ltd | Vitamin D analogue | II | Psoriasis |
| MQX 5902, Methotrexate | Mediquest Therapeutics | Dihydrofolate reductase inhibitor | II | Psoriasis |
| LEO 80185 (Taclonex) | LEO Pharma | Anti-inflammatory/skin cell inhibitor (vitamin D/steroid) | II | Psoriasis (sensitive skin areas) |
| WBI-1001 | Welichem Biotech Inc. | Anti-inflammatory (proprietary) | II | Psoriasis |
| CT 327 | Creabilis Therapeutics | Skin cell inhibitor (Trk kinase blocker) | II | Psoriasis |
| M518101 | Maruho Co. Ltd. | Anti-inflammatory/skin cell inhibitor (proprietary) | II | Psoriasis |
| LAS41004 | Almirall, S.A. | Anti-inflammatory/skin cell inhibitor (proprietary) | II | Psoriasis |

12 weeks, in the treatment of plaque type psoriasis. Results are not yet available [12].

Initial trials with AN-2728 have been encouraging, demonstrating an improvement of psoriatic plaques when compared with vehicle and comparable efficacy to tacrolimus ointment 0.1 % and betamethasone valerate cream 0.1 % [13]. AN-2728 has not been shown to have systemic side effects, but the compound has not been studied extensively in long-term trials. AN-2728 holds promise as a non-steroidal alternative [10].

## AS101: Anti-inflammatory (Cytokine Blocker); BioMAS Ltd. [14]

AS101, Ammonium-trichloro tellurate, is a white crystalline, synthetic, low molecular tellurium compound bonded to an organic moiety.

It is a potent in vitro and in vivo immunomodulator, with a wealth of potential therapeutic applications. AS101 has been shown to have beneficial effects in inflammatory diseases such as asthma, rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease and shows promise for the treatment of other diseases including cancer and stroke. Mechanism of AS101 is related to its ability to inhibit specific family of adhesion and signaling molecules, integrins, that mediate cell-cell, cell-extracellular matrix, and cell-pathogen interactions. Key cysteines within integrin subunits are required for optimal ligand binding function. It has recently been shown that the tellurium-thiol chemistry of the AS101 enabled it to inhibit the ligand binding activity of both the integrins αvβ3 and VLA-4. Alpha-vβ3 integrin is one of the most prevalent integrins, known to have a major role in several distinct processes. VLA-4 is a key cell receptor expressed on most leukocytes. It also plays an important role in the process of adhesion, migration, and activation of inflammatory leukocytes at sites of inflammation.

AS101 holds promise for the treatment of psoriasis. AS101 has shown an inhibitory effect on IL-17 secretion from activated mice spleen cells, and to inhibit caspase-1 and subsequently to decrease IL-18 expression. In

addition, AS101 has been shown to inhibit the pro-inflammatory VLA-4 Integrin, which has an important role in the generation of the immune response, by its effect on leukocytes activation. Inhibition of VLA-4 has shown to prevent or ameliorate disease severity in animal autoimmune models. BioMAS has recently conducted a phase II placebo controlled clinical trial to test the safety and efficacy of a 4 % AS101 ointment for the treatment of mild to moderate psoriasis. The results show that 62.5 % of the AS101 treated patients reached more than 50 % improvement in modified PASI as compared to 13 % of the placebo treated patients. No serious adverse events were reported in the trial.

## INCB18424 (Ruxolitinib); Anti-inflammatory (Jak1-2 Blocker) Incyte Corporation [15].

INCB18424 is a Janus Kinase Inhibitor used to treat inflammation as well as neoplastic conditions. Janus kinases (JAK) are enzymes that mediate signaling of several important drivers of myeloproliferative neoplasms (MPNs), other hematological malignancies and inflammatory diseases. There are four JAK enzymes: JAK1, 2, 3 and TYK2. Aberrant activation of the JAK-STAT pathway has been documented in a variety of cancers. Several cytokines with pathogenic roles in psoriasis signal through JAK kinases (Fig. 17.1) [16]. Known inflammatory cytokines, such as IL-6, IL-12, and IL-23, signal through JAKs to promote inflammation.

Ruxolitinib is a potent, selective JAK 1/JAK 2 inhibitor formulated in a cream to treat mild to moderate plaque psoriasis. Topical ruxolitinib 1.5 % applied twice daily showed efficacy as compared to vehicle in a phase IIa trial in patients with mild to moderate psoriasis. No pathological skin thinning was observed. The ruxolitinib 1.5 % twice daily decreased mean total lesion scores by 54 % compared to 27 % with vehicle treatment, on day 28 ($p \leq 0.05$). Topical ruxolitinib cream was well tolerated with no serious adverse events reported [17].

## DPS-101, Calcipotriol + Niacinamide Cream, Dermipsor LTD. [18]

DPS-101 is a combination of calcipotriol 0.05 % (calcipotriene; a vitamin D3 analog) and Nicotinamide 0.05–1.4 % (a vitamin B3 derivative) in an ointment formulation.

DPS-101 has two active ingredients with complimentary mechanisms of action, as an anti-proliferative and as an immunoregulatory agent. Calcipotriol is an established anti-proliferative agent which normalizes differentiation. It acts by binding to the vitamin D receptors expressed in a variety of cell types in the skin including keratinocytes and T-cells. It affects psoriasis by reducing keratinocyte proliferation and through its immunomodulatory effect on T-cells. Nicotinamide is a Th1 immunoregulatory agent, with additional anti-inflammatory and anti-proliferation effects.

A double-blind Phase IIb split body trial in 168 patients, with plaque psoriasis in Europe was completed in 2009. The goal was to evaluate the efficacy of various doses of DPS-101 (calcipotriol concentration fixed at 0.005 %, nicotinamide concentration varying from 0.05 to 1.4 %). The study showed that 50 % of patients who received the highest dose of DPS 101 achieved a state of "clear to almost clear" after 12 weeks. High dose DPS 101 demonstrated significant efficacy versus placebo ($p = 0.002$), significant efficacy versus niacinamide alone ($p = 0.02$), and a trend towards statistical significance versus calcipotriol as single agent ($p = 0.096$). DPS 101 was well tolerated at all its doses. The frequency of mild and moderate adverse events was similar (8 %) to that of placebo. DPS-102 is also being investigated in a vehicle appropriate for the treatment of scalp psoriasis [18].

## MQX 5902, Methotrexate; Mediquest Therapeutics [19]

MQX-5902 is a topical formulation of methotrexate for the treatment of nail psoriasis. It is a dihydrofolate reductase inhibitor. MQX-5902 utilizes topical amphimatrix (TAM) technology to deliver

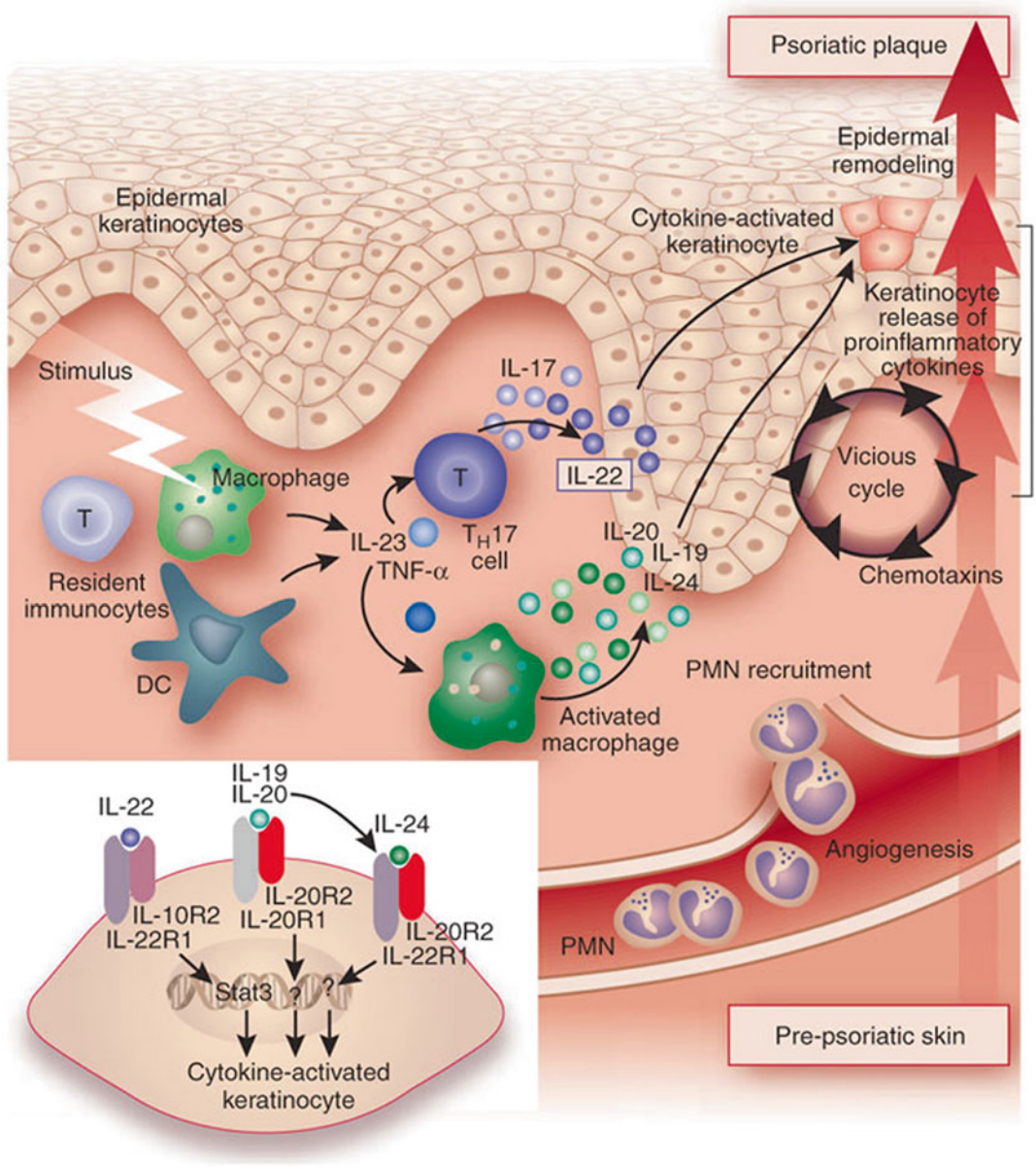


**Fig. 17.1** Cytokines that signal through JAK/STAT pathway implicated in psoriasis (Reprinted by permission from Macmillan Publishers Ltd: Nickoloff [16])

methotrexate, a proven anti-inflammatory and auto-immune agent, through the nail and nail surroundings. TAM technology is capable of rapidly delivering either hydrophilic or hydrophobic active agents through thickened skin and nails to the site of the inflammation or infection. Pre-clinical studies have demonstrated actives in TAM will penetrate finger and toe nails in as short as 5 days.

A randomized, double-blind, dose-comparison Phase IIb trial in 83 patients was performed to evaluate safety and efficacy of MQX-5902, it was applied to affected nail and adjacent skin folds daily for 3 months. Three different concentrations: 0.05, 0.25 and 1.0 % were evaluated. Improvement was assessed in the appearance of the target fingernail, utilizing photography for

imaging and independent photograph evaluators on monthly basis. Measurement was performed using a modification of the Nail Psoriasis Severity Index [20]. Results are not yet available.

## LEO 80190 (Taclonex); Vitamin D3 analog/Anti-inflammatory

LEO 80190 is mixture two of the mainstays of topical psoriasis treatment: the Vitamin D3 analog calcipotriol (also known as calcipotriene) and the low potency steroid hydrocortisone. It is being developed specifically for treating psoriasis on sensitive areas of the skin, including the face and skin folds. The efficacy and safety of two calcipotriol/hydrocortisone dose combinations were compared with two concentrations of calcipotriol in the same ointment vehicle in patients with psoriasis on the face and body. Patients were randomized to receive 8 weeks once daily treatment with calcipotriol 25 mcg/g or 50 mcg/g, either alone or combined with hydrocortisone 10 mg/g. On the body and face overall, no statistically significant differences in efficacy were observed between the calcipotriol/hydrocortisone formulations versus the calcipotriol alone formulations nor between the two concentrations of calcipotriol (50 mcg/g versus 25 mcg/g). On the face alone, calcipotriol/hydrocortisone was significantly more effective than calcipotriol alone ($P < 0.001$) but no consistent significant difference was found between the two concentrations of calcipotriol. There was a significant benefit of combining hydrocortisone with calcipotriol in the incidence of adverse drug reactions on the body and face ($P = 0.006$) and on the face ($P < 0.001$) but no significant difference was found between the two concentrations of calcipotriol either on the body and face or on the face. In facial psoriasis, combining hydrocortisone with calcipotriol resulted in an improved efficacy and tolerability compared to calcipotriol alone [21]. Further studies are currently on hold.

## WB I-1001; Weilchem Biotech; Inc. [22]

WBI-1001 is a non-steroidal and non-immunosuppressive anti-inflammatory Compound.

WBI-1001 has been shown to significantly inhibit the expression of pro-inflammatory cytokines such as IL-2, IL-13, IL-17A, and TNF-α. WBI-1001 strongly inhibited the migration of peripheral blood mononuclear cell towards leukotriene B4 (LTB4) at sub-toxic doses, indicating that WBI-1001 may block the infiltration process of lymphocytes in vivo, playing a critical role in the pathogenesis of various inflammatory diseases. In a mouse ear edema model, WBI-1001 exhibited a dose-dependent response by reducing both ear skin redness and thickness.

Phase I clinical trials performed in Canada have shown efficacy with excellent safety in both psoriasis and atopic dermatitis. Phase II trials are currently in progress. Preliminary animal studies are being conducted in other inflammatory disorders such as inflammatory bowel disease.

## CT 327; Creabilis Therapeutics [23]

CT327 is a TrkA kinase modulator. TrkA is the high affinity receptor for Nerve Growth Factor (NGF). CT327 has demonstrated antiproliferative activity on keratinocytes and is effective in pre-clinical models of hyperproliferative skin diseases. It is in phase II clinical development as a novel topical treatment for psoriasis and atopic dermatitis.

CT327 was well tolerated with no reported application site irritation in all the clinical settings proposed so far. A randomized, double-blind, placebo controlled phase II, multi-center trial was performed studying of the efficacy and safety of CT 327, a topical cream formulation, when administered twice daily for 8 weeks to patients with mild to moderate psoriasis vulgaris.

Primary outcome measure was reduction from baseline in modified-Psoriasis Area Severity Index Scale (m-PASI – modified to exclude area assessment) of >50. Secondary outcome measurement was m-PASI-score of >75 % a Week 8 [24]. Results are not yet available.

## M518101 (Oxarol); Vitamin D Derivative

Maxacalcitol is an active vitamin D3 derivative that inhibits proliferation and induces differentiation of epidermal keratinocytes. Oxarol® Ointment 25 μg/g and Oxarol® Lotion 25 μg/g were approved for treatment of psoriasis vulgaris and palmoplantar pustulosis in Japan as of November 2008.

Oxarol is indicated, twice daily, for treatment of psoriasis vulgaris, ichthyosis, palmoplantar keratosis and palmoplantar pustulosis. Additional trials have been conducted for an extended indication [25].

## LAS41004; Almirall, S. A

LAS41004 has anti-inflammatory activity and capacity to inhibit cellular proliferation through topical administration for the treatment of psoriasis and/or atopic dermatitis.

An Investigator-blind, controlled exploratory study was conducted to assess the efficacy and safety of different concentrations of LAS 41004 compared to a placebo and to active control for plaque psoriasis. The primary outcome measured decrease in plaque thickness at Day 1 (baseline) vs. day 15 day. Measurement was performed by ultrasound. Scoring of total symptom score (0–12), change in erythema, change in induration and change in scaling score was performed by investigator, comparing data from baseline (day 1) vs end of trial (day 15) [26]. Results from this 15 day trial are not yet available.

### Conclusion

Psoriasis is a frustrating disease for both patients and physicians. Patients struggle to overcome the physical and emotional toll. Physicians seek treatments that are safe, effective, durable and affordable. Topical medications remain the gold standard for mild to moderate psoriasis patients. The pipeline of potential treatments holds great promise for expanding out armamentarium to safely and effectively treat this difficult disease.

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# Research Pipeline II: Oral Therapeutics

18

Phoebe D. Lu and Joni M. Mazza

**Abstract**

Recent insights into the pathophysiology of psoriasis have led to the identification of putative targets for pharmacological intervention. With the investigation for small molecule compounds that can inhibit or activate cellular signal transduction cascades, a number of new, promising targeted treatment options for psoriasis are being tested in clinical trials. Medications that are currently in phase III studies apremilast, CF101, tofacitinib, voclosporin, and LAS410008. Numerous other drugs targeting new and old pathogenic pathways are in phase II trials. This chapter will review some of the oral treatment options for psoriasis that are currently being investigated in phase II and III clinical studies.

**Keywords**

Small molecules • Oral medications • Apremilast • Tofacitinib • Voclosporin • CF101

## Introduction

The development of biologic therapies targeting TNF-alpha and the IL-23/Th17 pathway have revolutionized the treatment of psoriasis. Oral medications, on the other hand, have remained relatively unchanged since the introduction of methotrexate, cyclosporine, and acitretin decades ago. However, as the molecular pathways involved in the pathogenesis of psoriasis are being elucidated, a number of promising new targeted agents are on the horizon and should be available in the next several years.

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## Oral Drugs in Phase III Clinical Studies

Oral medications that have advanced into phase 3 clinical studies include apremilast, CF101, tofacitinib, voclosporin, and LAS410008 (Table 18.1). These medications target several different pathways involved in the pathogenesis of psoriasis.

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**Table 18.1** Novel oral therapies for psoriasis currently in phase III trials

| Name | Other names | Company | Mechanism of action | Indication |
|---|---|---|---|---|
| Apremilast | CC-10004 | Celgene Corporation | Phosphodiesterase 4 inhibitor | Psoriasis and psoriatic arthritis |
| CF101 | IB-MECA | Can-Fite Biopharma | Adenosine A3 receptor agonist | Psoriasis |
| LAS41008 | | Almirall, S.A. | Undisclosed | Psoriasis |
| Tofacitinib | Xeljanz® CP-690,550 | Pfizer Inc. | JAK kinase inhibitor | Psoriasis and psoriatic arthritis |
| Voclosporin | ISA247 | Isotecknika | Calcineurin inhibitor | Psoriasis |

## Apremilast: Phosphodiesterase Inhibitor

Apremilast (Celgene) is a small molecule inhibitor of phosphodiesterase type 4 (PDE4) (Fig. 18.1). Expressed in epithelial cells, smooth muscle cells, neurons, chondrocytes and keratinocytes within the dermis, PDE4 serves as one of the major cAMP selective phosphodiesterases [1–3]. PDE4 works to decrease intracellular cyclic adenosine monophosphate (cAMP), promoting pro-inflammatory signals, such as TNF-alpha, IFN-gamma, IL-23 and IL-2, while simultaneously decreasing anti-inflammatory mediators, such as IL-10. Conversely, inhibition of this enzyme via PDE4 increases cAMP within the cells and preferentially blocks pro-inflammatory cytokines and increases anti-inflammatory mediators [4]. Preclinical and *in vitro* studies supported this mechanism of action and clinical trials of apremilast in patients with psoriasis and psoriatic arthritis have demonstrated statistically significant therapeutic effect as well as positive tolerability and safety profiles [5].

In a Phase II, open-label, single-arm pilot study performed at three investigative centers, patients with severe plaque-type psoriasis (at least 15 % body surface area involvement for 6 months) received 20 mg apremilast orally for 29 days. The primary endpoint in the study was a decrease in epidermal thickness ≥20 %; patients who achieved this reduction were classified as responders. Eight of the 15 subjects from which all skin biopsies were available had a ≥20 % reduction in epidermal thickness. Skin biopsies from lesional skin of the test subjects showed a mean decrease in thickness of 20.5 % from baseline. Biopsies also showed a reduction in T-cells of 28.8 and 42.6 %, respectively, in the dermis and epidermis of responders. Reductions in CD11c cells also followed a similar trend. iNOS mRNA decreased, as did stimulation of TNF alpha production in a whole blood LPS *ex vivo* assay. 73.7 % of patients had an improvement in their PASI scores. Adverse effects occurred in 14 patients (73.7 %) and were considered mild, including headache (five patients) and nausea (three patients). Nausea (three patients) and dizziness (two patients) were the most common side effects attributed to apremilast. None of the 18 patients who participated in the 28-day follow up period after discontinuing apremilast showed a flare in their psoriasis. This study also looked at the pharmacokinetics in a small number of patients, and established a mean half-life of 8.2 h [6].

A phase II randomized, multi-center study consisting of 260 patients with moderate-to-severe plaque type psoriasis showed that 24.4 % of patients treated with 20 mg apremilast every 12 h had a ≥75 % reduction in there PASI score after 84 days ($p=0.023$) vs. 10.3 % in patients treated with placebo. Additionally, 57 % of patients in the apremilast arm showed a ≥50 % reduction in their PASI score ($p<0.001$) as compared to 23 % of patients given placebo. Dermatology Life Quality Index scores were also improved in the apremilast arm 7 points ($p<0.001$) vs. 2.7 points in the placebo arm. Adverse events included headache (12.9 % vs. 10.3 %), nasopharyngitis (14.1 % vs. 13.8 %), diarrhea (5.9 % vs. 2.3 %), and nausea (5.9 % vs. 0 %) [7].

A phase II, multicenter, double-blind, placebo-controlled study was conducted over a 12 week treatment phase, where patients were randomized to receive apremilast 20 mg twice daily, apremilast 40 mg once daily, or placebo, followed by a

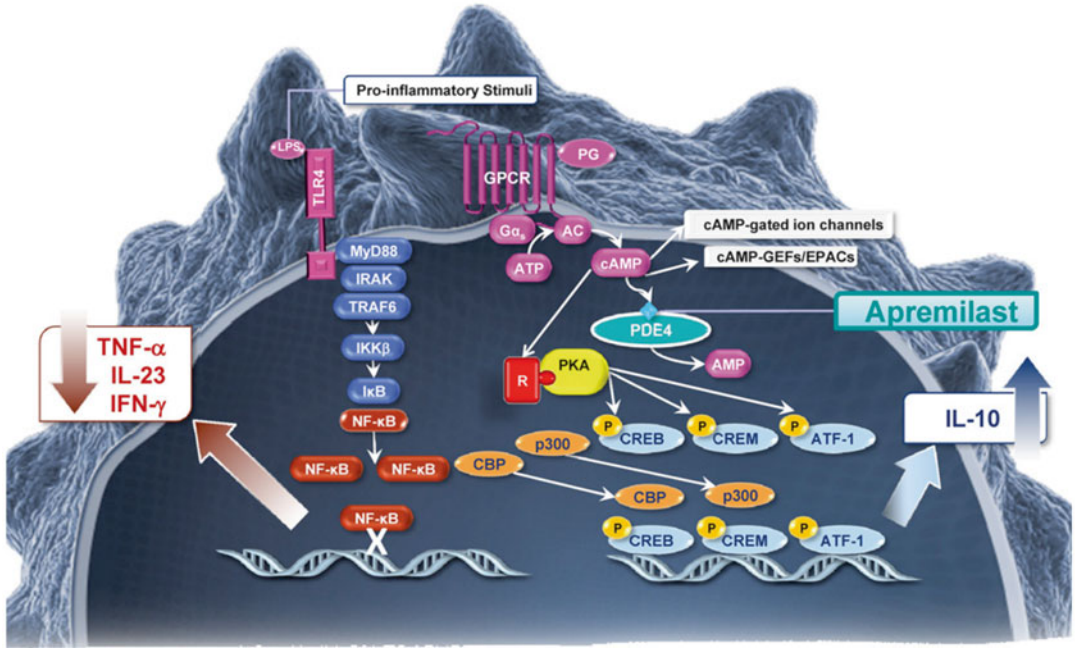


**Fig. 18.1** Apremilast specifically targets PDE4 and modulates expression of a network of pro-inflammatory and anti-inflammatory mediators. The inflammatory process in psoriasis and arthritis results from an interplay between innate immune cells (dendritic cells, macrophages, and neutrophils), adaptive immune cells (T cells), and even non-immune cells (keratinocytes, synovial fibroblasts, and chondrocytes). The production of pro-inflammatory and anti-inflammatory mediators is modulated in these cell types through the enzyme phosphodiesterase 4 (*PDE4*). Pro-inflammatory signals such as those emanating from the toll-like receptor (*TLR4*) pathway in cells such as monocytes and dendritic cells result in activation of the transcription factor nuclear factor-kappa B (*NF-κB*) and the expression of pro-inflammatory mediators such as interleukin *(IL)-23*, tumor necrosis factor *(TNF)-α*, and interferon *(IFN)-γ*. Simultaneously, signals emanating from G-protein coupled receptors (*GPCRs*) such as those binding prostaglandin (*PG*) act via the stimulatory G protein alpha subunit ($G\alpha_s$) to activate adenylyl cyclase (*AC*), resulting in production of cyclic adenosine monophosphate (*cAMP*). In white blood cells such as monocytes and dendritic cells, cAMP is degraded to AMP largely through hydrolysis by PDE4. PDE4 inhibition by apremilast increases cAMP levels within the cells, which results in activation of protein kinase A (*PKA*), as well as cyclic nucleotide-gated ion channels, or the exchange protein activated by cAMP(Epac). PKA activation results in phosphorylation of the cAMP responsive element (*CRE*) binding family of transcription factors, including cAMP responsive element binding protein (*CREB*), cAMP responsive element modulator (*CREM*), and activating transcription factor 1 (*ATF-1*). In certain cell types such as monocytes, these factors bind to CRE sites within promoters of genes such as IL-10, resulting in increased gene expression. CRE-driven transcriptional activation recruits coactivators such as CREB binding protein (*CBP*) or the homologous protein p300, which have histone acetyl transferase activity. Recruitment of CBP and p300 away from NF-κB results in inhibition of NF-κB transcriptional activity, and a reduction in NF-κB dependent gene expression, thereby resulting in a decrease in IL-23, TNF-α, and IFN-γ production. The decreased inflammatory response may lead to lower levels of infiltration by other immune cells, as well as reduced activation and proliferation of keratinocytes and synoviocytes. Together, this may lead to decreased epidermal thickening in psoriasis and decreased synovial damage in arthritis (Reprinted from Schafer [5], with permission from Elsevier)

12 week extension phase where patients in the placebo group were re-randomized to receive apremilast. Patients were then followed over a 4-week observational stage. The primary endpoint was the proportion of patients who achieved The American College of Rheumatology criteria for 20 % improvement (ACR20) at week 12. At the end of week 12, 43.5 % of patients receiving 20 mg twice daily and 35.8 % of patients receiving 40 mg once daily, achieved an ACR 20 compared with 11.8 % in the placebo group. Patients in the placebo group who were re-randomized to

receive apremilast at week 12 experienced similar results as those who received the treatment at baseline. By week 24, 42.5 %, 43.5 %, 40.0 %, and 45.0 % of patients achieved an ACR 20 in apremilast 20 mg twice daily, 40 mg daily, placebo then drug 20 twice daily, and placebo then drug 40 daily, respectively. 84.3 % of all patients in the study reported ≥1 adverse event. Diarrhea, headache, nausea, fatigue and nasopharyngitis were among the most common adverse events. No grade 4 or 5 (life-threatening/disabling or death) adverse events were reported during the treatment phase. Overall, apremilast 20 mg twice daily or 40 mg daily was shown to be efficacious in the treatment of plaque psoriasis as compared with placebo. Adverse events that were mild to moderate did not limit the use of the treatment in the majority of patients, supporting the role of apremilast in the treatment of moderate to severe plaque psoriasis [8].

In a phase IIb double-blind, randomized, placebo-controlled study involving 352 patients randomized to 10, 20, or 30 mg twice daily apremilast or placebo, 41 % of patients in the 30 mg arm achieved PASI-75 after 16 weeks ($p < 0.001$), 29 % in the 20 mg arm ($p < 0.001$), and 11 % in the 10 mg arm vs. 6 % in the placebo group. Common side effects in this study were similar to the previous study and included headache, nausea, upper respiratory tract infection, and diarrhea. There was a higher overall rate of infection of 48 % in the 20 mg group as compared to the 33 % in the placebo group. In the 30 mg group, 14 % discontinued due to adverse events as compared to 6 % in the placebo group [9, 10].

Apremilast's effect on patient-reported outcomes (PROs) was also included as part of the aforementioned study. Patients were asked to complete Dermatology Life Quality Index (DLQI), pruritus visual analog scale (VAS), and Short-Form Health Survey (SF-36). At 16 weeks, statistically significant improvement in DLQ was noted in the 20 mg twice daily (49.4 %) and 30 mg twice daily (44.3 %) as compared with placebo (25 %). 60.9 % of the 20 mg twice daily group and 66.3 % of the 30 mg twice daily group also reported improvement in VAS compared with placebo (44.3 %). Overall, this study demonstrated improvement in health-related quality of life (HRQOL) in patients with moderate to severe plaque psoriasis treated with apremilast [11].

Currently several Phase III clinical trials are underway for apremilast in the treatment of psoriasis and psoriatic arthritis. PALACE-1, PALACE-2 and PALACE-3 are actively ongoing studies, while PALACE-4 is in recruitment phase. Started in 2010, PALACE-I is a multi-center, double-blind, placebo-controlled, parallel group study with two active treatment groups. Participants included patients with psoriatic arthritis who had received an oral disease-modifying anti-rheumatic drug (DMARD), a biologic, or had failed an anti-TNF-alpha inhibitor. Approximately 500 participants were randomized 1:1:1 to receive apremilast 20 mg, 30 mg or placebo twice daily for 24 weeks, with a subsequent extension where all patients would receive the drug. Apremilast was used either alone or in combination with a DMARD. Statistical significance was achieved using the American College of Rheumatology criteria with an improvement of 20 % at 16 weeks as compared to baseline (ACR20). Participants were also reported to have maintained significant improvement in arthritis related endpoints at week 24. The overall safety profile was consistent with that of Phase II trials and side effects such as GI upset, upper respiratory infections and headache were the same in both the treatment and the placebo group [12].

ESTEEM-1 (NCT01194219) and ESTEEM-2 (NCT01232283) are two phase III randomized, placebo-controlled studies evaluating apremilast in subjects with a diagnosis of moderate-to-severe chronic plaque psoriasis for at least 12 months prior to screening, and who were also candidates for phototherapy and/or systemic therapy [13]. Approximately 1,250 patients were randomized 2:1 to receive either apremilast 30 mg twice daily or placebo for the first 16 weeks, followed by a maintenance phase from weeks 16–32, in which placebo subjects were switched to apremilast 30 mg twice daily. This was followed by a randomized withdrawal phase for responders from weeks 32–52 based

on their initial apremilast randomization and PASI response. At the American Academy of Dermatology 2013 meeting, Celgene presented the results from ESTEEM 1. ESTEEM 1 evaluated efficacy and safety in a range of patients. Approximately one-third of the study population was systemic and/or phototherapy treatment-naïve. Nearly 30 % of the overall study population had prior biologic therapy, which included biologic- failures. A significantly higher percentage of apremilast-treated patients demonstrated PASI- 75 at week 16 than did placebo patients (33.1 % vs. 5.3 %; $P<0.0001$). Significantly higher PASI-75 scores at week 16 were demonstrated across all patient segments enrolled in this study, including systemic-naïve and biologic- naïve patients receiving apremilast 30 mg twice daily compared with placebo (38.7 % vs. 7.6 %; $P<0.0001$ and 35.8 % vs. 5.9 %; $P<0.0001$ respectively). Apremilast demonstrated maintenance of effect over time, as measured by the mean percent change from baseline in PASI score over 32 weeks, with apremilast demonstrating a 54.9 % reduction at week 16 and a 61.9 % reduction at week 32 [13].

Apremilast is also being studied for use in conditions such as ankylosing spondylitis, rheumatoid arthritis, and in the near future, rosacea. Additional studies, particularly comparing the use of apremilast to classic systemic treatments, would be beneficial. However, given its overall efficacy and good safety profile, apremilast will provide an additional treatment option for dermatologists and rheumatologists in the management of psoriasis and psoriatic arthritis, particularly when other treatment options have failed.

## CF101: $A_3$ Adenosine Receptor Agonist

CF101, formerly known as IB-MECA (N6-(3-iodobenzyl)-50-N-methylcarboxamidoadenosine, Can-Fite BioPharma), is a highly specific, oral anti-inflammatory agent that functions as an $A_3$ adenosine receptor ($A_3$ AR) agonist. The $A_3$ AR is a Gi protein-associated cell surface receptor, which is activated by adenosine, a purine nucleoside, thereby inhibiting adenylate cyclase and the production of cyclic AMP (cAMP). $A_3$ AR is found to be over-expressed in synovial and paw tissues of rats with arthritis, with little or no receptor function in healthy cells [14–16]. Additionally, over-expression of $A_3$ AR has been demonstrated in the peripheral blood mononuclear cells (PBMCs) derived from patients with rheumatoid arthritis (RA), Crohn's disease and psoriasis [15]. In preclinical studies, CF101 was shown to have anti-inflammatory effects and downregulates PI3K, PKB/Akt, IKK, NF-KB, and TNF-alpha in animal studies of adjuvant-induced arthritis [17]. These anti-inflammatory properties have therefore made CF101 a potential novel approach for the management and treatment of psoriasis.

In a Phase I study in healthy subjects, CF101 was found to be safe and well tolerated [18]. In a Phase IIa study conducted in patients with rheumatoid arthritis, CF101 administered twice daily for 12 weeks resulted in amelioration of disease signs and symptoms. In addition, analysis of $A_3$ AR expression levels at baseline showed statistically significant correlation with patient response to CF101, suggesting $A_3$ AR could be used as a biomarker for prediction of patient response to the drug prior to initiation of treatment [19].

In a 2010 phase 2 randomized multicenter, double-blinded, placebo-controlled clinical trial, 75 patients with moderate to severe plaque psoriasis were randomized to receive CF101 at 1, 2, or 4 mg doses twice daily or placebo. 84 % of participants completed the study, which showed a statistical significance between the 2 mg group versus placebo at 12 weeks. In the 2 mg group, 35.3 % of patients achieved a PASI response of ≥50 % at 12 weeks [20]. An improvement in the mean change from baseline PASI score in the 2 mg CF101 group vs. placebo was observed which was statistically significant at weeks 8 and 12 ($p=0.047$ and $p=0.031$, respectively). The 4 mg group resulted in less improvement that the 2 mg group, and the 1 mg group had no effect, consistent with the previously reported bell curve distribution of dose-related efficacy in the prior rheumatoid arthritis study. In addition, 23.5 % of

the patients in the 2 mg CF101-treated group achieved a PGA score of 0 or 1, indicating slight or no clinical signs, at 12 weeks, as compared to 0 % of the placebo-treated group.

CF101 appears to be safe and well tolerated. In the psoriasis study, the incidence of adverse effects was 58.3 % in the 1 mg group, 17.6 % in the 2 mg group, and 13.3 % in the 4 mg treated group, as compared to 21.1 % in the placebo group. The most commonly reported side effects in the 1 mg group were pruritus (12.5 %; 3 patients), arthropathy (8.3 %; 2 patients), and psoriasis (8.3 %; 2 patients). These studies support the use of CF101 in the management of inflammatory conditions, such as psoriasis, particularly given the excellent tolerability of the drug.

A phase II/III clinical study is in progress with patients being randomized into three arms: placebo, 1 mg CF101 q12h, and 2 mg CF101 q12h (NCT01265667). After the initial 12 week treatment period, patients in the placebo group will be randomized to one of the two CF101 treatment groups.

## Tofacitinib: JAK Kinase Inhibitor

Janus kinases (JAKs) are a family of non-receptor tyrosine kinases involved in a major signal transduction cascade downstream of cytokine, chemokine, and growth factor receptors. The JAK family consists of four members: JAK1, JAK2, JAK3, and TYK2. By phosphorylating and activating the STAT (Signal Transduction and Transcription) family of transcription factors, JAKs regulate the transcription of STAT-dependent genes.

Tofacitinib (CP-690,550, tasocitinib, Xeljanz®, Pfizer) is an orally active and highly selective inhibitor of JAK1 and JAK3 which had been initially evaluated as an immunosuppressive treatment for the prevention of allograft rejection and for treatment of autoimmune diseases. More recently, it has been FDA approved as a second-line treatment for moderate to severe rheumatoid arthritis in adults. Inhibition of JAK3 in T cells is thought to suppress the activation of downstream inflammatory mediators including IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 which are involved in T lymphocyte activation and proliferation. Recent studies suggest that tofacitinib may suppress Th1 and Th17 [21]. JAK1/JAK2 are thought to have roles in interferon signaling.

In a phase I randomized, double-blind, dose-escalation study, 59 patients with plaque-type psoriasis were treated with tofacitinib at doses of 5, 10, 20, 30, or 50 mg twice daily or 60 mg once daily or placebo for 14 days [22]. Evaluation at baseline and on follow-up at days 4, 7, 14, and 28 were performed using the Psoriatic Lesion Severity Sum (PLSS) score and the Physician's Global Assessment (PGA) scores. A dose-dependent improvement in PLSS scores and PGA scores was observed in the tofacitinib groups versus placebo. In skin biopsies at day 14 from 3 patients receiving 30 mg tofacitinib twice daily, there was a marked histological improvement (to normal or near normal) as compared to baseline. The most commonly reported adverse events associated with tofacitinib were headache and nausea. Laboratory abnormalities including elevated lipids and serum creatinine have also been reported [23].

A randomized, double-blind, phase IIb study was performed using 2, 5, and 15 mg tofacitinib twice daily, compared with placebo. 197 patients with moderate to severe chronic plaque psoriasis were randomized into each group to assess safety and efficacy. The primary endpoint of achieving a PASI score of $\geq$75 was significantly higher at week 12 in treatment groups, compared with placebo, with 25.0, 40.8 and 66.7 % in the 2, 5, and 15 mg groups, respectively. The most frequently noted adverse effects included upper respiratory tract infection, nasopharyngitis, and headache. Tofacitinib was noted to result in mild, dose-related drops in hemoglobin, decreases in mean absolute neutrophil count (ANCs) at higher doses of drug, and small increase in serum creatinine (mean 0.04 mg/dL) in the 15 mg group. Overall the results of this trial supported the use of oral tofacitinib as a short-term treatment for moderate to severe plaque psoriasis [24] The 197 patients enrolled in this trial were also asked to complete six surveys to assess overall quality of life: Dermatology Life Quality Index, Itch Severity Score (ISS), Short Form-36 questionnaire 2

(SF-36), Pain/Discomfort Assessment (PDA), Patient Satisfaction with Study Medication (PSSM), and Patient Global Assessment of Psoriasis. Starting as early as weeks 2 through 4, improvements in QoL were noted. By week 12, Dermatology Life Quality Index, ISS and SF-36 were all significantly higher in all treatment groups as compared with placebo. Significant numbers of patients in all treatment groups were also more likely to report "clear" or "almost clear" on the Patient Global Assessment, starting at week 4, in both the 5 and 15 mg groups and at week 8 in 2 mg group. This study is the first to report an improvement in quality of life for patients treated with oral tofacitinib [25].

Tofacitinib is currently in phase III trials for the treatment of moderate-to-severe chronic plaque psoriasis, using dosing of both 5 mg twice daily and 10 mg twice daily.

Already approved as a second-line treatment for rheumatoid arthritis, it is also being investigated in clinical trials for rheumatoid arthritis, inflammatory bowel disease, dry eye syndrome, and transplant rejection. In addition, a phase 2 trial of a topical formulation of tofacitinib applied twice daily for 28 days has recently been completed and it has now entered phase 3 testing. At the time of writing, two other JAK inhibitors are in phase 2 clinical trials, ASP015K (Astellas Pharma Inc.), an inhibitor of JAK3 (NCT01096862), and LY3009104 (Eli Lilly and Company and Incyte Corporation), an inhibitor of JAK1/JAK2 (NCT01490632).

## Voclosporin: Calcineurin Inhibitor

Cyclosporine is a well-known immunosuppressant that has been widely used since its discovery in the 1970s for the treatment of psoriasis. It belongs to a family of calcineurin inhibitors, which block lymphocyte activation via the binding of cyclophilin. The cyclosporine-cyclophilin complex inhibits the calcium dependent serine-threonine phosphatase, calcineurin. This inhibition suppresses the downstream production of proinflammatory cytokines IL-2 and TNF alpha. Although cyclosporine is a mainstay of treatment for solid organ transplant recipients, its use has been limited to short term management of chronic skin disease due to the drug's side effect profile, most notably nephrotoxicity [26].

Voclosporin (ISA 247, made by Isotechnika Pharma) is a novel calcineurin inhibitor which differs from cyclosporine by the modification of a functional group at the first amino acid residue. This modification results in a more complete inhibition of calcineurin through a higher affinity interaction between voclosporin and calcineurin, and allows for faster elimination of metabolites by shifting the major site of metabolism away from the first amino acid residue. Preclinical studies in animals suggested that voclosporin was less nephrotoxic than cyclosporine [27, 28].

In a phase II clinical study consisting of 201 patients with psoriasis $\geq$10 % body surface area randomized to receive placebo, voclosporin 0.75 mg/kg/day, or voclosporin 1.5 mg/kg/day, PASI 75 was achieved at week 12 in 0 % of patients in the placebo group, 18.2 % of patients in the 0.75 mg/kg/day, and 66.7 % of patients in the 1.5 mg/kg/day group ($p<0.0001$) [29]. Although there was no difference in the adverse events between patients at the 0.5 mg/kg/day dose as compared with placebo, there was a significant increase in the mean creatinine levels over baseline between the 1.5 mg/kg/day group as compared with placebo. Importantly, however, these levels still remained within the normal range and most patients who developed a 30 % increase in creatinine were also taking ACE inhibitor medications. There was no significant difference in infection rates, changes in blood pressure or lipid parameters between the two groups during the 12 week study [29].

In 2008, a phase III trial assessing the efficacy of ISA247 versus placebo was conducted. 451 patients with plaque psoriasis of at least 10 % body surface area were randomly assigned to receive 0.2, 0.3 or 0.4 mg/kg twice a day for 12 weeks. PASI 75 scores were achieved in 16, 25, and 47 %, respectively, demonstrating greater efficacy at higher doses. Notably, adverse events were reported by 82 % of the 451 participants. Thirty-nine percent of these

adverse events in the placebo group and 54, 44, and 55 %, respectively, of events in the treatment groups were attributed to the medication. Headache, nasopharyngitis, and upper respiratory tract infection were the most commonly reported. Mild to moderate reduction in GFR was seen in 2 % of patients during the study, and while most reductions in GFR were transient and resolved by the end of the study, reduced GFR was the most common adverse event to result in discontinuation of the study. Based on this trial, ISA247 appeared to provide an efficacious alternative in the treatment of plaque psoriasis, with an improved safety profile [30].

Two studies investigating the effect of voclosporin on quality of life have been reported. In a phase 2 randomized, placebo-controlled study, patients treated with voclosporin scored better on two different quality of life scales, with a greater effect at the higher dosage of 1.5 mg/kg/day [31]. Additionally, a recent Canadian phase 3 placebo-controlled study assessed quality of life in patients with chronic, plaque psoriasis who were treated with voclosporin as compared with placebo. A total of 451 patients, aged 18–65 with >10 % BSA plaque psoriasis, were randomized to receive 0.2, 0.3, or 0.4 mg/kg twice daily versus placebo for up to 24 weeks. The participants were administered two quality of life scales- the Dermatology Life Quality Index (DLQI) and the Psoriasis Disability Index (PDI)- at the start of the trial and then at weeks 2, 4, 8, 12, 16, 20, and 24. Overall results indicated the voclosporin improved quality of life among the 76 % of participants who completed the trial. Statistical significance was achieved at 12 weeks in the 0.3 and 0.4 mg/kg on the DLQI scale and in the 0.4 mg/kg group on the PDI scale, and most of the improvement was maintained at 24 weeks. This marked improvement in quality of life, along with high tolerability of the drug, make this calcineurin inhibitor a promising treatment option for moderate to severe plaque psoriasis [32]. A phase III head-to-head trial comparing voclosporin to cyclosporine has been completed (NCT00408187). Other areas of application of voclosporin include noninfectious uveitis and transplantation.

### LAS41008: Unknown Mechanism

Almirall, S.A. has recently registered a multicenter, randomized, double-blind, three-arm phase III clinical trial of LAS41008 vs. the active comparator LASW1835 (Fumaderm®, see below) vs. placebo in patients with moderate to severe chronic plaque psoriasis (NCT01726933). The mechanism of action of LAS41008 is unknown.

## Oral Drugs in Phase II Clinical Studies

An increasing number of orally available small molecule activators and inhibitors of diverse pathways key to the pathogenesis of psoriasis are entering phase II clinical trials (Table 18.2). They include drugs that target novel pathways as well as others that are mechanistically similar to current medications used to treat psoriasis.

### Sotrastaurin: Protein Kinase C Inhibitor

Sotrastaurin (AEB071, Novartis) is an orally administered selective inhibitor of protein kinase C (PKC) currently in phase II clinical trials for patients with plaque psoriasis. The protein kinase C (PKC) family of serine/threonine kinases are involved in T-lymphocyte activation downstream of the T-cell receptor and CD28 co-receptor [33]. *In vitro*, sotrastaurin blocks T cell proliferation and inhibits the production of IL-17, IFN-gamma, IL-2, and TNF-alpha by activated T cells. In a small cohort of 32 patients treated with sotrastaurin 25–300 mg twice daily for 2 weeks, a dose-dependent improvement in psoriasis was observed over the 2-week treatment period which paralleled immunohistochemical findings [34]. A mean reduction in PASI of 69 % over baseline was observed in the 300 mg twice daily group, with 4 of the 6 patients in that cohort achieving PASI75. PASI was reduced by 35 % when compared to baseline in patients who were treated with 200 mg twice daily. Relapse

**Table 18.2** Novel oral therapies for psoriasis currently in phase II trials

| Name | Other names | Company | Mechanism of action |
|---|---|---|---|
| ACT-128800 | Ponesimod | Actelion | Sphingosine 1 phosphate 1 receptor agonist |
| AEB071 | Sotrastaurin | Novartis | Protein kinase C inhibitor |
| Alitretinoin[a] | 9-cis retinoic acid | Basilea Pharmaceutica | Retinoid |
| Apo805K1 | | ApoPharma | Unknown |
| ASP015K | | Astellas Pharma Inc. | JAK kinase inhibitor |
| BMS-582949 | | Briston-Myers Squibb | p38 MAP kinase inhibitor |
| FP187 | | Forward-Pharma GmbH | Fumaric acid ester |
| Doxercalciferol | Hectorol® | Genzyme | Vitamin D analog |
| LEO 22811 | | LEO Pharma | Unknown |
| Lestaurtinib | CEP-701 | Teva Pharmaceutical Industries | Multikinase inhibitor |
| Ly30009104 | INCB28050 | Eli Lilly & Co. | JAK1 and JAK 2 inhibitor |
| Masitinib | AB1010 | Alain MOUSSY, AB Science | Tyrosine kinase inhibitor |
| R3421 | BCX-4208 | Roche/BioCryst | Purine nucleoside phosphorylase inhibitor |
| RWJ-445380 | | Alza Corporation | Cathepsin S inhibitor |
| SRT2104 | | GlaxoSmithKline | Sirtuin activator |
| Talarozole | R115866 | GlaxoSmithKline | CYP26 inhibitor |
| VB-201 | | VBL Therapeutics | Oxidized phospholipid |

[a]Under investigation for treatment of pustular psoriasis

occurred in all of the treatment groups in the 2 weeks after discontinuation of the medication, with the exception of the 300 mg twice daily group. Adverse effects were mild, and included nausea in two patients and a nonspecific elevation in ALT in two patients which normalized despite continued treatment.

AEB071 is currently in phase II clinical trials for the treatment of moderate-to-severe psoriasis (NCT00885196). Several other applications of AEB071 are being investigated including the prevention of allograft rejection after renal and liver transplantation, metastatic uveal melanoma, and CD79-mutant diffuse large B cell lymphoma.

## VB-201: Oxidized Phospholipids

Oxidation of phospholipids may occur through free radicals and reactive oxygen species or enzymatic processes. These modifications are thought to impart new biological activity to phospholipids, which are otherwise not associated with metabolic activity. Oxidized phospholipids are found at sites of inflammation where they may serve as antigens or ligands for various receptor-mediated signal transduction cascades. Whereas oxidized phospholipids are considered to be mostly pro-inflammatory mediators, there is evidence to suggest that oxidized phospholipids may have anti-inflammatory properties [35]. *In vitro*, oxidized phospholipids inhibited the secretion of IL-12/23p40 and TNF-alpha and the reduced the capacity of dendritic cells to stimulate T cell proliferation.

VB-201 (VBL Therapeutics) is a synthetic oxidized phospholipid analog and a member of the Lecinoxoid family. It is a proprietary, first-in-class, innate immunity disease-modifying agent. The mechanism of action of VB-201 includes antagonizing CD-14, the co-receptor for Toll-Like Receptor (TLR)-2 and TLR-4 and inhibiting the migration of monocytes to inflamed tissue [36]. In a mouse model of CNS inflammation, VB-201 treatment reduces the expression of Th1 cytokines IFN-gamma, TNF-alpha, IL-12/23p40, and IL-10 and may restrict Th1 differentiation *in vivo* [37].

Phase 1 clinical trials involving 120 patients have been completed demonstrating that the

drug is safe and well tolerated [38]. Recently, data from a phase 2 clinical trial of 184 patients randomized to VB-201 (20 or 80 mg) vs. placebo once daily for 12 weeks was reported [38, 39]. The study cohort was composed primarily of overweight men with a BMI of 30 kg/m$^2$ with an average age of 45 years. There were statistically significant improvements on the Physician Global Assessment and patient Global Assessment scales. VB-201 had a modest effect on PASI with 8.1 % of patients in the 20 mg group and 8.5 % in the 80 mg group achieving PASI 75. Interestingly, in a PET/CT substudy of 47 patients with cardiovascular risk factors, there was a dose-related reduction in atherosclerotic inflammation. In the 80 mg VB-201 group, a dose-responsive mean reduction of 12.7 % of the inflammation associated with vascular endothelial lesions was observed over the 12-week dosing period ($p = 0.04$). In patients already on statin therapy, additional responses of 10–68 % reduction in vascular inflammation was reported. No treatment-related serious adverse events occurred and VB-201 demonstrated an excellent safety and tolerability profile.

A phase II, randomized, double-blind, 12 week, placebo controlled study to assess the efficacy and safety of oral VB-201 in patients with moderate to severe plaque psoriasis was completed in 2011 (NCT01001468). Results have not yet been published. Currently another phase II trial to assess safety and efficacy at higher drug doses is recruiting participants (NCT 01837420).

Given recent emerging evidence that psoriasis is associated with an increased risk of cardiovascular disease, this novel medication is a promising oral agent for treating both inflammatory conditions.

## SRT2104: Sirtuin Activator

SRT2104 (GlaxoSmithKline) is a small-molecule activator of Sirtuin 1 (SIRT1), a NAD+-dependent histone deacetylase that has been implicated in cellular metabolism, stress responses, and aging [40]. *In vitro* evidence suggests that SIRT1 activation may inhibit TNF alpha-induced inflammation. Furthermore, SIRT1 activation in keratinocytes promotes differentiation and inhibits proliferation [41]. Peripheral blood mononuclear cells from psoriasis patients had reduced levels of SIRT1 expression and decreased global H4 histone acetylation as compared to controls, which negatively correlated with disease activity [42]. The effects of IL-22, which has a pathogenetic role in psoriasis, are mediated by the acetylation and phosphorylation of STAT3. SIRT1 negatively regulates IFN-gamma mediated STAT3-dependent IL-22 signaling in keratinocytes and by downregulating SIRT1 expression in psoriatic skin lesions, IFN-gamma may render psoriatic keratinocytes more responsive to IL-22 [43]. Thus, an activator of SIRT1 such as SRT2104 may be beneficial in psoriasis by inhibiting STAT3 acetylation and the downstream activation of IL-22.

SRT2104 was well tolerated in phase I studies and no serious adverse effects were observed [44]. A phase 2 clinical study of SRT2104 (250, 500, or 1,000 mg) vs. placebo has recently been completed (NCT01154101) but the results have yet to be published. In addition, a second phase I study of new oral formulations of SRT2104 (NCT01702493) has also been recently completed. Results are not yet published.

## Doxercalciferol: Vitamin D Analog

Topical formulations of vitamin D analogs such as calcipotriene (Dovonex®) and calcitriol (Vectical®) are currently approved for the treatment of psoriasis. The active form of vitamin $D_3$ (1α,25-dihydroxyvitamin $D_3$) has been shown to both regulate calcium homeostasis and also to exert antiproliferative effects [45]. It is this latter function that has led to the use of Vitamin D analogs in the treatment of psoriasis.

Doxercalciferol (Hectorol®, CYP24A1, Genzyme) is an oral vitamin $D_2$ pro-hormone analog that is activated by 25-hydroxyvitamin D-24-hydroxylase (CYP24A1) to the naturally occurring active form of vitamin $D_2$, 1α,25-

dihydroxyvitamin D2. It is currently approved for the treatment of secondary parathyroidism in patients with stage 3 or 4 chronic kidney disease or chronic kidney disease on dialysis. Preclinical, *in vitro* studies showed that CYP24A1 can activate and inactivate vitamin D prodrugs in skin and other target cells [46].

A phase 2 clinical study of 136 patients randomized to 24 weeks of 24 mcg daily doxercalciferol vs. placebo for the treatment of moderate to severe chronic plaque type psoriasis was completed in June 2009 (NCT00601107). Results have yet to be published.

## BMS-582949: p38 MAP Kinase Inhibitor

Mitogen-activated protein kinases (MAPKs) are a family of conserved signal transduction molecules in mammalian cells. Two members of this family ERK1/2 and p38 MAPK, are involved in the production of TNF and downstream proinflammatory cytokines. Levels of both ERK1/2 and p38 are increased in psoriatic skin [47]. TNF alpha inhibitor therapy decreases the activity of p38 MAPK and downregulates p38 MAPK-regulated cytokines in psoriatic skin, suggesting that this pathway may be an important mechanism of action of anti-TNF alpha therapy in psoriasis [48, 49].

BMS-582949 (Bristol-Myers Squibb) is a small molecule inhibitor of p38 MAP kinase. Phase 2 clinical trials of BMS-583949 for the treatment of rheumatoid arthritis, atherosclerosis, and psoriasis have recently been completed but not yet published.

## ACT-128800: S1P1 Receptor Inhibitor

Sphingosine 1 phosphate (S1P) is a sphingolipid produced by platelets and cells of the innate immune system that can function as a bioactive signaling molecule. S1P binds to a family of G protein coupled receptors consisting of five subtypes, with S1P1 being expressed in the skin. S1P has been shown to inhibit keratinocyte proliferation and induce keratinocyte differentiation and stimulate the migration of T-cells from lymphoid organs. Interestingly, S1P receptor agonists have been shown to inhibit the egress of T-cells from the thymus, Peyer's patches, and lymph nodes perhaps by triggering the downregulation of S1P1 from the cell membrane into intravesicular vesicles or by affecting the barrier function of the endothelial stroma [50].

ACT-128800 (Ponesimod, Actelion) is a selective S1P1 receptor agonist that is being investigated for the treatment of psoriasis. A phase II study of 66 patients with moderate-to-severe chronic plaque psoriasis and a second study involving 320 patients have been completed (NCT00852670). ACT-128800 and another S1P1 receptor agonist, GSK2018682 (GlaxoSmithKline) are also in clinical trials for multiple sclerosis. One member of this class, fingolimod (FTY720, Gilenya®, Novartis), is a S1P agonist which binds to S1P receptor subtypes 1, 3, 4, and 5, and has recently been approved by the FDA for the treatment of relapsing forms of multiple sclerosis.

## FP187: Fumaric Acid Esters

Fumaric acid esters have been used in Europe as a treatment for psoriasis since the 1950s. In Germany, Fumaderm®, an enteric-coated preparation consisting of dimethylfumarate (DMF) and three salts of monoethylfumarate (MEF), has been available since 1994 for the treatment of psoriasis. Their mechanism of action is not well understood but is thought to have an antiproliferative effect of keratinocytes as well as modulate T-cell responses [51]. Dimethylfumarate has been shown to decrease epidermal proliferation and reduce T-cell subsets in psoriatic lesions [52] and inhibit angiogenesis [53], which are key features in psoriasis. Adverse effects of fumaric acid esters include flushing, diarrhea, and relative lymphocytopenia. The medication is not known to have any teratogenic effects and long term data has not shown any increased susceptibility to infections or malignancy [51].

Recently, in a randomized, head-to-head trial of 60 patients with moderate-to-severe psoriasis comparing fumarates (according to a standard dosing regimen of 30 mg followed by 120 mg daily) to methotrexate (15 mg per week) for 12 weeks, 42 % of the patients in the fumarate group achieved PASI-50 as compared to 60 % in the methotrexate group ($p=0.325$) [54]. Fumarates were well tolerated with no serious adverse effects. Two patients discontinued the study due to diarrhea, worsening psoriasis, and itch. Flushing was more common in the fumarate group than in the methotrexate group (13 vs. 2; $p=0.002$). Reversible, transient eosinophilia and leucocytopenia was also observed. The authors concluded that fumarates were equally effective to methotrexate in the treatment of moderate-to-severe psoriasis.

Fumaderm® is not available in the United States. However, FP187 (Forward-Pharma GmbH), a fumaric acid ester is currently registered as an ongoing randomized, double-blinded, placebo-controlled phase 2 clinical study of 252 patients receiving different doses/dosing regimens (NCT01230138). A phase 3 study comparing fumaric acid esters to fumaric acid esters plus narrowband UVB phototherapy for psoriasis is recruiting participants (NCT01321164). Another fumaric acid ester, dimethylfumarate (BG00012, Panaclar) is being investigated in phase 3 studies as a treatment for multiple sclerosis.

## RWJ-445380: Cathepsin S Inhibitor

The cathepsins are a family of lysosomal enzymes that are involved in proteolysis. Cathepsin S is a cysteine protease involved in MHC Class II-mediated antigen presentation and extracellular matrix remodeling. Cathepsin S expression is upregulated in psoriatic keratinocytes, which may be due to stimulation from T-cells and the release of interferon gamma and TNF alpha [55]. The role of cathepsin S expression in the pathogenesis of psoriasis is unclear.

Phase II trials of RWJ-445380 (Johnson and Johnson; Alza Corporation), a cathepsin S inhibitor, have been completed in 60 patients with psoriasis (NCT00396422) and 259 patients with rheumatoid arthritis (NCT00425321). The studies were completed in 2007 and 2008, respectively, but there has been no data published regarding the medication and no further trials have been registered.

## R3421/BCX-4208: Purine Nucleoside Phosphorylase Inhibitor

R3421/BCX-4208 (Roche/BioCryst) is a small molecule inhibitor of purine nucleoside phosphorylase (PNP), an enzyme essential for the proliferation of activated T cells. A phase II study to evaluate R3421/BC-4208 in treating patients with moderate to severe plaque psoriasis was announced in 2007 [56]. A total of 66 patients were enrolled for this multi-center, randomized, double blinded, placebo-controlled, three arm study (NCT00504270), which was completed in 2009. However, no further information is available regarding this study and the drug is no longer listed as being in the pipeline on either company's website [57, 58].

## Alitretinoin: Retinoid

Oral retinoids, such as acitretin (Soriatane®), are vitamin A derivatives that are frequently used in the management of psoriasis and other proliferative skin disorders, although their exact mechanisms of action are not yet fully elucidated. Oral alitretinoin (9-cis retinoic acid, Basilea Pharmaceutica) is a physiological, endogenous retinoid. It is believed to interfere with cytokine-induced chemokine production in structural cells of the skin and to impair the recruitment of leukocytes into the skin. Additionally, alitretinoin is thought to modulate the function of leukocytes in antigen presentation, proliferation and expansion. These immunomodulatory and anti-inflammatory properties have supported the use of this drug in the treatment of inflammatory conditions, such as psoriasis [59].

Palmoplantar pustular psoriasis (PPP) is a variant of psoriasis that is particularly recalcitrant to treatment but has been shown to be responsive to systemic retinoids [60, 61]. Recently, alitretinoin has been increasingly utilized as a novel treatment for chronic hand eczema [62], leading to its investigation as a possible medication for the treatment of palmoplantar pustular psoriasis. A recent report of seven patients with recalcitrant PPP treated with alitretinoin showed encouraging results. The patients had been previously tried on topical steroids ($n=7$), vitamin D derivates ($n=7$), calcineurin inhibitors ($n=2$), tar ($n=7$), phototherapy ($n=5$), acitretin ($n=4$) and methotrexate ($n=2$) with limited improvement. The participants in this report were treated with once daily 30 mg alitretinoin for 12 weeks and found to have patient-assessed clinical improvement of 60–90 %, with decreased pain and pruritus reported by all participants [63]. A phase 2 clinical trial to assess efficacy of alitretinoin in patients with pustular psoriasis is in the recruitment phase (NCT01245140).

## Talarozole: CYP26 Inhibitor

CYP26 is a P450 isozyme with retinoic acid (RA) as its only substrate [64]. It has been detected primarily in the basal layer of the epidermis and is induced by retinoic acid in cultured keratinocytes [65]. Talarozole (R115866; Rambazole; Barrier Therapeutics/Stiefel, a GSK Company) is an all-trans retinoic acid metabolism blocking agent (RAMBA) serving as a specific inhibitor of CYP26 which induces, *in vivo*, an increase in tissue levels of retinoic acid by blocking RA catabolism. The mechanism of action of this drug is therefore to increase retinoic acid levels in plasma and skin, and thus potentiate their already established, beneficial effects.

Pre-clinical studies found both oral and topical R115866 to induce epidermal hyperplasia, formation of a granular layer, and transformation from parakeratosis to orthokeratosis in murine models [66]. A Phase II open label, single-arm trial of 19 patients treated with 1 mg/day for 8 weeks, demonstrated a significant reduction in PASI from baseline to end of therapy. The drug was also shown to be well-tolerated with only one patient requiring dose reduction due to hypertriglyceridemia [67]. A larger scale Phase II study comparing doses of 0.5, 1.0, and 2.0 mg and placebo was conducted (NCT00725348). Results have not yet been published on this study.

## Masitinib: Tyrosine Kinase Inhibitor

Masitinib mesilate (AB1010) is a potent and selective tyrosine kinase inhibitor that targets KIT and is particularly efficient in controlling the survival, migration and degranulation of mast cells, and thereby lessening their pro-inflammatory effects. *In vitro*, it appears to have higher affinity and selectivity than other TK inhibitors and does not inhibit kinases that are linked to toxic effects. Masitinib also potently inhibits recombinant PDGFR, and to a lesser degree FGFR3 [68]. Promising results have been reported from human clinical trials of masitinib in neurological and inflammatory disorders such as Alzheimer's disease, rheumatoid arthritis, asthma, mastocytosis, and most recently multiple sclerosis [69–72]. Recently, a double-blind, placebo-controlled, randomized phase III trial, comparing oral AB1010 (Masitinib) to placebo in the treatment of moderate to severe plaque psoriasis, has been completed (NCT0104557) but have not yet been published.

## Lestaurtinib: Multikinase Inhibitor

Lestaurtinib (CEP-701) is a multikinase inhibitor with activity against JAK2 and protein kinase C related kinase 1 (PKN1) [73, 74]. The use and study of this drug has primarily been limited to myeloproliferative disease but recently a phase II clinical trial was completed to assess the efficacy, safety and tolerability of lestaurtinib in the treatment of severe, recalcitrant, plaque type psoriasis (NCT00236119). Results have not yet been published.

### Apo805K1: Mechanism Unknown

A phase 2 clinical study of Apo805K1 (ApoPharma) is currently in recruitment phase (NCT01483924). The mechanism of action is unknown.

### LEO 22811: Mechanism Unknown

LEO 22811 (Leo Pharma) is a proprietary oral solution for the treatment of psoriasis which has been evaluated in a prospective, randomized, double-blinded, placebo-controlled four arm phase 2 clinical trial (NCT01116895). No further information regarding mechanism of action, safety, or efficacy was available at the time of writing.

## Conclusion

Psoriasis, in its many forms and presentations, has been shown time and again to severely impact the quality of life of those affected. While there are numerous treatment options currently available to patients, from topical medications to phototherapy to biologics, the disease tends to persist and in some cases is recalcitrant to multiple regimes. For this reason, it is vital that new drugs continue to be developed to add to the dermatologist's repertoire of therapeutic options in the management of this disease. As this chapter reflects, there are currently multiple promising new oral agents in phase II and III trials that will hopefully aid in the care of our psoriasis patients in the very near future.

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# Research Pipeline III: Biologic Therapies

19

Arielle R. Nagler and Jeffrey M. Weinberg

**Abstract**

Psoriasis is a chronic, inflammatory skin condition mediated by activated T-cells. Psoriasis, particularly moderate to severe disease, has a dramatic impact on patient's quality of life, making effective treatment a priority. Moderate to severe disease often requires systemic therapy. Over the last decade, we have been introduced to several different classes of biologic therapies. The first generation biologics in psoriasis, which are currently widely used, were targeted mostly at tumor necrosis factor alpha (TNF-α). Several new classes of biologic therapy are currently in development. This review will focus on biologic therapies in the pipeline, particularly targeted to treat moderate-to-severe disease. These agents target the IL-12/IL-23 and IL-17 pathways.

**Keywords**

Biologics • TNF-alpha • Interleukin-12 • Interleukin-23 • Interleukin-17 Clinical trials • Ustekinumab • Briakinumab (ABT 847) • MK-3222 Secukinumab (AIN457) • Ixekizumab (LY2439821) • AMG 827/Brodalumab • Guselkumab (CNTO 1959)

## Introduction

Psoriasis is a chronic, inflammatory skin condition mediated by activated T-cells. It is estimated that 20–30 % of patients with psoriasis have moderate to severe disease that impacts their quality of life [1].

For mild psoriasis, various topical treatments are considered long-term safe and effective, but they are ineffective in more severe disease. Moderate to severe disease often requires more aggressive systemic therapy. Previously, psoriasis

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was thought to be a disorder of keratinocyte proliferation and therapies were non-specific, immunosuppressive, and toxic. These therapies included among others, phototherapy, methotrexate, and cyclosporine. In the last several years, our understanding of psoriasis has improved dramatically as we have begun to understand the role of T cells, first T-helper 1 (Th1) cells and, more recently, T-helper 17 (Th17) cells, as well as the role of specific inflammatory cytokines in the pathogenesis of psoriasis. As a result of our better immunological understanding, more targeted therapies, specifically biologics, have been developed.

Biologics are proteins derived from living organisms that block or mimic the function of naturally occurring proteins [2]. While biologic therapies still are associated with increased risk of infections and malignancies due to immunosuppression, they are more benign than less specific systemic therapy. The first generation biologics in psoriasis, which are currently widely used, were targeted mostly at tumor necrosis factor alpha (TNF-α). These agents are effective by decreasing levels of TNF-α (alpha), a cytokine that promotes inflammation. While effective, in a meta-analysis, TNF-α (alpha) targeted agents were associated with serious adverse events including increased risk of serious infection as well as dose-dependent increases in malignancy [3].

## Clinical Trial Organization

In Phase I trials, researchers test an experimental drug or treatment in a small group of people (20–80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects. The volunteers in Phase I trials tend to be healthy volunteers, although they may include patients.

In Phase II trials, the experimental study drug or treatment is given to a larger group of people (100–300) to see if it is effective and to further evaluate its safety. The subjects in these studies are patients.

In Phase III trials, the experimental study drug or treatment is given to large groups of people (1,000–3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug to be used safely. These are large, multi-center, randomized, controlled trials. While not required in all cases, it is typically expected that there be at least two successful Phase III trials, demonstrating a drug's safety and efficacy, in order to obtain approval from the Food and Drug Administration (FDA).

In Phase IV trials, post-marketing studies delineate additional information including the drug's risks, benefits, and optimal use.

## Psoriasis Biologics Pipeline

### IL12/IL 23 and IL 17 Pathways

Interleukin-12 (IL-12) is produced by dendritic cells, skin Langerhans cells, B lymphocytes and phagocytic cells [4]. IL-12 induces the differentiation of naïve CD4 cells into Th1 cells [5]. These T cells produce interferon-γ (gamma) and other type I cytokines such as IL-2 and tumor necrosis factor beta (TNF-β). Type 1 cytokines induce T cell migration into the epidermis and stimulate keratinocyte proliferation in psoriasis [6]. The role of IL-12 in psoriasis was suggested by that fact that IL-12 mRNA and protein are increased in psoriatic lesions [7].

While psoriasis was more traditionally considered a Th1 mediated disease, recent evidence suggests that it may also rely heavily on a distinct set of helper T cells, Th17 cells. Th17 cells produce a different set of pro-inflammatory cytokines, including IL-6, IL-22, TNF-α, and, most importantly, IL-17 family cytokines. The differentiation of Th17 cells is stimulated by IL-23. The role of IL-23 in the pathogenesis of psoriasis has been suggested in many studies. IL-23 is over-expressed in psoriatic skin lesions as compared to uninvolved skin in humans [8]. In addition, detailed genetic studies of the IL-23 receptor gene have shown that two non-synonymous single nucleotide polymorphisms have a protective effect against psoriasis [9].

As Th17 cell differentiation is stimulated by IL-23, Th17 cells produce IL-17. IL-17 promotes

the production of IL-6, IL-8, granulocyte macrophage colony stimulating factor (GMCSF), all of which synergize with IFN-γ (gamma) to increase inflammation. IL-17 is thought to be one of the key inflammatory cytokines produced by Th17 cells in the development of psoriasis. IL-17 mRNA is found at detectable levels in psoriatic lesions, but not in non-lesional skin. Also, IL-17 producing cells have been isolated from the dermis of psoriatic lesions [10].

Psoriasis is likely the result of both the Th1 and Th17 mediated pathways. Consequently, IL-12, IL-23, and IL-17 are currently being investigated as therapeutic targets. Despite the fact that IL-12 and IL-23 are involved in different arms of T-cell autoimmunity in the development of psoriasis, they share a structural subunit, p40. As a result of their shared structure, IL-12 and IL-23 are targeted together by biologic drugs. IL-17 is the target of a separate class of biologics.

## Il-12/Il-23

### Ustekinumab

Ustekinumab is a fully human, monoclonal antibody that blocks the activity of p40, the protein subunit shared by IL-12 and IL-23 [11]. It acts to neutralize both IL-12 and IL-23 bioactivity by blocking their interactions with receptors [12].

Ustekinumab is an injectable medication that is currently approved for the treatment of moderate to severe psoriasis. Three large phase III trials including 2,899 patients were used to assess the efficacy and safety of ustekinumab for FDA approval. In the first, PHOENIX1, 67.1 % patients receiving ustekinumab 45 mg, 66.4 % receiving ustekinumab 90 mg, and 3.1 % receiving placebo achieved 75 % improvement in the Psoriasis Area and Severity Index (PASI 75) at week 12 ($p<0.0001$ for 45 mg, $p<0.0001$ for 90 mg) [13]. The Psoriasis Area and Severity Index (PASI) is the gold standard for the assessment of psoriasis and it is a measure of the average redness, thickness, and scaliness of the lesions (each graded on a 0–4 scale), weighted by the area of involvement. PASI 75, or a 75 % improvement in PASI, is considered a clinically meaningful endpoint in clinical trials. In the PHOENIX1 trial, adverse events occurred in 54.5 % of the patients receiving ustekinumab and 48.2 % of the patients receiving placebo. Serious adverse events occurred in 1.2 % of the patients receiving ustekinumab and in 0.8 % of the patients receiving placebo. The PHOENIX 2 trial assessed the efficacy of dosing intensification in ustekinumab partial responders. This study found that significantly more partial responders at week 28 who received increased frequency of dosing as opposed to those who were maintained on the current regimen achieved PASI 75 at week 52 ($p=0.004$) [14]. The ACCEPT trial, the first to compare two biologic agents, found that at week 12, patients receiving ustekinumab at week 0 and 5 achieved significantly better response than patients receiving high dose etanercept administered twice weekly for 12 weeks [15]. With these phase III studies, ustekinumab was approved by the FDA for use in patients with moderate to severe psoriasis.

In all of these trials, all patients enrolled were over the age of 18, however, psoriasis can often affect younger individuals, particularly adolescents. Ustekinumab is currently not approved for individuals less than 18 years old, however, there is currently a phase III trial specifically targeting patients with psoriasis between the ages of 12 and 18. This study, called the CADMUS trial, enrolled patients ages 12–18. The study is ongoing, and is comparing low and high doses of ustekinumab (weight based) with placebo. The primary end-point is the proportion of patients who achieve a Physician's Global Assessment (PGA) score of 0 'cleared' or 1 'minimal disease' at 12 weeks. PGA is an instrument that provides a subjective overall evaluation of disease severity. Typically, the physician rates the disease on a seven point scale with zero being 'clear' and seven being 'severe. This scale more realistically reflects clinical practice.

Psoriatic arthritis is another indication for ustekinumab that is under investigation. A successful phase II study for ustekinumab in psoriatic arthritis patients has been completed [16]. In this double-blind, randomized, placebo-controlled crossover study, patients with active

psoriatic arthritis were randomized to receive subcutaneous ustekinumab at weeks 0, 1, 2, and 3, followed by placebo at weeks 12 and 16, or placebo at weeks 0, 1, 2, and 3 followed by ustekinumab at weeks 12 and 16. The primary endpoint was percentage of patients achieving an ACR 20 at week 12. ACR 20 is defined as at least a 20 % improvement in both tender joint and swollen joint count. At week 12, 42.1 % of the ustekinumab-dose patients achieved an ACR20 response as compared to only 14.3 % of the placebo-dosed cohort. At week 36, 34 % of patients retained their ACR 20 response. Additionally, when the placebo-dosed group received ustekinumab at weeks 12 and 16, 45 % of the group achieve an ACR20 response 12 weeks later. Of note, in this study, patients were allowed to continue to use methotrexate, non-steroidal anti-inflammatory drugs, and oral corticosteroids. The inclusion of patients on additional therapy, distinguishes this study from TNF-alpha studies, making a comparison difficult. Still, in patients with psoriatic arthritis the TNF inhibitors are still first line. Investigation into the role of ustekinumab in patients with psoriatic arthritis continues as two phase III were performed [17].

PSUMMIT I evaluated the efficacy and safety of ustekinumab in patients with active psoriatic arthritis despite treatment with conventional therapy (anti-TNF-alpha naïve) through 108 weeks [17]. Patients were randomized to receive subcutaneous ustekinumab 45 or 90 mg or placebo at weeks 0, 4 and then every 12 weeks.

At week 24, the percentage of patients who achieved the primary endpoint of ACR 20 responses were the following in the different arms of the study: 42.4 % of patients receiving ustekinumab 45 mg, 49.5 % of patients receiving ustekinumab 90 mg, 22.8 % of patients receiving placebo ($P < 0.001$ for both comparisons). Patients who qualified for early escape at week 16 were considered non-responders for the primary and major secondary analyses at week 24 [17].

Following week 24 assessment, patients receiving ustekinumab 45 and 90 mg continued to receive maintenance therapy every 2 weeks, and placebo patients were crossed over to receive ustekinumab 45 mg induction (at weeks 24 and 28) and maintenance therapy every 12 weeks thereafter. Observed data showed that ACR 20 continued to increase between weeks 24 and week 52, with: 55.7 % in the ustekinumab 45 mg, 60.3 % in the ustekinumab 90 mg, 65.2 % of patients in the placebo crossover groups [17].

A similar proportion of patients experienced at least one adverse event (AE) or serious AE through week 16, the placebo controlled period of PSUMMIT I. Safety through week 52 was consistent with that observed during the placebo-controlled period between ustekinumab 45 and 90 mg groups in the incidence of AEs (66.8 and 64.7 %, respectively) and serious AEs (5.9 and 3.4 %, respectively). No malignancies, cases of TB, opportunistic infections or deaths occurred through week 52. Investigators reported three major adverse cardiovascular events (MACE) in ustekinumab-treated patients in patients with multiple pre-existing cardiovascular risk factors [17].

PSUMMIT II evaluated the efficacy and safety of ustekinumab in patients with active psoriatic arthritis, including those previously treated with one to five tumor necrosis factor (TNF) inhibitors, disease-modifying antirheumatic drugs (DMARDs), or nonsteroidal anti-inflammatory drugs (NSAIDs) [18]. Patients were randomized to receive subcutaneous ustekinumab 45 or 90 mg or placebo at weeks 0, 4 and then every 12 weeks.

At week 24 ACR 20 responses were the following in the different arms of the study: 43.7 % of patients on ustekinumab 45 mg, 43.8 % of patients on ustekinumab 90 mg, 20.2 % of patients receiving placebo, $P < 0.001$ for both comparisons. Compared with patients previously treated with TNF inhibitors, TNF-naïve patients improved more than those previously treated. The ACR 20 responses were 36.7 % of patients on ustekinumab 45 mg, 34.5 % of patients on ustekinumab 90 mg, 14.5 % of patients receiving placebo $P = 0.006$ for ustekinumab 45 mg, $P = 0.011$ for ustekinumab 90 mg [18].

In PSUMMIT II, similar proportions of patients experienced at least one AE through

week 16, the placebo controlled period, among those receiving ustekinumab 45 mg (63.1 %), ustekinumab 90 mg (60.6 %) and placebo (54.8 %), with infections being the most common AE. Serious AEs reported among the groups were: ustekinumab 45 mg (0 %), ustekinumab 90 mg (1.0 %), and placebo (4.8 %). No cases of tuberculosis (TB), opportunistic infections, major adverse cardiovascular events (MACE) or deaths occurred. Through week 24, one serious infection due to complications of pre-existent interstitial lung disease was reported in the placebo group and one skin malignancy (squamous cell carcinoma in situ) occurred in the ustekinumab 90 mg group [18].

### Briakinumab (ABT 874)

Briakinumab (ABT-874) is a fully human, anti IL-12/IL-23 monoclonal antibody directed against the common p40 subunit [19].

Phase II trials showed efficacy of treatment and retreatment of moderate to severe psoriasis with a favorable safety profile. In one phase II trial evaluating the efficacy of treatment, the percentage of patients achieving a PASI 75 at week 12 was statistically significantly greater in all of the briakinumab treatment groups than in the placebo group ($p<0.001$). In this study, treatment with briakinumab was well tolerated with the most common adverse events being injection-site reaction, nasopharyngitis, and upper respiratory tract infection. There were no serious infectious adverse events in the study [19]. Phase III studies to test the safety and efficacy were also completed. Four separate studies were performed comparing ustekinumab to placebo, methotrexate, and etanercept [20–23] group achieved the primary end-point than of the control group (whether it be, placebo, methotrexate, etanercept). In these studies, serious adverse events in the briakinumab group included malignancy, convulsion, infection, and major adverse cardiac events. In one of the phase III studies comparing briakinumab to placebo more adverse events, although not significantly more, occurred among patients receiving briakinumab as compared to patients receiving placebo. In this study, there were seven major cardiac adverse events in the experimental group and none in the placebo group [20]. Although not specifically citing these results, the manufacturer withdrew the application for FDA and EMA approval for briakinumab in 2011.

### MK-3222

MK-3222 is a monoclonal antibody to the p19 subunit of IL-23. MK-322 specifically binds to IL-23 neutralizing it thereby inhibiting Th17 cell activation.

In one study, patients received placebo or MK-3222 at doses of 3 or 10 mg/kg at weeks 0, 4, and 8. Clinically patients experienced dose-related improvement in their skin lesions. In addition, skin biopsies taken before dosing and after week 12 were compared in a subset of 22 patients. After treatment with MK-3222, epidermal changes in lesional skin resolved, and lesional skin was comparable to non-lesional skin. For example, there was significant reduction in the number of CD3 cells, neutrophils, and macrophages [24]. Results presented at the American Academy of Dermatology Conference in Miami in 2013 also suggested therapeutic potential for MK-3222 [25]. Papp et al. reported in an oral presentation at the conference that patients with chronic plaque psoriasis in a randomized controlled, dose-ranging study experienced significant improvement after 16 weeks of treatment with MK-3222. Patients were randomized to receive doses of 5 mg, 25 mg, 100 mg, 200 mg or placebo injected at weeks 0,4 and every 12 weeks for 52 weeks. PASI 75 responses occurred in 33, 64, 66, 74, and 4.4 % respectively. The results were statistically significant for each dose compared to controls.

In a proof-of-concept study presented at the annual congress of the European Academy of Dermatology and Venereology in 2012, 18 % of patients treated with just three doses of the antibody developed anti-drug antibodies [26]. Of the nine patients in this study that developed anti-drug antibodies, five had serum concentrations of MK-3222 that were significantly lower than subjects without anti-drug antibodies. Interestingly, the patients with the anti-drug antibodies did not differ from others in terms of PASI score.

Merck, the drug developer, currently is enrolling participants in a Phase III study to assess the efficacy and safety of the drug with a long-term extension study in patients with moderate to severe chronic plaque psoriasis.

### CNTO 1959/Guselkumab

CNTO 1959 is a fully human monoclonal antibody that targets the p19 subunit of IL-23. A phase I trial demonstrated encouraging results that were reported at the 6th International Congress of Psoriasis. PASI 75 was observed in all patients in a 300 mg treatment cohort [27]. Phase II studies, under the name X-PLORE, are currently underway to investigate efficacy and safety. This is a randomized controlled study in patients with moderate to severe plaque psoriasis that will compare CNTO 1959 at 5, 15, 50, 100, and 200 mg subcutaneously dosed at weeks 0, 4, 16 and then every 12 weeks for 40 weeks to placebo and adalimumab.

## IL-17

### Secukinumab (AIN457)

*Secukinumab* (AIN-457) is a fully human IgG1κ monoclonal anti-IL17 antibody that selectively neutralizes IL-17A. It is an intravenous drug that is being studied in psoriasis.

A proof of concept clinical trial was performed in 36 patients with chronic plaque psoriasis. In this study, patients received two doses of 3–10 mg/kg given intravenously 3 weeks apart. The PASI score was reduced in 58 % of patients on secukinumab, and in only 4 % of the placebo patients ($p<0.0001$) [28]. These responses were maintained at 12 weeks ($p=0.0005$). In addition, the effect of secukinumab was detected on a molecular level as reverse transcription polymerase chain reaction and microarray analysis of skin samples from patients with psoriasis on secukinumab revealed down-regulation of cytokines of autoimmunity.

Phase II studies for secukinumab have shown positive results. These studies included patients with moderate to severe plaque psoriasis and were designed as double-blind, parallel group trials with the primary endpoint of PASI 75 at 12 weeks. In one study, three doses (25, 75 and 150 mg) given at weeks 0, 4 and 8 were tested against placebo. Among patients receiving 150 mg doses, 83 % of patients achieved a PASI 75, compared to 57 % of patients receiving 75 mg, and 9 % of patients in the placebo group [29]. In this study, no antibodies to secukinumab were detected in the samples collected from the patients. Serious adverse reactions were not attributed to the study drug. Minor side effects included nasopharyngitis and headache in such small numbers that significance could not be assessed. Similarly, a second phase II study examining different induction schedules showed that at 12 weeks, secukinumab 150 mg dosed at weeks 0, 1, 2, and 4 as well as secukinumab 150 mg dosed at weeks 0, 4, and 8 was associated with PAS75 in 55 and 44 % of patients respectively [30]. Only 2 % of the patients in the placebo group achieved a PASI 75 ($p<0.001$). In addition, 15 weeks after the last study drug administration, less then 10 % of patients relapsed. Despite the brief duration of this study, adverse events were reported in 3.2 % of patients during induction and 4.7 % of patients during maintenance. Grade 1 or 2 neutropenia was detected in 4.7 % induction phase and in 7.9 % in the maintenance phase. All cases of neutropenia resolved during the coarse of the study.

There are three separate phase III trials underway studying secukinumab in patients with moderate to severe psoriasis. One trial is comparing different dosages and dosing regimens. A second trial is comparing intravenous to subcutaneous administration, and a third is looking at long-term efficacy at 52 weeks.

A randomized, phase II placebo controlled study was also performed to evaluate the safety and efficacy of secukinumab in patients with psoriatic arthritis [31]. In this study 42 patients were randomized to receive two intravenous secukinumab doses of 10 mg/kg 3 weeks apart or to receive placebo. The primary end point was a 20 % improvement in the American College of Rheumatology score. ACR20 responses at week 6 were 39 % for secukinumab versus 24 % for placebo ($p=0.27$). Despite the fact that the primary outcome was not

met, acute phase reactants and quality of life scores were improved in secukinumab patients as compared to placebo patients.

### LY2439821/Ixekizumab

Ixekizumab, also known as LY2439821, is a humanized anti-IL-17 monoclonal IgG4 antibody that is injected subcutaneously. Phase I studies were completed in rheumatoid arthritis and psoriasis patients [32]. Skin lesions from 40 patients who participated in the phase I trial for izekizumab were examined [33]. There were significant dose-dependent reductions from baseline keratinocyte proliferation, hyperplasia, epidermal thickness, and infiltration into the dermis and epidermis of T cells at 2 weeks. By 6 weeks, the skin appeared normal. Quantitative RT-PCR microarrays revealed ablation of the disease defining mRNA expression with in 2 weeks of the first dose.

Phase II trials have been completed in patients with psoriasis. In a double-blind study, 142 patients were randomized to receive subcutaneous injections of 10, 25, 75 or 150 mg of LY2439821 or placebo at weeks 0, 2, 4, 12, and 16 [34, 35] endpoints included proportion of patients with greater than 90 and 100 % improvement in PASI (PASI 90 and PASI 100 respectively). At week 12, significantly more patients achieved PASI 75 in the 150 mg (82.1 %), 75 mg (82.8 %), and 25 mg (76.7 %) groups compared with the placebo ($p<0.001$ for all dosages). In terms of the secondary endpoints, significantly more patients achieved PASI 90 and PASI 100 in the 150, 75, and 25 mg groups compared with the placebo (PASI 90 $p<0.001$, and PASI 100 $p\leq0.001$). In fact, significant differences in response rates were detected at as early as 2 weeks. The frequency of adverse of events was 61 % for all of the experimental groups combined and 63 % for the placebo group. Infection occurred in 32 % of the patients in the experimental groups and in 26 % of the patients in the placebo group. The most common adverse events included upper respiratory infection, headache, and injection site reaction. No serious adverse events occurred before 20 weeks.

The first Phase II trial was limited due to its short duration of follow up. In the United States clinical trial database, there is currently an ongoing phase II study with a duration extending to 240 weeks. There are also three Phase III trials, UNCOVER-1,2 and 3, which are underway or actively recruiting participants. UNCOVER-1 examines three dosing schedules of 80 mg of ixekizumab compared to placebo. UNCOVER -2 and 3 include an etanercept arm. These studies will be completed in 2014.

### AMG 827/Brodalumab

Brodalumab is a human monoclonal antibody directed against the IL-17A receptor. A Phase II randomized, double-blind, placebo controlled, dose-ranging study was completed in patients with moderate to severe plaque psoriasis. The results of the study were published in the *New England Journal of Medicine* [36]. In this study, 198 patients with at least 10 % of their body surface area were randomized to receive brodalumab (70, 140 or 210 mg on day 1 and weeks 1, 2, 4, 6, 8, 10) or placebo. The primary endpoint was percentage improvement from baseline PASI score at week 12. At week 12, a mean percentage improvement in the PASI score was 45 % among patients receiving 70 mg of brodalumab, 85.9 % among those receiving 140 mg, 86.3 % among those receiving 210 mg and 16 % receiving placebo ($p<0.001$ for all comparisons with placebo). PASI 75 and PASI 90 were achieved at week 12 in 77 and 72 % of patients in the 140 mg and the 210 mg brodalumab groups respectively, as compared to 0 % in the placebo group ($p<0.001$). Despite the significant improvement in plaque psoriasis at week 12, there were 2 cases of grade 3 neutropenia in the 210 mg brodalumab group. Other adverse events included nasopharyngitis (8 %), upper respiratory tract infection (8 %), and injected site erythema (6 %).

Given brodalumab's efficacy, three phase III trials, AMAGINE 1,2, and 3, are all underway. AMAGINE 1 is designed to assess the safety and efficacy of brodalumab at two different doses, as well as the effect of withdrawal and retreatment. AMAGINE 2 and 3 are comparing efficacy and safety of brodalumab to placebo and ustekinumab. These clinical trials are expected to be completed in 2014.

## Summary

Psoriasis can be a devastating dermatological condition that affects the quality of life of those who suffer from it. Not only does it create a significant psychological burden, but also it has been associated with severe systemic health manifestations including increased cardiovascular risk. For these reasons, finding a safe and effective treatment is essential.

From examining biologics that are currently in phase II and phase III clinical trials, there are obvious trends. Most apparently, the biologics are more specifically targeted to pathways that effect T cells and the downstream signaling cascade in order to limit the secondary side effects. In addition, many of the newer biologics are orally available and therefore are more attractive and easier for patients.

The biologics discussed in this chapter include only a small sliver of the therapeutic targets being investigated. There are many more biologics currently in phase I and phase II trials. The number of drugs in development reflects our greater understanding of the disease. As our knowledge of the pathophysiology of psoriasis deepens, so to will our ability to successfully devise drugs that safely and effectively inhibit disease.

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# Pediatric Psoriasis

# 20

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**Abstract**

Psoriasis is a chronic multi-system inflammatory condition with an autoimmune component. One-third to one-half of cases have onset in childhood. There are a variety of pediatric variant types of psoriasis, including generalized disease, that is similar to adult psoriasis, and types distinctive to childhood, including diaper involvement and pityriasis amiantacea. Pediatric psoriasis is associated with infectious triggers and exacerbation by the Koebner phenomenon. Children with psoriasis may have more of a tendency toward obesity as reflected by a large waist circumference. More extensive disease in childhood is associated with a poor quality of life. Therapeutics of pediatric psoriasis generally requires a global approach including identifying infectious triggers, addressing health risks including obesity, and psychological support. Prescription care includes application of mid-potency topical corticosteroids and/or calcipotriene, phototherapy with Narrowband UVB or excimer laser. In severe cases, cyclic prescribing of systemic agents for 6–12 months including methotrexate, cyclosporine and etanercept can aid in disease clearance with minimization of side effects.

**Keywords**

Psoriasis • Autoimmunity • Streptococcus • Psoriatic arthritis • Methotrexate • Cyclosporine • Narrowband UVB • Excimer laser • Calcipotriene • Topical corticosteroids • Obesity

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## Introduction

Psoriasis is a chronic inflammatory disorder, believed to have an autoimmune basis. It is characterized by aberrant T cell activity causing hyperproliferation of epidermal keratinocytes, with development of erythematous skin plaques covered by a silvery or micaceous scale [1, 2]. Pediatric psoriasis differs from adult onset psoriasis in types of environmental triggers, with trauma, stress, and bacterial infection being the most common pediatric disease triggers [1, 3], while drug-reactions, smoking, alcohol use, and underlying HIV infection are triggers more common in adulthood [4]. Recently, obesity and the metabolic syndrome have been linked to both pediatric and adult psoriasis [5]. Treatment options are similar for adult and pediatric psoriasis patients, although therapy selection for pediatric psoriasis varies according to patient age and is limited by the fact that systemic treatments for pediatric psoriasis are off-label.

In the United States, high-potency topical corticosteroids were the most frequently prescribed outpatient treatment for pediatric patients overall from 1979 to 2007 [6]. Few therapies for psoriasis are approved by the FDA for the pediatric age group, and drug dosages must be altered based on weight and/or age in children. This chapter will explore the epidemiology, pathogenesis, diagnosis, and therapeutic management options of pediatric psoriasis, with a special focus on aspects of the disease specific to the pediatric patient.

## Epidemiology (Table 20.1)

Psoriasis vulgaris is a common dermatologic disorder, affecting 3.15 % of the United States population and 1.5 % of the population in the United Kingdom [7, 8]. Onset occurs before 16 years of age in approximately one third of all cases [9, 10], making psoriasis a significant dermatological problem in the pediatric population.

The peak age of onset varies in the literature, but usually ranges anywhere between 2 and 11 years of age [1, 3, 11, 12]. The mean age at diagnosis has been reported to be between 10 and 11 years of age by a recent large population-based study [13]. Onset may occur slightly earlier for females [14], although studies have shown nearly equal male to female prevalence ratios [11, 12, 15]. Onset may also occur earlier in those with a positive family history of psoriasis [14]. Table 20.1 shows a review of worldwide presentation of pediatric psoriasis.

The annual incidence of psoriasis has been shown to be increasing, nearly doubling (from 29.6 cases per 100,000 to 62.7 cases per 100,000) from 1970 to 2000 in both pediatric and adult patients [13, 16]. Plaque psoriasis (Figs. 20.1 and 20.2) is the most common variant, occurring in 34–74 % of children, with the majority of lesions localized to the extensor surfaces of elbows and knees, scalp, face (Fig. 20.3), trunk, and posterior auricular region (Table 20.1) [11–13, 15]. Guttate psoriasis is more common in pediatric patients, occurring in approximately 6–33 % of cases of pediatric psoriasis (Fig. 20.4) [1, 14]. Pustular disease, is a relatively uncommon presentation in children, however, a Turkish group reported 13 % of their pediatric patients had pustular lesions [1, 11].

A single study from Greece sited 8 % of children as having erythroderma [17] however, most studies demonstrate that <1 % of children present this way [3, 10, 11, 14]. Glossitis and mucosal diseases are uncommon in childhood [1, 3, 10, 11, 14].

In infants and toddlers (less than 2 years old), psoriatic diaper rash is the most common presentation sometimes involving the intertriginous neck and axillary areas (Fig. 20.5) [15]. Psoriasis presenting in infancy has a better prognosis for long-term remission than childhood psoriasis [17]. Involvement of the folds, i.e. inverse psoriasis, is uncommon seen in older. Inverse psoriasis in any age group can be exacerbated by concurrent cutaneous overgrowth of streptococcal, staphylococcal and candidal species.

Nail psoriasiscan arise in the setting of plaque-type psoriasis, psoriatic arthritis, or with isolated nail disease. Psoriatic arthritis with active joint involvement is less common in childhood than adulthood, but should remain in the differential

**Table 20.1** Worldwide demographics of pediatric psoriasis

| Author, year | Country | Number of kids | Sex distribution (M:F and %M; %F) | Race and or ethnicity | Ages of kids (range, median, mean) | Types of psoriasis (%) | Areas of involvement | Triggers | Family history |
|---|---|---|---|---|---|---|---|---|---|
| Seyhan et al. 2006 [1] | Turkey | 61 | 1:1.7<br>38; 62 | Not discussed (Turkish) | Onset mean 6.9 ± 4.1<br>At time of study 10.0 ± 4.1 | Plaque 54 %<br>Guttate 33 %<br>Pustular 13 %<br>Inverse 7 %<br>Erythrodermic 3 %<br>Palmoplantar 2 % | (At onset)<br>Trunk 44 %<br>Scalp 36 %<br>Extremities 54 %<br>Diaper rash 5 %<br>Nails 21 % | URTI 15 %<br>+Group B strep culture 21 % | 23 % |
| Kumar et al. 2004 [3] | India | 419 | 1.1:1<br>52; 48 | Not discussed (Indian) | Onset mean 9.1 overall<br>(M) 8.1 ± 2.1<br>(F) 9.3 ± 2.3<br>Range 4–14 | Plaque 61 %<br>Guttate 10 %<br>Pustular <1 %<br>Inverse <1 %<br>Erythrodermic 1 %<br>Palmoplantar 6 %<br>Plantar 13 %<br>Nails 3 % | (At onset)<br>Trunk 8 %<br>Extremities 35 %<br>Scalp 21 %<br>Soles 19 %<br>Palms 3 % | Only recalled by 7 % of participants<br>Trauma 14 pts<br>Throat infection ten patients<br>Psych 3 pts<br>Drug rxn 1 pt | 4.5 % |
| Raychaudhuri and Gross 2000 [9] | USA | 223 | 1:1.3<br>44; 56 | Not discussed | Not discussed | Not discussed | (At onset)<br>Scalp 57 %<br>Trunk 14 %<br>Extremities 52 %<br>Face 9 %<br>Nails 13 % | Trauma 50 %<br>Stress 50 %<br>Pharyngitis 28 % | 68 % |
| Fan 2007 [11] | China | 277 | 1:1.1<br>47; 53 | Not discussed (Chinese) | Median age of onset 10<br>Range:<br>9 months to 15 years | Plaque 69 %<br>Guttate 29 %<br>Pustular 1 %<br>Erythroderma 1 % | (At onset)<br>Scalp 47 %<br>Face 20 %<br>Trunk 43 %<br>Arms 51 %<br>Legs 66 %<br>Nail 6 %<br>Palmoplantar 37 % | Not discussed | 8 % (7 1st, 1 2nd) |

(continued)

**Table 20.1** (continued)

| Author, year | Country | Number of kids | Sex distribution (M:F and %M; %F) | Race and or ethnicity | Ages of kids (range, median, mean) | Types of psoriasis (%) | Areas of involvement | Triggers | Family history |
|---|---|---|---|---|---|---|---|---|---|
| Kwon 2011 [12] | Korea | 358 | 1.1:1<br>51; 49 | Not discussed | Mean age onset:<br>10.5 ± 4.3 | Plaque 67 %<br>Guttate 18 %<br>Generalized pustular pustulosis 7 %<br>Palmoplantar 4 %<br>Erythroderma 1 % | Trunk 70 %<br>Legs 65 %<br>Arms 48 %<br>Face 46 %<br>Palms/soles 22 % | Not discussed | 32 % |
| Tollefson 2010 [13] | USA | 357 | 1:1.1<br>48;52 | Mostly Caucasian but not specified | Median age of onset 10.6<br>Range 6.8–14.4 | Plaque 74 %<br>Guttate 14 %<br>Sebo-psoriasis 8 %<br>Pustular 1 % | Scalp 47 %<br>Extremities 60 %<br>Palms/soles 5 %<br>Trunk 35 %<br>Face 18 %<br>Genital/groin 9 %<br>Nails 17 % | Not discussed | Not discussed |
| Morris 2001 [15] | Australia | 1,262 | 1:1.1<br>47;53 | Not discussed | No median or mean described<br>Range:<br>1 month to 15 years | Plaque 34 %<br>Scalp 12 %<br>Diaper rash 13 %<br>Guttate 6 %<br>Face only 4 %<br>Pustular <1 %<br>Nail <1 %<br>Erythrodermic <1 % | Face 38 %<br>Otherwise not discussed | Not discussed | 71 % (based on 61 % who responded) |
| Vogel 2012 [6] | USA | 3.8 million outpt VISITS for ped psoriasis | 1:1<br>50;50 | Race<br>White 93 %<br>Black 3 %<br>Asian/Pacific Islander 3 %<br>American Indian/ Eskimo/Aleut 0.5 %<br>Ethnicity<br>85 % non-Hispanic<br>8 % Hispanic<br>7 % other | Mean age at visit 11.3 | Not discussed (NB: article discusses outpatient visits and treatment choices, not individual patients) | Not discussed | Not discussed | Not discussed |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Wu 2011 [26] | USA | 1,361 | 1:1.2<br>45; 55 | Non-Hispanic white 38 %<br>Hispanic white 38 %<br>Black 3 %<br>Asian or Pacific Islander 7 %<br>Others 3 % | 11.8 ± 4.4 in M<br>12.5 ± 4.4 in F | Not discussed | Not discussed | Not discussed | Not discussed |
| Stefanaki 2011 [104] | Greece | 125 | 1.4:1<br>59; 41 | 81 % Greek | Peak age of onset 9–10 grp<br>Range:<br><1–13 years<br>No mean or median given | Plaque 57 %<br>Scalp? 34 %<br>Guttate 12 %<br>Flexural 10 %<br>Erythrodermic 8 %<br>Nails only 5 % | Extremities 56 %<br>Scalp 48 %<br>Trunk 47 %<br>Nails 10 % | Not discussed | 16 % |

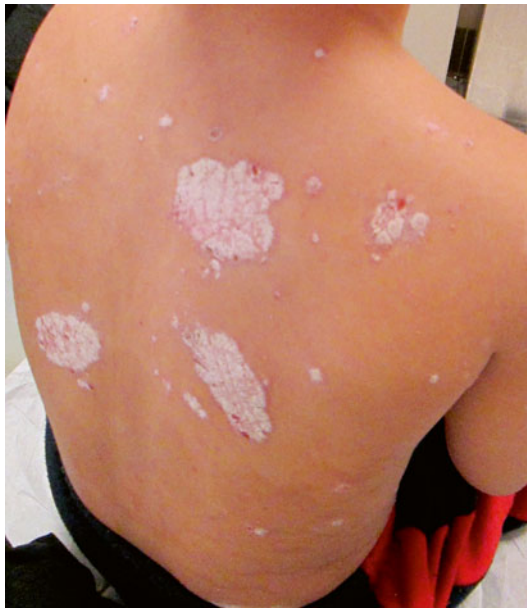


**Fig. 20.1** Untreated plaque psoriasis affecting the trunk with large circinate plaques with overlying micaceous scale (Reprinted with permission from Silverberg [63])

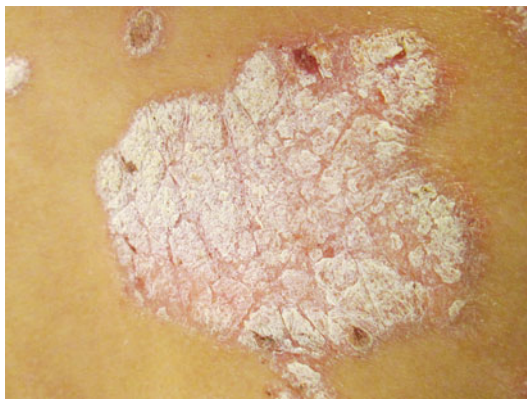


**Fig. 20.2** Close-up of plaque with micaceous scale demonstrates areas of Auspitz sign, pinpoint bleeding due to manual removal of scale

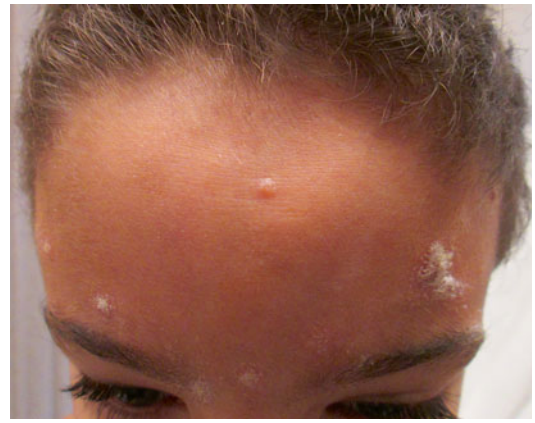


**Fig. 20.3** Facial psoriasis can be a challenging condition due to the combination of disfigurement, psychological distress and limitations of therapy on the thin-skinned face

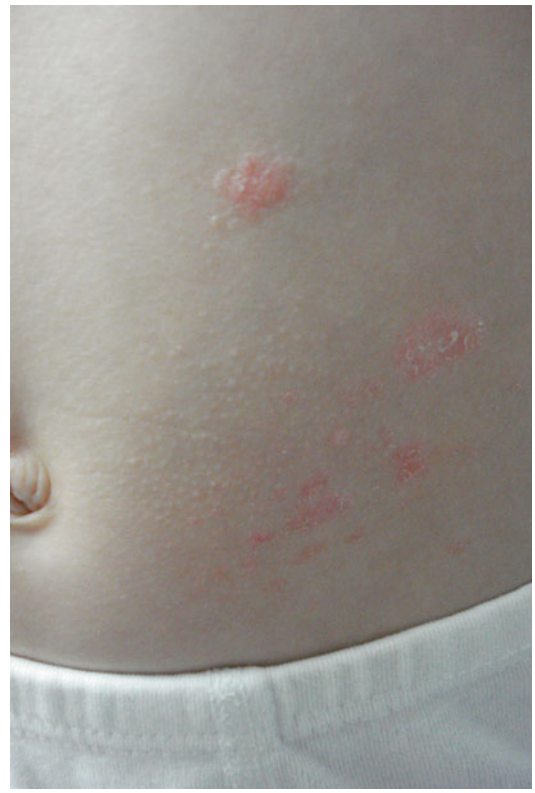


**Fig. 20.4** Guttate psoriasis of the trunk in a child with psoriasis flared by an upper respiratory infection (Taken from Silverberg [103] with permission)

for children with arthritis [3]. In the majority of children, dermatologic manifestations precede the onset of psoriatic arthritis [18].

There is a bimodal age of psoriatic arthritis onset with peaks during the first few years of life and in early adolescence [19]. The early onset form of psoriatic arthritis is most likely to be polyarticular, ANA (antinuclear antibody) positive, and favors the female sex [20, 21]. The adolescent-onset form of psoriatic arthritis has a higher incidence of axial joint involvement and

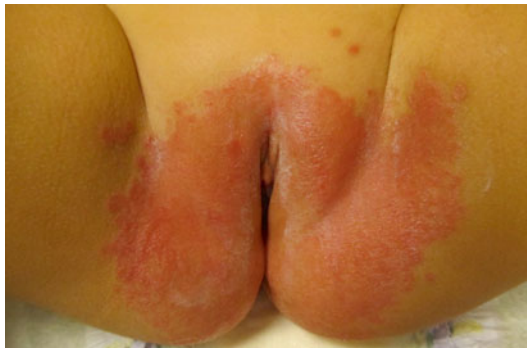


**Fig. 20.5** Inverse psoriasis in an infant (Taken from Silverberg [103] with permission)

favors the male sex. The proximal and distal interphalangeal joints of the hand, knees, and ankles are most commonly involved initially. Children often present with oligoarthritis, which may progress to polyarthritis; dactylitis can be associated. Psoriatic arthritis can be differentiated from idiopathic juvenile rheumatoid arthritis by the presence of blue discoloration of the joints, nail pitting and/ or nail dystrophy [18]. Predominant involvement of the wrists and small joints of the hands and feet also point toward a psoriatic etiology of arthritis in affected children [21].

Pediatric psoriasis has been shown to negatively affect quality of life. This may be more pronounced in younger children who have less developed coping mechanisms [22]. Children with moderate-to-severe psoriasis have similar health-related quality of life as compared to children with arthritis or asthma, but worse than children with diabetes [23]. Adult females with psoriatic arthritis suffer greater disability than their male counterparts, but no gender differences have been reported in children thusfar [24].

Lower psoriatic incidence has been noted in Inuit people, the single most prominent ethnic variation that has been noted. This information suggests that diets high in omega-3 fatty acids may be protective against the development of psoriasis [25]. One study of children in southern California found the highest prevalence of pediatric psoriasis to be in non-Hispanic whites and the lowest but not negligible incidence in blacks. Also of note, a lower overall prevalence was noted than historically would be seen in other areas of the country. The authors speculated that increased sunlight exposure and a lower population-based proportion of non-Hispanic whites may have lead to this observation [26].

## Pathogenesis

Although the exact pathogenesis of psoriasis has not yet been revealed, it is clear that both genetic and environmental factors play a role in the development of psoriasis. A positive family history is present in 23–71 % of pediatric psoriatic cases [1, 15, 27]. There is a higher rate of concordant psoriasis in identical as compared to fraternal twins (65–72 % vs. 15–30 % respectively) [28, 29].

Psoriasis vulgaris cannot be linked to a single gene. It appears that several genes may play a role in the genetic susceptibility of psoriasis, most notably HLA-Cw6 [28]. HLA-Cw6 may interact with the susceptibility alleles, caspase recruitment domain family member 15, CARD15; cyclindromatosis gene, CYLD; and transglutaminase 5, TGM5 [30]. Other genes that have been implicated include IL12-B9 (1p31.3); IL-13 (5q31.1); IL-23R (1p31.3); HLABW6; PSORS6, signal transducer and activator of transcription gene 2 STAT2 and IL-23A (12q13.2); tumor necrosis factor α-induced protein 3, TNFAIP3 (6q23.3); and TNFAIP3 interacting protein 1, TNIP1 (5q33.1) [28]. The role of these genes is regulation of Th2 andTh17 lymphocyte activity as well as the NF-κB signaling pathway, which indicates both Th2 and Th17 cells may play a role in the pathogenesis of psoriatic disease. Collections of Th17, Th2 and Th1 cells have been found in psoriatic skin lesions [28, 31]. The gene PSORS1 within HLA-C and PSORS2 (17q24-q25) have also been implicated as increasing the risk for psoriasis development [32, 33]. Yet another gene, PSORS6 (19p13), has been shown to interact with PSORS1 [32]. SCL12A8, which belongs to the solute carrier gene family, has also been named as a susceptibility gene [30].

New susceptibility genes are continually being discovered. Additionally, it appears that susceptibility genes for psoriasis may overlap with other

**Table 20.2** Suggested work-up for children with psoriasis (Wolverton [61])

| |
|---|
| **At onset**: |
| Throat culture or ASO (especially in guttate psoriasis) |
| Biopsy in atypical cases |
| **Annually**: |
| Joint evaluation (referral to rheumatology for specific symptoms) |
| Cardiac markers: weight, height, body mass index, blood pressure, lipid profile (cholesterol, triglyceride) |
| **Optional evaluations**: |
| Cultures of macerated or crusted lesions for diagnosis of superinfection (bacterial culture, fungal culture) |
| Celiac panel for children with stomach symptoms, difficulty with clearance or severe disease |
| Thyroid screen for co-morbid arthritis or vitiligo and in symptomatic cases |
| **Screening for medications** (co-manage with rheumatology when arthritis suspected): |
| Cyclosporine: blood pressure, complete blood count, complete metabolic profile, urinalysis, magnesium, fasting lipid profile (q1-2 weeks for 2 months or for dosage elevations then monthly); urine pregnancy screening at baseline in girls of child bearing age |
| Methotrexate: PPD (baseline and annually), complete blood count with platelets, liver function testing and renal function testing (every few weeks for dosage escalations and at initiation of therapy, then monthly), Hepatitis A, B and C screening, HIV testing for individuals at risk (at baseline); urine pregnancy screening at baseline in girls of child bearing age |
| Liver biopsies are rarely performed in children at this time. Comanagement with rheumatology and/or gastroenterology may be helpful in prolonged usage |
| Acitretin. Isotretinoin: complete blood count, liver function tests, cholesterol, triglycerides, urine pregnancy in girls of child bearing age (monthly for isotretinoin due to the iPLEDGE program for the duration of therapy; for acitretin after 6 months can change to quarterly labs); spiral xrays for suspected DISH; ophthalmology with prolonged usage |
| Etanercept/adalimumab/infliximab: PPD at baseline and annually; screening for prior hepatitis; periodic evaluation for lymph node enlargement; periodic laboratory evaluation |
| **Referrals**: |
| Endocrinology for comorbid endocrinopathy, obesity management, work-up for HPA axis suppression in chronic steroid users |
| Rheumatology for joint pains, limited mobility, co-management of methotrexate or biologics (optional, but suggested for cases with arthritis or suspicion of) |
| Gastroenterology for management/work-up of suspected comorbid inflammatory bowel disease, celiac disease; comanagement of methotrexate (optional) |
| Nutritionists/weight down programs |
| Ophthalmology screening for issues arising from oral retinoids |

autoimmune disorders. For example, the genes IL-12B and IL-23R are shared with Crohn's disease and IL-23R is shared with ulcerative colitis. Patients with Crohn's disease are five times more likely to develop psoriasis as compared to the general population, a fact that may be explained, as least in part, by shared susceptibility genes [28]. Decreased expression of the CD18 gene, mutations in which result in leukocyte adhesion deficiency type I, may also be low in certain patients with psoriasis [34]. No studies have shown a difference in the genetics of pediatric-onset psoriasis as compared to adult-onset psoriasis.

Table 20.2 gives a list of potential laboratory or diagnostic evaluations for children with psoriasis. The most common precipitating environmental factors in pediatric psoriasis appear to be stress and upper respiratory infections (Table 20.1), especially with group A β-hemolytic Streptococcus (*Streptococcus pyogenes*). Upper respiratory tract infections have been reported to be an inciting factor in 14.8–28 % of pediatric psoriasis cases, while 21.3 % of asymptomatic children have tested positive for group A ß-hemolytic streptococcus on throat culture prior to developing psoriasis [1]. Streptococcal pharyngitis may trigger up to 2/3 of all cases of guttate

psoriasis [35] as well as exacerbate existing plaque psoriasis [2]. It appears that patients with psoriasis have a unique host-specific response to the streptococcal antigens [35, 36].

Enterotoxin-producing *Staphylococcus aureus* and Human papillomavirus DNA has also been isolated from within psoriatic skin lesions, suggesting that these entities and the corresponding immune response to them may also play a role in the pathogenesis of psoriasis [37, 38]. Environmental factors, such as exposure to cigarette smoke, as well as obesity, have also recently been associated with the development of pediatric psoriasis [27].

Psoriasis is an autoimmune disease which, by definition, means it is characterized by the immune system mounting a response against self-antigens. Thus, it is of no surprise that psoriasis is associated with other autoimmune conditions, most frequently of the skin. Patients with morphea have been found to have a higher prevalence of psoriasis than the general population [39]. There have also been case reports of familial associations between psoriasis and vitiligo [40, 41]. Individuals with celiac disease are at increased risk for the development of psoriasis and this association is most pronounced in pediatric patients, meriting celiac disease screening in children with severe psoriasis [42]. An uncertain relationship remains between psoriasis and autoimmune thyroid diseases. In adults, psoriatic arthritis has been linked to a higher incidence of autoimmune thyroiditis than the general population, especially in patients with concomitant rheumatoid arthritis [43]. However no such correlation has been shown with psoriasis localized to the skin and without associated arthritis, as thyroiditis markers are statistically similar between psoriatic adults and age-matched controls [44]. Pediatric studies investigating a link between psoriasis and autoimmune thyroid diseases have yet to be reported. Since the data in the adult population is inconsistent and no studies with children participants exist to be used as guidelines, routine annual screening for thyroid disorders is not recommended in pediatric patients with psoriasis. Screening for thyroid disorders may be warranted in children with psoriatic arthritis or in psoriatic pediatric patients with concomitant vitiligo, or another autoimmune diseases that are more closely associated with thyroid abnormalities [45]. A suggested work-up for children with psoriasis is included in Table 20.2.

### Obesity and Metabolic Syndrome

Recently, an association between psoriasis and the various characteristics of the metabolic syndrome has surfaced in the literature. A growing body of evidence points to an increased risk of cardiovascular mortality in adult patients with severe psoriatic disease [46]. Increased rates of hypertension, hyperlipidemia, diabetes mellitus, and obesity are seen in children and adolescents with psoriasis, with the former three comorbidities occurring twice as often in pediatric psoriatic patients as compared to healthy controls [47]. Adolescents with psoriasis have been found to elevated plasma lipids irrespective of body mass index, suggesting psoriasis itself may lead to metabolic abnormalities [5]. Pubescent females (aged 12–13) with an elevated BMI appear to be at an increased risk for the development of severe psoriasis later in adolescence [48]. In adults with psoriasis, unhealthy lifestyle habits such as cigarette smoking, excess alcohol intake, and poor dietary choices have been linked to an increased risk of cardiovascular comorbidities [49]. This highlights the need for prevention through the early development of healthy habits in pediatric patients with psoriasis. Referrals to nutritionists, endocrinology, and weight-down programs are advisable interventions in obese adolescents with psoriasis.

## Diagnosis and Clinical Characteristics (Tables 20.1 and 20.3)

The various clinical variants of psoriasis are listed in Tables 20.1 and 20.3. The most common presentation in children is plaque type, with erythematous plaques with overlying silvery scale localized to the extensor surfaces and scalp (Table 20.3). In children, psoriatic lesions are

**Table 20.3** Clinical variants of pediatric psoriasis [21]

| Type of psoriasis | Clinical appearance | Diagnostic features and tests | Co-morbidities | Differential diagnosis | Treatment |
|---|---|---|---|---|---|
| Plaque-type | Erythematous plaques with micaceous scale<br>Typical areas: Scalp extending to forehead, nuchal, postauricular, elbows, knees, umbilical and buttocks | Usually a clinical diagnosis<br>Nail pitting can be noted as a clue to the diagnosis of psoriasis in children<br>Biopsy (when needed) features<br>Thickened epidermis, neutrophils in the horny layer, the spongiform pustules of Kogoj and the subcorneal microabscess of Munro (collections of neutrophils in the epidermis)<br>Pharyngeal bacterial culture or ASO testing | Check for recent pharyngitis, (Group A beta hemolytic *Streptococcus*)<br>Rule out secondary infection with *S. aureus*<br>Consider comorbid autoimmunity (e.g. thyroid disease, celiac disease)<br>In the setting of obesity, disease severity can be a marker of cardiovascular risk | Nummular dermatitis<br>Tinea capitis<br>ID reaction<br>Pityriasis rubra pilaris<br>Lichen planopilaris<br>Atopic dermatitis (overlap can rarely be seen) | Treatments must be tailored based upon: (1) the age of the patient, (2) quality of life issues, (3) surface area and (4) sites affected<br>Topical therapeutic regimens are prescribed including keratolytic agents, topical anti-inflammatory compounds (e.g. corticosteroids and calcineurin inhibitors) and topical vitamin A and D analogues<br>Systemic agents and phototherapy may be needed in moderate to severe disease |
| Guttate | Small, annular localized erythematous to salmon colored plaques with mild hyperkeratosis, sometimes micacous<br>Commonly noted on the trunk, abdomen and back | Clinical diagnosis is often possible<br>Biopsy is similar to that of plaque-type psoriasis<br>Check for recent pharyngitis, (Group A beta hemolytic *Streptococcus*), by Pharyngeal bacterial culture or ASO testing | Recent pharyngitis, (Group A beta hemolytic *Streptococcus*) | Nummular dermatitis<br>Pityriasis rosea<br>ID reaction<br>Tinea corporis<br>Pityriasis rubra pilaris<br>Pityriasis lichenoides | Topical therapy similar to plaque-type psoriasis<br>Oral antibiotics are often used initially due to presumptive infectious precipitating factors and for anti-inflammatory capabilities (erythromycin, azithromycin cephalosporins)<br>Systemic agents and phototherapy may be needed in moderate to severe disease unresponsive to oral antibiotics |
| Inverse | Erythematous, sometimes macerated thick plaques of the intertriginous skin, including axillae and groin<br>Can be associated with plaque type psoriasis in other sites | Although clinical diagnosis is often possible, similarity to other diseases may require biopsy for differentiation | Secondary infection with *Candida* and/or *Streptococcus* may require cutaneous culture for diagnosis and prescription of topical anti-infectives | Intertrigo<br>Erythrasma<br>Tinea corporis<br>Langerhans cell histiocytosis | Topical medications should be non-steroidal or low-potency topical corticosteroids to avoid atrophy of the occluded skin<br>Oral or topical anti-infectives should be added where appropriate |

| | | | | | |
|---|---|---|---|---|---|
| Nail | Pitting, oil spots, subungual hyperkeratosis trachyonychia: (i.e. Extensive pitting and subungual hyperkeratosis) | 1. Fungal culture and nail plate biopsy to rule out tinea infection or secondary candidal infection of the nail bed is needed when subungual hyperkeratosis is present<br>2. Avoid trauma orexcess manipulation (e.g. aggressive manicures) | Secondary infection with *Candida* and/or *Streptococcus*<br>And/or dermatophytes | Onychomycosis<br>Lichen planus<br>Pityriasis rubra pilaris<br>Trauma | 1. After treatment of any fungal super-infection, topical corticosteroids with tazarotene or calcipotriene can be applied to the paronychial skin. Intralesional kenalog can also be used in the same region to reduce the subungual inflammation<br>2. May require usage of topical anti-infectives |
| Napkin or diaper Psoriasis ("nappy") | Macerated shiny erythema of the groin region including the folds and the genital skin | Biopsy may need to be performed<br>Bacterial and fungal cultures may be needed for suspected secondary infections or perianal strep | Secondary infections or perianal strep | Irritant contact dermatitis<br>Diaper dermatitis<br>Candidal diaper dermatitis<br>Allergic contact dermatitis | Mild topical corticosteroids with or without topical anti-candidal agents can be helpful<br>Barrier therapy with zinc oxide pastes reduces secondary irritant reactions |
| Erythroderma | Generalized erythema and thickening of the skin, sometimes with hyperkeratosis | Two biopsies are generally required from separate sites to differentiate psoriatic erythroderma from other causes of erythroderma in childhood | Fever, chills and malaise can accompany erythroderma, making bacteremia a possible co-morbidity which should be ruled out conclusively ivia blood cultures | Atopic dermatitis<br>Pityriasis rubra pilaris<br>Mycosis fungoides<br>Staph scalded skin syndrome | Topical anti-inflammatory agents can be used similar to the therapy of extensive plaque-type psoriasis, however, control of extensive disease is difficult with topical agents and systemic anti-inflammatory agents and/ or phototherapy are often required to control severe and extensive disease<br>NB: Special care must be taken to acoid systemic corticosteroids which can precipitate a pustular flare |
| Pustular | Erythroderma accompanied by sterile pustule formation, sometimes localized to the distal extremities, sometimes generalized. Prior history of oral steroid usage may be noted | 1. Biopsy is often needed<br>2. Bacterial culture of the pustules<br>3. Fungal culture of the pustules<br>4. ASO titers can be drawn to rule out streptococcal precipitant | Bacterial or fungal infections should be ruled out through culture | Blistering distal dactylitis<br>Tinea infection with *Tinea mentagrophytes*<br>Herpetic whitlow<br>Hand foot mouth disease | Topical therapy (see plaque-type psoriasis) are often ineffective and systemic agents (especially cyclosporine, acitretin) or topical PUVA may be needed |
| Mucosal/oral | Annular plaques on the tongue may be noted in patients with psoriasis | Generally a clinical diagnosis, however, biopsy is similar to that of pustular psoriasis | Rarely has any morbidity | Aphthosis<br>Lichen planus<br>White sponge nevus | No therapy is usually needed, however topical medicaments in an oral base can be used when needed |

Source: Modified from Silverberg [17]

generally thinner, possess less scale and are more pruritic as compared to adults [50]. Certain physical findings are characteristic of psoriasis, including pediatric cases. These findings include: (1) The Koebner phenomenon, (2) postinflammatory pigmentary alteration, especially in children of color, (3) the presence of punctate bleeding spots when scales are removed or the Auspitz sign, and (4) nail pitting [51].

The scalp is the leading site of psoriatic lesions in all age groups. Typical presentation include thick erythematous plaques of the scalp, extending onto the forehead, over the ears and onto the nape of the neck. The forehead is an especially important site in childhood psoriasis due to the fact that facial disease is more prevalent in childhood (Fig. 20.2). It is important to differentiate scalp psoriasis from tinea capitis [52]. A specific scalp finding that is associated with psoriasis, but may be noted even in the absence of psoriasis, is pityriasis amiantaceia, presenting as thick hyperkeratotic concretions attached to the hairs accompanied by scalp erythema. Children in Scandinavia with pityriasis amiantaceia have a stronger family history and personal tendency towards psoriasis than children in the general population [53]. Some authors believe pityriasis amiantaceia is de facto psoriasis, often scalp limited, and usually of childhood. Staphylococcal overgrowth is noted in a majority of cases of pityriasis amiantaceia and may play a causative role in disease [52].

Several case studies in the literature have reported oral mucosal changes in adult patients with psoriasis and there is debate over whether these changes are part of the spectrum of psoriatic disease. Lesions of all areas of the oral cavity, including the tongue, lips, buccal mucosa, gingivae and palate have been reported. However, the overall incidence among patients with psoriasis is low [54]. Fissured tongue and geographic tongue (also called benign migratory glossitis) are the most commonly reported oral lesions [54, 55], and the incidence of geographic tongue increases as the severity (as measured by the PASI score) of psoriasis increases [55]. Cases of geographic tongue in children with psoriasis have been also reported [56]. The histopathology of geographic tongue resembles that of pustular psoriasis, leading some experts in the field to believe that geographic tongue and psoriatic skin lesions may be two manifestations of the same disease process [57]. Even in light of these findings, a recent review of the literature failed to find convincing evidence that oral psoriasis is a discrete clinical entity [54].

The PASI score was devised to give objective measurement to the severity of psoriasis, especially in regards to clinical research, however the score has not been validated in childhood and may not adequately reflect severity of childhood disease especially as it lacks a pruritus or quality of life component. It is a calculation based upon the severity of psoriatic lesions (determined by erythema, induration, and scale), location of lesions, and total body surface area involved. This calculation is outlined in Table 20.4, ranges from 0 to 72, and can be used in older children and adults [4]. A website is also available to simplify the PASI calculation [58].

Other methods of psoriasis scoring base the overall severity of psoriasis on total body surface area involved, quality of life impairment, and the presence or absence of psoriatic arthritis. Still others are based solely upon the total body surface area involved, with <3 % being mild disease, 3–10 % being moderate disease, and >10 % being severe disease. However, the latter method may be oversimplified, as quality of life may be significantly impaired with minimal total body surface area involvement [59, 60]. One such example is psoriatic lesions localized to the face, which is much more common in children (affecting 38 %) than their adult counterparts [15]. Alterations of PASI with extra weighting for head and neck disease in children may more adequately reflect body surface area distribution in smaller children. Facial disease in our experience is the leading cause of patients and parents seeking systemic therapy.

## **Differential Diagnosis** (Table 20.5)

The differential diagnosis of pediatric psoriasis includes other papulosquamous diseases of childhood, including psoriaform id reactions, pitryiasis rosea, and pitryiasis rubra pilaris (PRP), as

**Table 20.4** Psoriasis area severity index (PASI) calculation [4]

| **Severity of psoriatic lesions**<br>0 = none; 1 = slight; 2 = moderate; 3 = severe; 4 = very severe | | | | |
|---|---|---|---|---|
| **Body locations** | **Head** | **Trunk** | **Upper extremity** | **Lower extremity** |
| Erythema | 0–4 | 0–4 | 0–4 | 0–4 |
| Induration | 0–4 | 0–4 | 0–4 | 0–4 |
| Scaling | 0–4 | 0–4 | 0–4 | 0–4 |
| Totals | Head severity total | Trunk severity total | UE severity total | LE severity total |
| **Surface area (SA) of psoriatic involvement**<br>0 = none; 1 = 10 % or less; 2 = 10–29 %; 3 = 30–49 %; 4 = 50–69 %; 5 = 70–89 %; 6 = 90–100 % | | | | |
| Degree of involvement | 0–6 | 0–6 | 0–6 | 0–6 |
| Totals | Head SA total | Trunk SA total | UE SA total | LE SA total |
| Multiply severity total × SA total | Head combined total | Trunk combined total | UE combined total | LE combined total |
| **Correction factor** (based on area of involvement) | 0.10 | 0.30 | 0.20 | 0.40 |
| Multiply combined totals × correction factor | Head corrected total | Trunk corrected total | UE corrected total | LE corrected total |
| Add together Corrected Totals for each Body Location to obtain final PASI score | | | | |

Source: Van de Kerkhof and Schalkwijk [4]

well as lichen planus, dermatomyositis and lupus erythematosus; as well, pustular disease and nail changes can be mimicked by cutaneous infections. Like psoriasis, the distribution of dermatomyositis can include extensor surfaces especially elbows and knees. However, patients with dermatomyositis have skin changes that show poikiloderma, atrophy, a heliotrope sign, and nailfold changes (on dermoscopy or capillaroscopy), none of which are typically seen in psoriasis [4]. Lupus erythematosus, however, usually lacks involvement of extensor surfaces. Furthermore, psoriasis is generally improved by, not exacerbated by UV exposure [4]. The eruption of pityriasis rosea is typically located on the upper arms, trunk, and thighs with a duration of a few weeks. A herald patch is frequently noted, and lesions are typically oval and follow skin cleavage lines. Individual lesions only have a collarette of scale and have crinkling of the epidermis [4]. PRP with its small follicular papules, disseminated yellowish-pink scaling patches, and palmoplantar hyperkeratosis is distinguished from psoriasis by the scales, which in psoriasis are silvery, light and overlapping as well as by the papules with extend peripherally to form patches in PRP [4].

Only about 1–4 % of cases of lichen planus are seen in children. Lichen planus mainly affects the flexor surfaces of the wrists and ankles with puirple to violaceous, pruritic papules Nail changes in lichen planus include longitudinal ridging and pterygium formation. In addition, chronic plaque psoriasis may need to be distinguished from mycosis fungoides. As both can have scaling and fissures, palmoplantar plaque psoriasis mimics keratotic eczema of the palms and soles. Examination of the rest of the skin for evidence of psoriasis as well as margination of the lesions, which favors psoriasis, can provide clues to the diagnosis. Further, chronic lesions of dermatitis may look clinically and histologically similar to partially treated psoriasis. Histological examination via biopsy is usually the best method to differentiate these skin disorders from true psoriasis [4].

In the case of guttate psoriasis, the differential diagnosis includes small plaque parapsoriasis, pityriasis lichenoides chronica (PLC), and pityriasis rosea. Small plaque parapsoriasis typically occurs in the middle aged and elderly, but can occur in childhood. However, the lesions of guttate psoriasis do not typically affect the palms or soles and are often more erythematous than those of parapsoriasis. In PLC, the papules are erythematous to red–brown and scaly. There is no Auspitz sign when the scale is lifted off. The

**Table 20.5** Differential diagnosis of pediatric psoriasis

| **Differential diagnosis of psoriasis** | |
|---|---|
| **Differential of generalized psoriasis** | **Clues to diagnosis** |
| Lichen planus | Purple, polygonal, planar papules over the extensor surfaces |
| | Hypertrophic shin lesions in individuals of color |
| | Oral white erosive plaques |
| | Nail changes include longitudinal ridging and pterygium formation |
| Pitryiasis rubra pilaris | Small follicular papules, disseminated as well as notably over anterior shins |
| | Disseminated yellowish-pink to salmon scaling patches including scalp |
| | Palmoplantar hyperkeratosis |
| Dermatomyositis | Poikiloderma, atrophy, heliotrope sign, nailfold changes |
| | Prominent hyperpigmentation in patients of color |
| Cutaneous lupus erythematosus | Does not typically involve extensor surfaces |
| | Discoid lupus with follicular hyperkeratosis, including ear comedones and scarring |
| | SCLE usually more annular and in sun-exposed areas |
| | Photoexacerbation noted |
| | Nasal bridge and cheeks more commonly involved than forehead/ nuchal |
| | Malar rash/ photosensitivity associated with systemic disease |
| Pityriasis rosea | Herald patch may be present |
| | Disease comes up over 6 weeks and resolves over 6 weeks |
| | Typically oval lesions with a collarette of scale that follow skin cleavage lines of Langer |
| **Differential of scalp psoriasis** | |
| Seborrheic dermatitis | Greasy and yellowish scale |
| Tinea capitis | Positive potassium hydroxide stain and fungal culture (for dermatophyte) |
| | Broken-off stumps of hairs, often with pustules, alopecia and cervical lymph nodes |
| **Differential of guttate psoriasis** | |
| Small plaque parapsoriasis | Variably erythematous (but often less intense than psoriasis) |
| | Covered with a fine scale |
| Pityriasis lichenoides chronica | Red–brown and finely scaly papules |
| | Indolent course and recurrent crops |
| Pityriasis rosea | See above |
| **Differential of inverse psoriasis** | |
| Tinea | Annular appearance with central clearing |
| | Positive potassium hydroxide prep and fungal culture |
| Candidiasis | Beefy red macerated plaques |
| | Satellite pustules |
| Erythrasma | Coral red fluorescence on Wood's lamp evaluation |
| Contact dermatitis | Usually follows the pattern of contactant exposure |
| | Generally spares inguinal folds |
| Langerhans cell histiocytosis | Typically also have scalp scaling and crust |
| | Adenopathy may accompany lesions |
| **Differential of palmoplantar psoriasis** | |
| Atopic dermatitis | Intensely pruritic vesicles and/or bullae |
| | May have other classic areas of involvement (flexural surfaces) |
| Juvenile plantar dermatosis | balls of feet toe pads, and hands symmetrically tender and reddened, dry with shiny appearance, may have scale and painful cracks and fissures |
| Palmoplantar keratoderma | Hereditary vs Acquired thick, yellow hyperkeratosis, involves the lateral aspects of the hands and feet transgredient vs non-trasgredient |
| Reiter's syndrome | Urethritis, arthritis, ocular findings, and oral ulcers in addition to psoriasis form skin lesions |
| | Lesions on the plantar surface with thick yellow scale and often pustular (keratoderma blennorrhagicum) |

lesions of PLC come up in successive crops every 6–8 weeks and regress over weeks to months, often with postinflammatory hypopigmentation in individuals of color. Tinea corporis is also on the differential of guttate psoriasis, when the lesions are more limited number or are annular.

Psoriasis of the flexures (inverse psoriasis) is one cause of intertrigo. Other etiologies include tinea corporis, cutaneous candidiasis, erythrasma, and contact dermatitis. Candidiasis will usually present with a beefy red color and satellite pustules. Contact dermatitis (usually irritant in infants) typically spares the inguinal folds, unlike psoriasis. Erythrasma can be differentiated by using a Wood's lamp, demonstrating coral red fluorescence. Tinea corporis typically shows an annular border. In infants especially, the possibility of Langerhans cell histiocytosis needs to be considered. In these patients, there may also be scalp involvement with scaling and crust, lymph node enlargement and internal organ involvement.

On the scalp, tinea capitis, and seborrheic dermatitis often mimic psoriasis. Distinguishing feature of tinea capitis are broken-off stumps of hairs, often in patches in which there are crusts and pustule. When examined, the broken-off hairs are loose and found to be surrounded by or contain the fungus. Seborrheic dermatitis often co-exists with psoriasis, although it's uncommon past infancy and prior to puberty. Although typically the scales in psoriasis are dry, shiny and white, versus those of seborrheic dermatitis which are greasy and yellowish, distinguishing the two requires fungal culture.

## Biopsy and Histology

Psoriatic lesions contain characteristic histologic features when biopsied that can help differentiate psoriasis from other skin diseases if the clinical picture is unclear. A mixed inflammatory perivascular infiltrate is commonly seen in the dermis. The epidermis appears acanthotic with focal areas of spongiosis containing inflammatory cells. There is thinning of the suprapapillary plate, and the stratum granulosum may be absent. Parakeratosis, the persistence of nucleated keratinocytes in the stratum corneum, is common.

There are two possible pathognomonic findings in psoriasis histology. The first is the spongiform pustule of Kogoj, characterized by a spongiotic pustule filled with neutrophils in the stratum spinosum. The second is the microabscess of Munro, characterized by the presence of neutrophils in the stratum corneum. As the lesion progresses, the rete ridges elongate and become blunted, and the hyperproliferation of the epidermal keratinocytes becomes more apparent histologically. In pustular psoriasis, there are more marked accumulations of neutrophils in the epidermis, similar to the spongiform pustules of Kogoj and microabscesses of Munro [4].

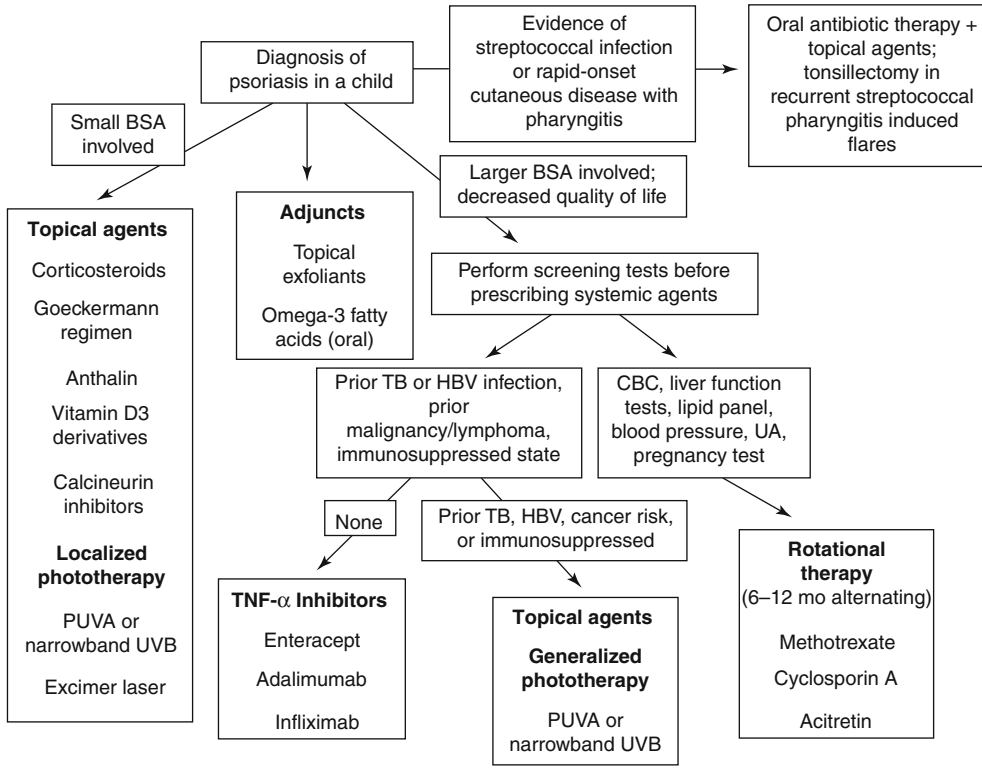
## Therapeutic Management (Table 20.2 and Fig. 20.6) [61]

### Topical Therapies

Topical therapies are the initial treatment of choice for pediatric patients with limited psoriasis of the skin (i.e. in the absence of joint disease). In general, thicker vehicles, such as ointments, are more effective, but the location of [61] involvement and patient preference will ultimately affect the decision of which vehicle will be used. Thinner preparations are commonly used on the scalp and face while thicker ones are used on the extremities [62].

Keratolytics, such as urea, salicylic acid, and α-hydroxy acids, are the most simplified of the topical therapies. The mechanism of action of these agents is through removal of the characteristic superficial hyperkeratosis of psoriatic lesions, allowing for better penetration of other topical therapies [62, 63]. Salicylic acid application can lead to percutaneous salicylism in infants and is therefore avoided in this age group [62].

One of the earliest topical therapies developed, and still in use today in some areas of the world, is the Goeckermann regimen. It involves topical application of coal tar, or a modified version with addition of a cream called liquor carbons detergents, followed by exposure to UV light. It is




BSA = body surface area, TB = tuberculosis, HBV = hepatitis B virus,
CBC = complete blood count, UA = urinalysis, TNF-α = tumor necrosis factor alpha
PUVA = psoralen plus UVA

**Fig. 20.6** Schema of psoriasis therapy in childhood, based on Silverberg [63]

proven to be effective in children, with 85 % achieving >80 % clearance in psoriatic skin lesions [64]. The mechanism of action remains unclear, but antimitotic effects, inhibition of DNA synthesis, and enzyme inactivation may play a role [62]. Despite its effectiveness, the Goeckermann treatment has fallen out of favor in industrialized nations due to concern over its long term consequences. The coal tar contains polycyclic hydrocarbons and, when exposed to UV irradiation, this combination has been shown to cause increased chromosomal abnormalities in peripheral lymphocytes and an elevated Heat Shock protein (specifically Hsp70) response in children [65]. However, there is no concrete evidence demonstrating that treatment with coal tar or its derivatives leads to an increase in skin cancer risk as compared to the general population [62] A milder variation on this theme is to use dilute tar bath additives the night before narrowband UVB therapy (1–2 caps tar added to tub and soak 10–15 min).

Unfortunately, there are no Food and Drug Administration (FDA) (United States) topical therapies specifically approved for the treatment of psoriasis in children under 12 years of age, but there have been several studies demonstrating efficacy of off-label agents, including topical corticosteroids, vitamin $D_2$ and $D_3$ derivatives, and immunosuppressants (e.g. calcineurin inhibitors) [66–68]. The strength and formulation of therapies should be based on the patient's age, PASI score, and impact on quality of life. A recent systematic review of 64 studies from The Netherlands proposed an algorithm of beginning with topical synthetic vitamin $D_3$ derivatives with or without topical corticosteroids, followed by anthralin cream [66]. However, in the United States, topical corticosteroids are usually the initial treatment of choice [62].

Topical corticosteroids are frequently employed by practitioners for the treatment of pediatric psoriasis. The choice of which topical steroids to use depends upon the skin areas involved, and parallels the treatment algorithms for atopic dermatitis in children. Low potency steroids (classes 5–7) are used for more sensitive areas such as the head, neck, and intertriginous regions. Moderate potency (classes 2–4) steroids are generally used on the scalp and extremities. Higher potency (class 1) steroids are reserved for persistent, thickened lesions that do not respond to lower potency steroids [62, 63]. Two class 1 corticosteroids, clobetasol and halobetasol, have been studied and found to be effective in children. Clobetasol (in some specific preparations) is approved for children >12 years of age for 2 weeks or less, while halobetasol is not currently FDA-approved for use in children. Treatment duration with class 1 steroids is often limited to 2 weeks in children, as these agents have an extensive side effect profile with long-term use, including skin atrophy, striae, and potential hypothalamic-pituitary-adrenal (HPA) axis dysfunction [66, 67, 69]. All topical corticosteroids if used prolongedly and especially over large surface areas, including classes 2–7, are theoretically associated with these adverse effects as well. The risk of systemic absorption and HPA dysfunction increases with the body surface area to which the steroid is applied increases. This is of particular concern in children, as they have usually not yet reached their growth potential [63]. The incidence of adverse events can be decreased by rotating the use of topical corticosteroids with other topical treatments listed below [62].

Anthralin 1 % cream, or dithranol, is a topical therapy that can be used for localized areas of psoriasis. It is an anti-proliferative and immunosuppressive agent which inhibits T-lymphocytes through an unclear mechanism of action. Adverse effects are minimal due to limited systemic absorption and include irritation and staining of clothing or hair [62, 66]. Short contact therapy for several minutes a day minimizes staining and irritation of the skin [62].

Vitamin $D_3$ derivatives, such as calcipotriol/calcipotriene or calcitriol, have also been proven to be effective in children with psoriasis. Side effects include local reactions such as erythema, irritation and pruritis. There is also a theoretical risk of systemic absorption leading to elevated serum calcium levels, especially when applied to a large body surface area [66, 70]. Doses of calcipotriene up to 45 g/m$^2$/week have been shown to have no significant effect on calcium homeostasis in children [62]. A head-to-head comparison of calcipotriol and anthralin showed similar efficacy in psoriatic children [71].

Tazarotene, a topical retinoid, is also effective for limited psoriatic skin disease and nail psoriasis [62]. Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, have also been shown to promote the clearance of psoriatic lesions in children [66, 72]. These agents are immunosuppressants that inhibit cytokine production (IL-2 in particular) by T lymphocytes and thus limit their proliferation. Tacrolimus (0.03 % for children ages 2–15 years and 0.1 % ointment for ages 16 years and over) and pimecrolimus 1 % cream are approved for the treatment of atopic dermatitis in children >2 years of age, but its use is off-label for psoriasis [62, 72]. The advantage of these agents is the lack of potential skin atrophy, allowing their use in more sensitive areas such as the face, neck, and intertriginous areas [62, 72]. Side effects most frequently noted include local irritation and pruritis [66]. This class of topical medication also carries a black box warning in the US due to a theoretical increased risk of skin cancer and lymphoma. Sun protection is therefore advisable concurrent with calcineurin inhibitor products [73].

## **Systemic Therapies** (Table 20.2 and Fig. 20.6)

Systemic therapies for the treatment of pediatric psoriasis are usually reserved for those patients who have failed topical treatments, have extensive body surface area involvement, have significant impairment in quality of life and/or psychological health, or have concomitant psoriatic arthritis. Like all systemic medications, the agents available for use in pediatric psoriasis

have side effects. For this reason, many physicians employ a cyclic approach for systemic therapy, alternating between different available treatments every 6–12 months to minimize long-term adverse events. Systemic therapies include oral antibiotics, methotrexate, cyclosporine A, retinoids, and TNF-α inhibitors.

Oral antibiotics are considered the safest of the systemic agents due to their superior side effect profile. Benefits with oral antibiotics are most impactful in the setting of severe, rapid-onset cutaneous disease following streptococcal pharyngitis or perianal streptococcal disease, and in pustular and guttate psoriasis [74–76]. A recent controlled trial of 50 patients (ages 13–63 years) found that a 48-week course of azithromycin therapy (4 days of azithromycin 500 mg tab once-daily, followed by 10 days off therapy, with repeat of the cycle every 2 weeks) resulted in a PASI 75 of 80 % at 48 weeks in the treatment group as compared to no significant difference in the control group. Only 12 patients had a positive ASLO test for streptococcal infection [77]. Despite this and other studies demonstrating an association between streptococcal infection and the onset of psoriasis, it remains unclear whether antibiotic therapy improves PASI scores or disease clearance in children or adults. Therefore, the use of systemic antibiotics for the treatment of pediatric psoriasis remains controversial [66, 75, 78]. Tonsillectomy has been recommended by some as a treatment for recurrent guttate psoriasis [76], but this has also not been proven to be effective in an evidence-based manner [66, 78].

Methotrexate was the original therapy available for extensive psoriasis. It is generally safe in children and is a well-established treatment for moderate to severe psoriatic disease. Methotrexate is also the drug of choice for patients with psoriatic arthritis in addition to skin disease [79]. Methotrexate is associated with a >75 % improvement in PASI score [80]. Dosages used range from 0.2 to 0.7 mg/kg per week [79–81]. The most common side effect in children is nausea and vomiting. Although routine monitoring of blood counts and liver function tests are recommended, bone marrow suppression, such as microcytic anemia and pancytopenia, and liver toxicity are rare adverse drug events.

Liver toxicity appears to be relatively rare in children, although obesity and associated fatty liver changes are associated with an increased risk of this adverse reaction [66, 79, 81]. Concomitant folic acid supplementation (1 mg/day) is protective against bone marrow suppression and liver enzyme abnormalities [82].

Cyclosporine, another immunosuppressant which inhibits cytokine signaling by lymphocytes, may be effective for psoriatic skin disease in children. In doses ranging from 2 to 4 mg/kg/day, cyclosporine can improve the overall severity and appearance of skin lesions, but studies investigating its effectiveness in children are limited [66, 83]. In addition, its use is hindered by the side effects of nephrotoxicity, secondary hypertension, and immunosuppression as well as the requirement for close monitoring of blood pressure and renal functioning (Table 20.2) Cyclosporine is of particular benefit for the therapy of pustular psoriasis (Poster SPD). Reports of an increased cancer risk secondary to immunosuppression have also been reported, but the low doses, short courses and rotational therapies used in treatment of skin-limited psoriasis decrease these risks [79].

Retinoids, such as acitretin or etretinate, are other treatment options for children with psoriasis, although they are not as extensively studied or as safe as methotrexate [66]. Adverse effects include teratogenicity, elevation of liver enzymes, impaired lipid profile, alterations in blood counts, and bony abnormalities. Due to the ability of retinoids to cause severe birth defects, oral contraceptives are recommended for 1 month before initiating therapy and for 3 years after the cessation of therapy in girls of child bearing age. Close monitoring of liver function tests and lipid profiles during therapy are necessary as well. High-dose systemic retinoids used for greater than 2.5 years have been associated with premature epiphyseal closure in children. Hyperostosis and osteoporosis are other potential bony side effects [84]. However, cyclic short-term therapy for 6–12 months, as indicated in rotational therapy, decreases the risk for bony abnormalities. Longer

courses of treatment in children require periodic skeletal surveys [79].

TNF-α inhibitors, such as etanercept, adalimumab, and infliximab, can and has been used to treat pediatric psoriasis, but are not FDA approved for this purpose. TNF-α inhibitors have been used to treat rheumatoid arthritis, tumor necrosis factor 1-associated fever, juvenile idiopathic arthritis, ulcerative colitis and Crohn's disease in children for more than a decade [63]. The most extensive studies of the safety of TNF-α inhibitors in children come from research investigating their use in juvenile rheumatoid arthritis, with up to 8 years of published data on this subject. Side effects include reactivation of latent tuberculosis or hepatitis infections as well as increased risks for malignancies including lymphoma, opportunistic infections, and demyelinating disease. The FDA has recently placed a black-box warning on enbrel for pediatric psoriasis stating "Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including Enbrel."

In one study following pediatric patients with juvenile rheumatoid arthritis treated with etanercept, no cases of tuberculosis, opportunistic infections, malignancies, lymphomas, lupus, demyelinating disorders, or deaths were reported after 8 years [85]. The most commonly reported side effects with etanercept specifically are injection site irritation and non-opportunistic infection [66]. Interestingly, there are rare reports of TNF-α inhibitors triggering outbreaks of psoriasis in children and adults being treated for other autoimmune disease processes [86, 87]. Etanercept, which is the most extensively studied of the TNF-α inhibitors in children, has recently been approved for use in children 6 years and older with ulcerative colitis and Crohn's disease, but is approved to treat psoriatic arthritis and plaque psoriasis in adults only [88]. Etanercept at doses of 0.8 mg/kg weekly has been shown to achieve PASI 90 in 27 % and PASI 75 in 57 % of treated patients as compared to 11 and 7 % of placebo-treated patients after 12 weeks of treatment respectively [89]. This benefit appears to be maintained in the majority of patients after 96 weeks [90]. Etanercept has also been shown to improve overall and disease-specific quality of life in children with moderate to severe plaque-type psoriasis [91]. It has also been shown to improve depression in adults, irrespective of disease clearance. This suggests that the inflammatory response itself, rather than the psychological effects of an undesirable physical appearance, may contribute to depressed mood in psoriatic patients [92, 93]. Other TNF-α inhibitors have not been extensively studied in children with psoriasis [66].

## Phototherapy

UV light therapy is used to treat a variety of skin diseases in children, including atopic dermatitis, vitiligo, acne vulgaris and psoriasis [94]. Phototherapy is available in the form of broadband UVB, narrowband UVB or UVA in combination with psoralen (PUVA). Narrowband UVB (NB UVB) and PUVA therapy have shown the most success in treating children with psoriasis [62, 63, 94]. However, NBUVB (311 nm) is the treatment of choice, as PUVA therapy has been associated with an increased risk of carcinogenesis in adult patients with psoriasis [94]. NB UVB is also highly effective, with a response rate approaching 80 % in pediatric patients [95]. If PUVA therapy is used, topical psoralen is preferred, due to the necessity for 24 h of protective eyewear following treatment with oral psoralen. For this reason and the increased risk of other systemic adverse reactions, oral psoralen should be avoided children less than 12 years of age.

Common adverse events of phototherapy include local irritation and erythema. There is also the possibility of reactivation of a latent herpesvirus infection, photoaging, and the long-term risk of carcinogenesis [66, 94–97]. Phototherapy maybe administered in the form of a handheld laser, phototherapy booth, or hand/foot units. If a phototherapy booth is employed, the child must be old enough to remain still for the length of each therapeutic session [63]. Due to compliance issues in younger children, phototherapy is often more useful in adolescents [63, 94]. Therapy is required once or twice per week for a 1–3 months

before psoriatic lesions clear and a maintenance phase can be reached [63].

Excimer laser, a narrowband UVB 308 nm laser light source has been described to be effective for the therapy of localized psoriasis. Scalp, palms and soles and areas on the face and body can be treated. Some data on usage in childhood shows benefit for children with localized psoriasis, and children may experience superior benefit with excimer usage. Therapy has some ultraviolet light induced side effects, but is generally well tolerated [98].

## Natural Supplements

Various natural supplements have been investigated in the treatment of pediatric psoriasis and this is a common topic of inquiry among parents. No natural remedies have found to be curative, but a few may help alter the disease progress. Omega-3 fatty acids, such as those found in salmon and other fatty fish, may lead to slight improvements in PASI score. As previously mentioned, this finding is supported by the observation that Inuit populations, which consume diets high in omega-3 fatty acids, have a low incidence of psoriasis. The benefits of omega-3 fatty acid supplementation are superior to omega-6 fatty acid supplementation. The mechanism of action appears to be alterations in the level of eicosapentanoic acid and arachidonic acid, leading to decreased production of pro-inflammatory metabolites [25]. The benefits of omega-3 fatty acids are minimal or possibly non-existent, but this supplement appears to be essentially harmless, and thus safe for use in children. There may be a more important role for dietary changes in pediatric patients with metabolic syndrome and psoriasis, due to the recent association between these two disease entities. Diets low in fat and high in fiber have been found to beneficial in treating metabolic syndrome in children, and along with exercise, can even cure patients of this condition with lasting benefits into adulthood [99, 100].

Indigo naturalis, a traditional Chinese medicine, has been reported to aid in clearance of pediatric psoriatic lesions after 8 weeks of topical application in one anecdotal study [101]. Other traditional Chinese medicines and natural supplements may ultimately cause more harm than benefit and it is important for dermatologists to be aware of the potential side effects of these therapies [102].

### Conclusions

Psoriasis of childhood is a common and complex disorder that can occur from birth up through adolescence. Consideration for the child's emotional well-being and general health, including risk factors for the metabolic syndrome and possible side effects of therapy, have to be given when choosing therapy for this disease. Recent advances in phototherapy and biologic therapy have expanded the armamentarium of this disease. Greater research is needed to assess the benefits of therapy on long-term disease manifestations and the risks of lymphoma and other potential side effects of therapy.

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# Psoriasis and Comorbidities

# 21

Philip M. Laws, Helen S. Young,
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**Abstract**

Emerging evidence demonstrates that patients with psoriasis are more likely to suffer from hypertension, dyslipidaemia, obesity, diabetes, cardiovascular disease, stroke and atrial fibrillation. The relationship between psoriasis and these diseases is complicated by multiple confounder variables including diet, exercise, alcohol and smoking which differ between the general population and patients with psoriasis. Psoriasis is a disease of chronic systemic inflammation and it is increasingly clear that inflammation plays a pivotal role in the pathogenesis of cardiovascular disease, hypertension, diabetes and obesity. This provides a mechanism by which psoriasis may confer an additional risk of these comorbidities.

Patients with psoriasis are also at an increased risk of experiencing psychiatric illness (particularly depression) and malignancy. The nature of this relationship remains to be determined. Genome wide association studies have identified that patients with psoriasis have an increased risk of developing diseases associated with immune dysfunction (e.g. ulcerative colitis) and autoimmune disease (e.g. type 1 diabetes).

Recognition of comorbid disease is of great importance as this may affect treatment choice, treatment efficacy, morbidity and mortality.

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## Introduction

Historically psoriasis was considered a disease exclusively of the skin with little consideration of systemic sequalae. The identification of psoriatic arthritis as a distinct condition from rheumatoid arthritis and its association with cutaneous psoriasis heralded a new appreciation of psoriasis as more than "skin deep". More recently recognition of other complicating factors and disease associations has raised the profile of psoriasis as a systemic inflammatory disease with the need to manage patients holistically.

This chapter will cover the comorbidities (including cardiovascular disease [CVD], metabolic syndrome and malignancy) associated with psoriasis and consider how these factors may influence or impact on management of the patient. The reader is referred to Chap. 4 for a review of psoriatic arthritis.

Current evidence for psoriasis and associated comorbid diseases are subject to numerous limitations including:

1. Diagnostic criteria – Many studies involving large-scale databases utilise either diagnostic code or use of therapies specific to the relevant condition. Additionally, diagnostic criteria may differ by geographical location or clinical environment. This is particularly true for conditions such as dyslipidaemia where standardised criteria are not universally established.
2. Study cohort – may involve hospital (inpatient or out-patient), community or mixed groups. This can result in selection bias. Additionally exposure to health professionals increases for patients attending specialist clinics and may affect the detection rate of comorbid disease.
3. Confounders – psoriasis is associated with increased prevalence of adverse lifestyle behaviours which may also be associated with comorbid conditions.

## Obesity

Obesity, defined by a body mass index (BMI) of $\geq$30 kg/m$^2$, is a growing public health concern globally. It is associated with an increased risk of multiple comorbid conditions including hypertension, dyslipidaemia, Type II diabetes mellitus, coronary heart disease, stroke, osteoarthritis, sleep apnoea and certain cancers (endometrial, breast, ovarian and colon) [1–3].

The association between body weight and psoriasis was first suggested in 1986 in an observational study of 159,200 Swedish patients with psoriasis [4]. This was later supported by Henseler and Christophers who observed an association between psoriasis and obesity with an observed/expected ratio for obesity of 2.05 ($p<0.05$) [5]. More recently a study using the UK General Practice Research Database (GPRD), a primary-care records database established for large-scale epidemiological studies, examined a cohort of 127,706 patients with mild psoriasis and 3,854 patients with severe psoriasis and demonstrated a significantly increased obesity prevalence of 15.8 and 20.7 % respectively compared with 13.2 % in the control group [6]. For patients with severe psoriasis this equates to an odds ratio of 1.79 (95 % CI, 1.55–2.05) when compared with the control group [6]. These findings are supported by several other studies across a range of cultural and ethnic groups (Table 21.1) [8–11, 13, 14].

Recent large-scale clinical trials investigating the efficacy of biologic agents in the treatment of psoriasis emphasise the prevalence and impact of obesity in psoriasis management. A study of 2,897 patients with moderate to severe psoriasis (PASI $\geq$12) involved in the PHOENIX 1, PHOENIX 2 and ACCEPT studies demonstrated that 80.4 % of patients were overweight (BMI $\geq$25 kg/m$^2$) and 47.9 % were obese (BMI $\geq$30 kg/m$^2$) [15].

**Table 21.1** Table summarising large scale studies (n > 1,000) reporting risk of psoriasis and obesity

| Reference | Country | Cohort | Number patients | Number controls | Prevalence in cohort % (n) | Prevalence in controls % (n) | OR/PR (95 % CI) | Incidence/ prevalence |
|---|---|---|---|---|---|---|---|---|
| Henseler and Christophers [5] | Germany | DO | 2,941 | NA | 113 | NA | OE 2.05 | P |
| Neimann et al. [6] | UK | G | M 127,706 | 465,252 | 15.8 (13,404) | 13.1 (36,117) | 1.27 (1.14–1.42) | P |
| | | | S 3,854 | 14,065 | 20.7 (545) | 13.0 (1,093) | 1.79 (1.55–2.05) | |
| Cohen et al. [7] | Israel | G | 16,851 | 48,681 | 24.5 (3,060) | 15.6 (3,790) | 1.7 (1.5–1.9) | P |
| Kaye et al. [8] | UK | G | 44,164 | 219,784 | 6.3 (2,760) | 5.5 (11,996) | 1.18 (1.14–1.23) | I |
| Shapiro et al. [9] | Israel | DI | 1,079 | 1,079 | 13.3 (143) | 8.7 (94) | 1.32 (0.99–1.75) | P |
| Augustin et al. [10] | Germany | G | 33,981 | 1,310,090 | 17.8 | 10.4 | 1.72 (1.68–1.76) | P |
| Huerta et al. [11] | UK | G | 3,994 | 10,000 | 11.3 (452) | 8.8 (883) | 1.33 (1.16–1.52) | P |
| Langan et al. [12] | UK | G | 4,065 | 40,650 | 23.5 (887)[a] | 20.5 (7,678)[a] | 1.52 (1.37–1.68)[a] | P |
| | | | | | 17.5 (662)[b] | 13.1 (4,907)[b] | 1.78 (1.59–1.98)[b] | |

*M* mild psoriasis, *S* severe psoriasis, *G* general population, *DI* dermatology inpatient, *DO* dermatology outpatient, *CI* confidence interval, *HR* hazard ratio, *OR* odds ratio, *OE* observed/expected ration

[a]BMI 30–35

[b]BMI >35

Whilst the evidence linking psoriasis and obesity is compelling the relationship is complex. Herron et al. provided evidence that obesity is almost twice as common in psoriasis patients as in the general population (34 % compared with 18 %) [14]. Based on a questionnaire of patient perception of body weight and date of psoriasis disease onset it was concluded that psoriasis predisposed an individual to developing obesity, and that obesity was not a risk factor for onset of psoriasis.

In contrast the Nurses' Health Study II provided evidence that obesity increases the relative risk of incident psoriasis [16]. In an observational study involving 78,626 nurses followed up over 14 years the relative risk of developing psoriasis was 1.40, 1.48 and 2.69 for BMI of 25.0–29.9 kg/m$^2$, 30.0–34.9 kg/m$^2$ and ≥35 kg/m$^2$ respectively [16]. Additionally, this study suggested that the greatest risk of psoriasis was in those individuals who gained weight after the age of 18 years [16]. In support of this data an Italian cohort of 560 patients demonstrated the odds ratio for psoriasis was 1.6 and 1.9 for overweight (BMI 26–29 kg/m$^2$) and obese (BMI ≥30 kg/m$^2$) patients respectively [17]. The authors calculated the population attributable risk of psoriasis related to elevated BMI was 16 % [17].

The pathogenesis of psoriasis and obesity have some features in common and this may provide a mechanism for co-association of the two conditions. It is well established that psoriasis is a chronic, inflammatory disease of the skin which is mediated through immune cells including Th1, Th17 and Th22 lymphocytes; activated following interaction with antigen presenting cells including keratinocytes [18]. Proinflammatory cytokines (interferon-γ (gamma) (IFNγ (gamma)), tumour necrosis factor-alpha (TNFα (alpha)), interleukin(IL)-17 and IL-22) are up regulated in concert with this expansion of lymphocytes. This proinflammatory state results in elevated systemic inflammatory markers and is reversible with the treatment of skin disease [19, 20]. Obesity is a disease of chronic, low grade inflammation associated with elevated levels of C reactive protein (CRP), TNFα (alpha), IL-6 and other cytokines [21]. Weight loss is associated with reduced, or normal, levels of these proinflammatory cytokines [22]. It is also interesting to note that psoriasis has been reported to improve with weight loss strategies, including surgical interventions [23, 24].

Leptin is an adipokine directly related to the volume of adipose tissue. In addition to control of appetite leptin has immunomodulatory activity [18], influencing the development of a Th1 or Th2 inflammatory profile. Leptin activates macrophage and potentiates proinflammatory cytokines. The role of leptin and other adipokines (adiponectin, resistin, visfatin) in relation to psoriasis has been the focus of a recent review [25]. The relationship between psoriasis and adipokines, including leptin, remains to be fully elucidated but may prove important in understanding the relationship between metabolic dysfunction and psoriasis [18].

Treatment of psoriasis remains a significant challenge and is adversely affected by obesity. Standard systemic therapies are less effective in overweight patients and more frequently complicated by side effects (Table 21.2) [30].

Treatment of psoriasis with biologic therapies can be complicated by increased body weight and obesity [15]. Interestingly body weight, rather than BMI, has been noted to be most influential in determining clinical response to treatment in some biologic agents [31–33]. This is particularly true of fixed dose biologic therapies. Response rates with adalimumab decrease across weight quartiles such that in a cohort of 1,212 patients after 16 weeks weight groups 40–78 kg, 78–90 kg, 90–105 kg, and 105–204 kg achieve PASI 75 in 75, 80, 67 and 62 % respectively in comparison to 2.3–13.3 % in the placebo arm [34]. Treatment with etanercept is also markedly less effective in patients with increased body weight. In a cohort of 1,187 patients PASI 75 was achieved in 41 and 25 % for patients weighing <89 kg and ≥89 kg respectively for the 50 mg weekly arm of the study and 55 and 43 % for patients weighing <89 kg or ≥89 kg respectively in the 50 mg twice-weekly regimen [35]. Treatment with ustekinumab appeared to be adversely affected by body weight. Within the PHOENIX 2 cohort (n = 1,230) patients who

**Table 21.2** Table describing relative contraindications and risk of side effects of psoriasis treatments with respect to comorbid conditions observed in association with psoriasis

| | Diabetes | Dyslipidaemia | Obesity | Hypertension | NAFLD | CCF | IHD | Multiple sclerosis | Malignancy |
|---|---|---|---|---|---|---|---|---|---|
| Methotrexate | | | + Increased risk of hepatotoxicity | | + | | ?–[a] | | ?+ |
| Cyclosporine | + | ++ | + Increased risk of nephrotoxicity | ++ | | | | | ++ |
| Retinoids | | ++ | + Increased risk of dyslipidaemia | | + May cause elevation of liver function tests | | | | ?–[b] |
| Fumaric acid esters | | | | | + May cause elevation of liver function tests | | | | ?+ |
| Etanercept | | | + Decreased efficacy and may induce weight gain | | + May cause elevation of liver function tests | + Avoid in NYHA class II and IV | ?–[a] | ++ | + |
| Adalimumab | | | + Decreased efficacy and may induce weight gain | | | | ?–[a] | | |
| Infliximab | | | + May induce weight gain | | | | ?–[a] | | |
| IL-12/23 inhibitors | | | + Decreased efficacy and may induce weight gain | | | ?+ | | | + |

*NAFLD* non-alcoholic fatty liver disease, *CCF* congestive cardiac failure, *NYHA* New York Heart Association, *IHD* ischaemic heart disease
+ mild-moderate contraindication/side effect, ++ moderate-strong contraindication/side effect
[a]Evidence from limited studies suggest a reduced risk of CVD following effective treatment with methotrexate and TNFα inhibitors [26–28]
[b]Acitretin has been demonstrated effective in reducing progression of actinic keratosis to squamous cell carcinomas in small studies [29]

were partial responders (PASI 50–75) were on average 7.4 kg heavier than primary responders (PASI 75) [36]. This has been supported by review of clinical experience of ustekinumab [37, 38]. Response is more consistent for infliximab which is dosed according to body weight.

In summary, obesity and psoriasis are significantly related and share several pathogenic features. Given this relationship, and the reduced efficacy of treating psoriasis in obese individuals, weight loss strategies are clearly of great importance in managing these patients.

## Dyslipidaemia

The relationship between psoriasis and dyslipidaemia has been the focus of several recent studies (Table 21.3) [6, 8, 10, 12, 39–42, 44, 45]. These studies have suggested a potential link with elevated triglycerides (TG), low density lipoprotein (LDL), very low density lipoprotein (VLDL), and reduced high density lipoprotein (HDL). The relationship between psoriasis and lipid abnormalities is complicated by other features of the metabolic syndrome (see section "Metabolic Syndrome") which are themselves associated with psoriasis in addition to the absence of a clear definition of dyslipidaemia.

A recent systematic review of epidemiological studies found a trend towards dyslipidaemia in psoriatic patients in 7 of 12 studies with an odds ratio (OR) of 1.0 (95 % CI 1.0–1.3) to 2.09 (95 % CI 1.23–3.54) [46]. A study using the UK GPRD demonstrated a statistically significant increased prevalence of hypertriglyceridaemia and low HDL cholesterol in a pooled cohort of 4,065 psoriasis patients in which 35.7 and 24.7 % fulfilled criteria for hypertriglyceridaemia and low HDL cholesterol respectively compared to 27.5 and 20.1 % in the control group [12].

Mallbris et al. report that lipid abnormalities may be observed at the onset of disease [47]. This included elevation of apolipoprotein A-1 and cholesterol: triglyceride ratios. In a cohort of 200 patients with incident psoriasis (≤12 months duration) and 285 controls a modest elevation of VLDL cholesterol: triglyceride ratio, HDL-cholesterol concentration and HDL cholesterol: triglyceride ratio was identified in the psoriasis cohort [47].

Despite the diverse data sets and challenges of interpreting data associated with a variable definition of dyslipidaemia the evidence of an association with psoriasis is compelling [48]. The causality of this relationship is less clear and remains to be elucidated; complicated in part by other features of metabolic syndrome.

## Hypertension

Hypertension is associated with an increased risk of cardiovascular (CV) morbidity and mortality. The association between psoriasis and hypertension is complex and incompletely understood. Several large data sets, across a range of ethnic groups, have explored the relationship between psoriasis and hypertension (Table 21.4). Whilst the majority of studies indicate a small increased relative risk of hypertension this is not universal. Confounder variables undoubtedly account for some of this relationship including adverse lifestyle choices (smoking, alcohol), comorbidity, and medications (see Table 21.2). The role of inflammation has been implicated in several previous studies in psoriatic patients [7, 51]. Elevated serum concentrations of renin, known to increase blood pressure, have been reported in patients with psoriasis [52, 53]. Additionally serum levels of endothelin-1, a potent vasoconstrictor, appear to be elevated in patients with psoriasis [54].

In summary evidence of a link between psoriasis and hypertension requires further investigation. Based on published research to date psoriasis does appear to confer an increased risk of hypertension. The need for regular monitoring of blood pressure may be beneficial in earlier detection of hypertension and cardiovascular disease in patients with psoriasis.

## Non-alcoholic Fatty Liver Disease (NAFLD)

Whilst patients with psoriasis may be at increased risk of liver disease as a complication of alcohol intake and anti-psoriatic therapies, such as

**Table 21.3** Table summarising large-scale studies (n>1,000) reporting associated risk of psoriasis and dyslipidaemia

| Reference | Country | Cohort | Number patients | Number controls | Prevalence in cohort % (n) | Prevalence in controls % (n) | OR/RR | Incidence/ prevalence |
|---|---|---|---|---|---|---|---|---|
| Dreiher et al. [39] | Isr | G | 10,669 | 22,996 | 56.9 (6,074) | 47.3 (10,882) | 1.19 (1.40–1.55) | P |
| Neimann et al. [6] | UK | G | M127,706 | 465,252 | 4.72 (6,024) | 3.29 (15,297) | 1.16 (1.12–1.21) | P |
| | | | S3,854 | 14,065 | 6.02 (232) | 3.56 (501) | 1.04 (0.84–1.28) | |
| Kaye et al. [8] | UK | G | 44,164 | 219,784 | 4.3 (1,900) | 3.7 (8,111) | 1.17 (1.11–1.23) | I |
| Langan et al. [12] | UK | G | 4,065 | 40,650 | 35.7 (1,453)[a] | 27.5 (11,181)[a] | 1.49 (1.39–1.60)[a] | P |
| | | | | | 24.7 (1,007)[b] | 20.1 (8,180)[b] | 1.32 (1.22–1.43)[b] | |
| Tsai et al. [40] | Tai | G | 51,800 | 997,771 | 7.7 (3,968) | 5.4 (11,111) | 1.61 (1.54–1.68) | P |
| Yang et al. [41] | Tai | G | 1,685 | 5,055 | 18.5 312 | 15.1 762 | 1.28 (1.10–1.48) | P |
| Augustin et al. [10] | Ger | G | 33,981 | 1,310,090 | 29.9 | 17.05 | 1.75 (1.72–1.78) | P |
| Wu et al. [42] | USA | G | 1,127 | 1,127 | – | – | 1.35 (1.11–1.63) | P |
| Kimball et al. [43] | USA | G | 20,614 | 82,456 | 31.2 (6,432) | 31.6 (8,065) | 1.26 (1.22–1.30) | P |
| | | | 25,556 | 101,507 | 27.8 (22,941) | 26.8 (27,239) | 1.18 (1.14–1.22) | |
| Gelfand et al. [44] | UK | G | M 127,139 | 556,995 | 4.58 (5,822) | 3.33 (18,534) | 3.08 (2.93–3.23) | P |
| | | | S 3,837 | | 5.92 (227) | | 3.18 (3.02–3.36) | |

*Isr* Israel, *Ger* Germany, *Tai* Taiwan, *M* mild psoriasis, *S* severe psoriasis, *G* general population, *DI* dermatology inpatient, *DO* dermatology outpatient, *CI* confidence interval, *HR* hazard ratio, *OR* odds ratio, *OE* observed/expected ration

[a]Hypertriglyceridaemia (≥1.7 mmol l-1)

[b]low LDL (<1.04 mmol l-1 [men] and <1.29 mmol l-1 [women])

**Table 21.4** Table summarising large scale studies reporting the associated risk of psoriasis patients (n > 1,000) and hypertension

| Reference | Country | Cohort | Number patients | Number controls | Prevalence in cohort % (n) | Prevalence in controls % (n) | OR/RR | Incidence/ prevalence |
|---|---|---|---|---|---|---|---|---|
| Cohen et al. [139] | Isr | G | 12,502 | 24,285 | 38.8 (4,851) | 29.1 (7,057) | 1.37 (1.29–1.46) | P |
| Augustin et al. [10] | Ger | G | 33,981 | 1,310,090 | 35.6 | 20.6 | 1.73 (1.71–1.76) | P |
| Tsai et al. [40] | Tai | G | 51,800 | 997,771 | 20.1 (10,435) | 16.1 (33,353) | 1.51 (1.47–1.56) | P |
| Yang et al. [41] | Tai | G | 1,685 | 5,055 | 29.1 (491) | 25.5 (1,289) | 1.24 (1.07–1.43) | P |
| Shapiro et al. [9] | Isr | G | 1,079 | 1,079 | 51.5 (556) | 42.7 (461) | 1.42 (1.20–1.69) | P |
| Henseler and Christophers [5] | Ger | DO | 2,941 | 39,520 | 2.0 (58) | 0.01 (279) | 1.90 | P |
| Langan et al. [12] | UK | G | 4,065 | 40,650 | 31.1 (1,265) | 27.6 (11,204) | 1.2 (1.11–1.29) | |
| Huerta et al. [11] | UK | G | 3,994 | 10,000 | – | – | NS | P |
| Neimann et al. [6] | UK | G | M 127,706 | 465,252 | 14.7 (18,718) | 11.8 (54,840) | 1.03 (1.01–1.06) | P |
| | | | S 3,854 | 14,065 | 20.0 (769) | 13.2 (1,855) | 1.00 (0.87–1.14) | |
| Wu et al. [42] | USA | G | 1,127 | 1,127 | – | – | 1.49 (1.23–1.80) | P |
| Kaye et al. [8] | USA | G | 44,164 | 219,784 | 6.3 (2,765) | 5.8 (12,754) | 1.09 (1.05–1.14) | I |
| Gelfand et al. [44] | UK | G | M 127,139 | 556,995 | 14.57 (18,521) | 11.92 (66,366) | 1.26 (1.20–1.30) | P |
| | | | S 3,837 | | 19.86 (762) | | 1.25 (1.13–1.39) | |
| Kimball et al. [45] | USA | G | 20,614 | 82,456 | 35.5 (7,308) | 32.6 (26,886) | 1.14 (1.10–1.17) | P |
| | | | 25,556 | 101,507 | 29.3 (7,497) | 25.7 (26,037) | 1.20 (1.17–1.24) | |
| Qureshi et al. [140] | USA | G | 1,813 | 76,248 | 21.3 (3,860) | 19.6 (15,338) | RR 1.17 (1.06–1.30) | I |

*Isr* Israel, *Ger* Germany, *Tai* Taiwan, *M* mild psoriasis, *S* severe psoriasis, *G* general population, *DI* dermatology inpatient, *DO* dermatology outpatient, *CI* confidence interval, *OE* observed/expected ration, *RR* relative risk, *HR* hazard ratio, *OR* odds ratio

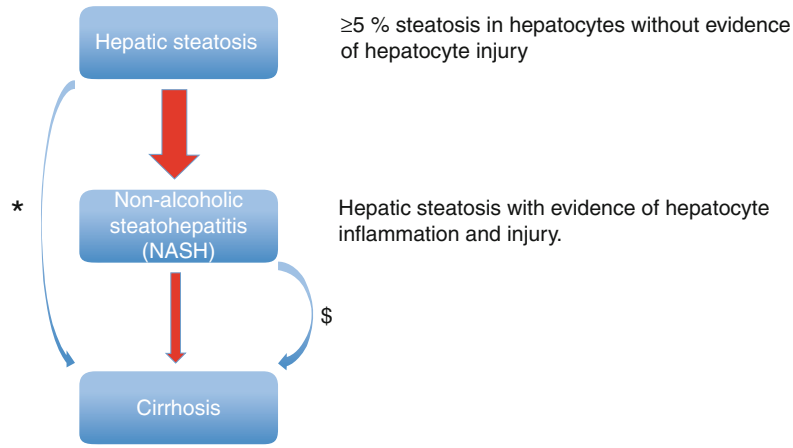


**Fig. 21.1** Schematic representation of spectrum of Non-Alcoholic Fatty Liver Disease (NAFLD). * 1–2 % may progress to cirrhosis over 15–20 years, $ 12 % may progress over 8 years (Adapted from Preiss and Sattar [55])

methotrexate, evidence for an independent link between non-alcoholic fatty liver disease (NAFLD) and psoriasis is emerging. NAFLD includes a range of liver diseases including hepatic steatosis and steatohepatitis and confers an increased risk of hepatic cirrhosis (not related to alcohol consumption; Fig. 21.1) [55]. NAFLD has been described as the hepatic manifestation of the metabolic syndrome [55].

Estimates on prevalence in the general population vary depending on country but are typically estimated to be 20–30 % in the developed world [55]. The prevalence of NAFLD in psoriatic patients has been reported in two small studies. In a cohort of 130 patients with psoriasis Gisondi et al. report a prevalence of NAFLD of 47 % (n = 61) [56], in comparison to 28 % in the control group. The severity of psoriasis was greater in those individuals with NAFLD compared with patients without NAFLD (PASI 14.2 ± 12.6 compared to 9.6 ± 7.4; $p < 0.01$) [56]. An Italian study of 142 unselected psoriasis patients attending dermatology outpatient clinic reported prevalence of NAFLD in 59.2 % (n = 84) of patients with psoriasis [57]. This study compared patients with psoriasis to individuals with biopsy proven NAFLD and no psoriasis (n = 125). This comparison indicated that patients with psoriasis had an adverse outcome and were more likely to suffer severe liver disease than the non-psoriatic patients with NAFLD [57].

Inflammation is a central feature of NAFLD pathogenesis. Gisondi et al. have speculated that the inflammatory mediators elevated in psoriasis contribute to the development of insulin resistance and progression of NAFLD [56]. Given that NAFLD would appear to be linked with an increased severity of psoriasis researchers have suggested that inflammation associated with NAFLD precipitates a more severe expression of psoriasis [56, 58].

The relationship between psoriasis and liver disease remains to be fully elucidated. Studies are clearly warranted to explore this relationship further. The physician should be aware of the high prevalence of liver disease in psoriatic patients and consider this in selecting systemic therapies (Table 21.2).

## Insulin Resistance and Type 2 Diabetes Mellitus

Type 2 diabetes, which is characterised by the development of insulin resistance and reduced secretion of insulin from the pancreas, is a global epidemic of increasing concern. It is estimated that 324 million people will be affected by diabetes globally by 2025; with a lifetime risk of 1 out of 3 individuals who will develop the disease [59]. It is well established that the metabolic syndrome is a strong predictor for the development of diabetes [60].

A recent meta-analysis of 22 eligible studies with a total of 3,307,516 participants provided evidence that patients with psoriasis are at modestly increased risk of diabetes when compared to

controls (OR 1.42, 95 % CI 1.40–1.45) [61]. This included data sets from a range of ethnic groups and compelling evidence for a link between psoriasis and diabetes. A small study (n = 39) evaluating insulin sensitivity has reported that psoriasis severity, as determined by PASI, is positively correlated with insulin resistance, as measured by homeostasis model assessment of insulin resistance (HOMA) [62]. This was supported in a further study by the same group who demonstrated a correlation between C-peptide and PASI in patients with a pathological HOMA (>2.5) [63].

Knowledge pertaining to the mechanistic link between the two conditions is limited. Th1 lymphocytes, and Th1 cytokines, are implicated in both diseases. TNFα (alpha) induces insulin resistance and is well established as a key cytokine of psoriasis pathogenesis. In addition a genetic association may increase susceptibility to Type 2 diabetes in patients with psoriasis and there is emerging evidence of a shared susceptibility loci including the CDKAL1 gene [64, 65]. Recent genotyping has further identified a novel association between IL2/IL21 and Type 1 psoriasis (onset <40 years of age) which is shared with a number of autoimmune diseases including Type 1 diabetes [65].

The link between psoriasis and diabetes has gained further interest following studies of improvement in psoriasis after initiation of therapies aimed at improving blood glucose control. Large-scale observational studies of patients treated for diabetes with thiazolidinediones have reported improved control of psoriasis in affected patients [66]. This has not been demonstrated for use of statins [67]. Improvement in psoriasis has also been reported in a case report of a patient treated with liraglutide (glucagon-like peptide-1 receptor agonist) [68]. Large scale prospective studies would be required to more comprehensively address any anti-psoriatic effect from standard treatments for diabetes.

## Metabolic Syndrome

The metabolic syndrome describes a clustering of CV risk factors (including obesity, hypertension, dyslipidaemia and insulin resistance) observed in association with one another more frequently than would be expected by chance alone [69]. Insulin resistance is a fundamental component of the metabolic syndrome and reflects the relative hyperinsulinaemia required in the fasting state to maintain euglycaemia. However, the existence of the metabolic syndrome as a distinct entity continues to generate controversy [70]. Despite this the European Group for Study of Insulin Resistance and the National Cholesterol Education Program: Adult Program Treatment Panel III (NCEP: ATP III) have described defining criteria (Table 21.5) [71, 72]. These features are more clinically relevant given that the data is extractable from standard patient assessment and do not require evaluation of insulin sensitivity. Other features associated with the metabolic syndrome include Non-alcoholic Fatty Liver Disease (NAFLD), see section "Non-alcoholic Fatty Liver Disease (NAFLD)" [73].

Within the background population prevalence of the metabolic syndrome is estimated at 15–25 % [74]. However, this prevalence is dependent on geographical location, gender, age and ethnicity [69]. In the United States 7 % of the population aged 20–29 years have a diagnosis of metabolic syndrome compared with 44 % of 60–69 years olds [74].

The metabolic syndrome is clinically relevant as it is predictive of the future development of diabetes and CV risk [75–77]. A hazard ratio of all cause mortality and CVD mortality in individuals diagnosed with the metabolic syndrome has been estimated as 1.44 (95 % CI, 1.17–1.84) and 2.26 (95 % CI, 1.61–3.17) respectively for men and 1.38 (95 % CI, 1.02–1.87) and 2.78 (95 % CI, 1.57–4.94) respectively for women [78].

Psoriasis is associated with the metabolic syndrome including many of its constituent components (Table 21.6). Sommer et al. described an odds ratio for metabolic syndrome of 5.92 (95 % CI, 2.78–12.8) for a cohort of hospitalised patients with psoriasis (n = 581) when compared with controls [80]. A similar study of 338 patients with psoriasis managed in a dermatology outpatient department demonstrated a prevalence of metabolic syndrome of 30.1 % compared with

**Table 21.5** Defining criteria for metabolic syndrome for European Group for Study of Insulin Resistance and National Cholesterol Education Program: Adult Program Treatment Panel III (NCEP:ATP III)

| European group for study of insulin resistance | National Cholesterol Education Program: Adult Program Treatment Panel III (NCEP: ATP III) |
|---|---|
| Insulin resistance or fasting hyperinsulinaemia (the highest 25 % of general population) | Three or more of the following |
| Two or more of the following | Fasting plasma glucose ≥6.1 mmol/L |
| Fasting plasma glucose ≥6.1 mmol/L | Central obesity |
| Central obesity | Waist circumference ≥102 cm (male) |
| Waist circumference ≥94 cm (male) | ≥88 cm (female) |
| ≥80 cm (female) | Hypertension |
| Hypertension | Blood pressure ≥135/85 mmHg |
| Blood pressure ≥140/90 mmHg | OR antihypertensive medication |
| OR antihypertensive medication | Dyslipidaemia |
| Dyslipidaemia | Triglycerides >1.7 mmol/L |
| Triglycerides >2.0 mmol/L | Low HDL cholesterol <1.0 mmol/L (male) |
| HDL cholesterol <1.0 mmol/L | <1.3 mmol/L (female) |

Adapted from Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [71]

**Table 21.6** Evidence for association between psoriasis and the metabolic syndrome

| Reference | Country | Cohort | Number patients | Number controls | Prevalence in cohort % (n) | Prevalence in controls % (n) | OR |
|---|---|---|---|---|---|---|---|
| Cohen et al. [7] | Israel | G | 16,851 | 48,681 | – | – | 1.3 (1.1–1.4) |
| Gisondi et al. [79] | Italy | DO | 338 | 334 | 30.1 (102) | 20.6 (69) | 1.65 (1.16–2.35) |
| Sommer et al. [80] | Germany | DI | 625 | 1,044 | 4.3 (25) | 1.1 (11) | 5.92 (2.78–12.8) |
| Al-Mutairi et al. [81] | Kuwait | DO | 1,661 | 1,835 | 16 (265) | 6.8 (124) | 2.62 (2.09–3.28) |
| Langan et al. [12] | UK | G | 4,065 | 40,650 | 34 | 24 | 1.41 (1.31–1.51) |

*G* general population, *DO* dermatology out-patient, *DI* dermatology in-patient, *OR* odds ratio

20.6 % for the control group; odds ratio 1.65 (95 % CI, 1.16–2.35) [79]. This report indicated that the prevalence of metabolic syndrome was independent of psoriasis severity. A Kuwaiti study of 1,661 dermatology outpatients with psoriasis demonstrated an odds ratio of metabolic syndrome of 2.62 (95 % CI, 2.09–3.20) [81]. Recent sub analysis of 2,899 patients included in ustekinumab phase III clinical trials (PHOENIX 1, PHOENIX 2 and ACCEPT) indicated prevalence of the metabolic syndrome to be approximately 36.2 %; all of whom were patients with severe psoriasis (PASI ≥12) [15].

Two large-scale database studies support the observation that metabolic syndrome is associated with psoriasis. Cohen et al. demonstrated an increased risk of metabolic syndrome in a cross sectional study of 16,851 patients, extracted from the Clalit Health Services (CHS) database in Israel, with an adjusted odds ratio of 1.3 (95 % CI, 1.2–1.5) [7]. Langan et al. have published data utilising The Health Improvement Network (THIN) General practice database in UK patients. A total of 4,065 patients were included and stratified into mild (BSA <2 %), moderate (BSA 3–10 %) and severe (BSA >10 %) disease. This revealed 34 % of patients with psoriasis had features of the metabolic syndrome compared to 26 % of controls in a "dose-response" manner. The odds ratio for metabolic syndrome increased with increasing severity of psoriasis [12]. These findings are in contrast to the previous reports by Gisondi et al. who demonstrated an association between metabolic syndrome and psoriasis but not in a "dose-response" relationship [79].

Increasing evidence suggests that inflammation is a central aspect of the pathogenesis of

both psoriasis and the metabolic syndrome [82]. Insulin resistance is a key facet of the metabolic syndrome and resistance to insulin is increased by inflammatory cytokines (e.g. TNFα (alpha)) which are also key drivers of psoriasis [69]. It has been suggested that a relative adipocyte hypoxia, through adipocyte hypertrophy and increased oxygen tension, stimulates release of these cytokines including TNFα (alpha), IL-6, CRP and fibrinogen [69, 83]. Visceral fat is considered 'dysfunctional adipose tissue' and particularly predisposes to this inflammatory state [84]. This facilitates the development of a cycle of inflammation which further exacerbates insulin resistance and increased adiposity.

The inflammatory milieu of the metabolic syndrome includes elevated levels of leptin which is also elevated in obesity. Leptin is a pro-inflammatory adipokine and known to activate macrophage and promote the development of a Th1 phenotype [85, 86]. Wang et al. suggested that hyperleptinaemia was predictive of development of metabolic syndrome in patients with psoriasis [86]. The observation of Langan et al. of a "dose-response" relationship between psoriasis and metabolic syndrome may indicate that more patients will suffer more severe cutaneous disease as the burden of obesity and metabolic syndrome increase in the background population.

The component features of the metabolic syndrome may complicate the management of patients with psoriasis. This presents two significant challenges to the dermatologist. First, it is important to treat the patient holistically and consider investigation and management of comorbid conditions; including use of primary prevention strategies. Secondly several systemic agents for the treatment of psoriasis have the potential to exacerbate or precipitate elements of the metabolic syndrome (Table 21.2). The metabolic syndrome is an epidemic of the developed world and associated with an energy rich diet. Given the relatively high prevalence of psoriasis in the general population it is reasonable to expect that the issue of patient management in the context of metabolic syndrome will increase in the future. The dermatologist must be aware of this association and should be vigilant for opportunities to address these comorbidities.

## Cardiovascular Disease (CVD)

Concern that psoriasis may be associated with CVD has been a topic of intense research interest for over 20 years [5]. Understanding the association between psoriasis and CVD is complicated by the increased prevalence of traditional CV risk factors including diabetes, obesity, smoking, hypertension and hyperlipidaemia present in both conditions. Additional potential confounders which are difficult to quantify include exercise, alcohol and diet.

The key mediators of psoriasis and atherosclerosis are similar and provide a mechanism by which the two may be linked (Fig. 21.2). Th1 and Th17 cells and their respective cytokines are implicated in the pathogenesis of both diseases [87]. Other cytokines common to both diseases include IL-1, IL-6, IL-10, leptin, and adiponectin [18].

Inflammation is a central theme underpinning a theoretical link between psoriasis and CVD. In addition to the above mentioned link between CRP and hypertension [88] it is well established that CRP is associated with adverse CV events [89, 90]. Inflammation is instrumental in the development of vascular disease and implicated in endothelial dysfunction and atheroma development [91, 92]. Activation of T cells and infiltration of the endothelium by macrophage are early steps in disease progression [92]. Development of lipid laden foam cells beneath the endothelium herald the onset of atherosclerotic plaques. This core region is the focus over which smooth muscle and matrix remodelling ensues, with the development of the fibrous cap of the atheroma. Activation of the plaque, and development of a thrombus, is implicated in subsequent ischaemic events. Both the plaque formation and plaque destabilisation are heavily driven by inflammatory cytokines, T cells and macrophage [92].

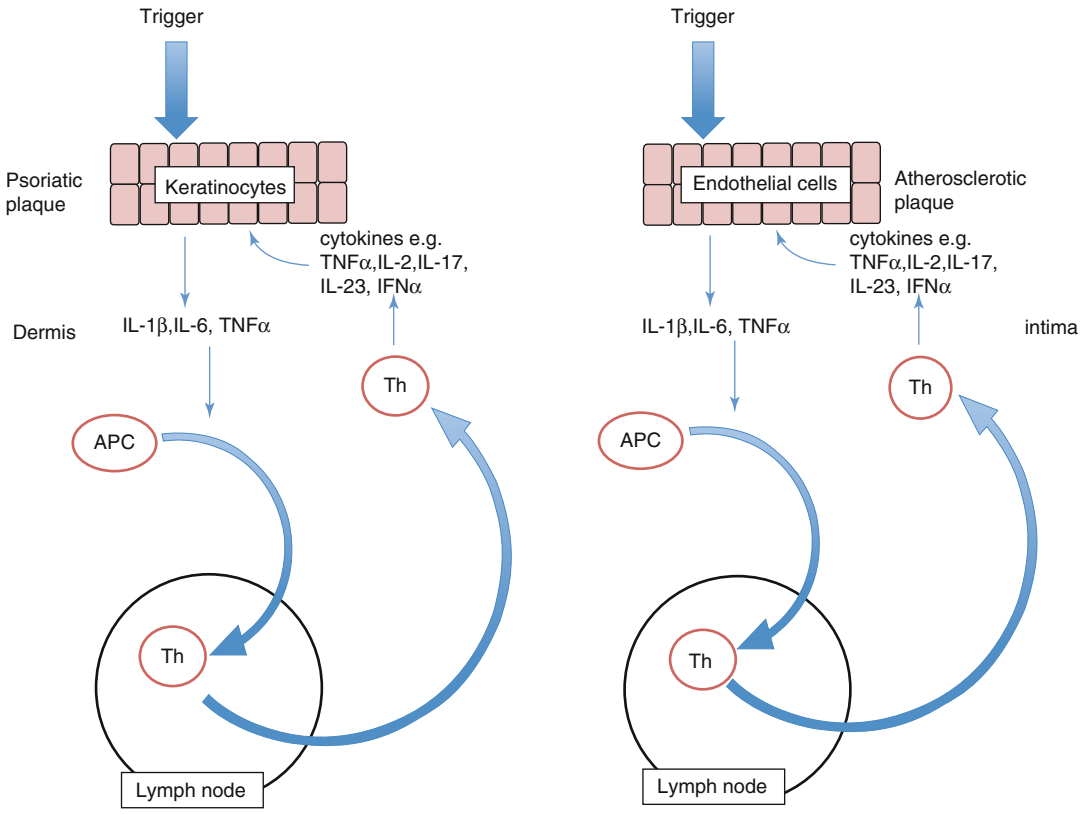


**Fig. 21.2** Overlapping pathogenesis of psoriasis and cardiovascular disease. *Th* CD4 lymphocyte (Th1 and Th17), *APC* antigen presenting cell

## Heart Disease

### Evidence for an Association Between CVD and Psoriasis

The association with CVD and psoriasis has been demonstrated in a number of studies [4, 5, 44, 93–99]. Recently the association between psoriasis and CVD has been the focus of intense scrutiny with the interrogation of large databases of patients with psoriasis. Gelfand et al. published data on a cohort of psoriasis patients in the UK with mild (n = 127,139) and severe (n = 3,837) disease extracted from the UK GPRD [44]. Multivariate regression demonstrated a significant increase in relative risk of myocardial infarction (MI), which was most marked in young patients with severe disease [44]. It was calculated that a 30 year old with mild disease has an adjusted relative risk of MI of 1.29 (95 % CI, 1.14–1.46) compared with 3.10 (95 % CI, 1.98–4.86) for severe disease [44]. This risk was independent of traditional CV risk factors. Patients were classified as having severe disease based on an appropriate clinical code and exposure to systemic therapies (including psoralen, phototherapy, methotrexate, azathioprine, cyclosporine, etretinate, acitretin, hydroxyurea, or mycophenolate mofetil). It is noteworthy that 16.4 % of patients with severe psoriasis had received azathioprine, a drug not typically used for the treatment of psoriasis. The same group have subsequently published further evidence that severe psoriasis confers an increased risk of major adverse CV events (MACE; including MI, stroke or death due to CV event) and CV death [97, 100, 101]. In a cohort of 14,330 UK based patients with severe psoriasis, extracted from the GPRD, the adjusted hazard ratio for MACE was 1.53 (95 % CI, 1.26–1.85); equating to an additional 6.2 % absolute risk of 10-year MACE [97].

Mehta et al. have also reported in a cohort of 3,603 patients with severe psoriasis that CV mortality was increased when compared with controls, independent of traditional factors; the adjusted hazard ratios for CV mortality was 1.57 (95 % CI, 1.26–1.96) [101].

A recently reported study in a Danish cohort of 34,371 and 2,621 patients with mild and severe psoriasis respectively followed over a 10 year observation period found supportive evidence of an increased risk of CV mortality [102]. For mild psoriasis the independent risk ratio for CV mortality was 1.14 (95 % CI, 1.06–1.22) and for severe psoriasis this increased to 1.57 (95 % CI, 1.27–1.94). An increased risk of CVD has also been reported in two large database studies of US psoriasis patients extracted from the IMS Health Integrated Claims Database (n = 20,614) and the MarketScan® Commercial Claims and Encounters Database (n = 25,556) [45]. The adjusted odds ratio for CVD was reported as 1.13 (95 % CI, 1.06–1.20) and 1.18 (95 % CI, 1.09–1.28) respectively [45]. Finally, the Nurses' Health Study II has provided additional support for an association between psoriasis and CVD disease in a study of 96,008 individuals with psoriasis. The multivariate-adjusted hazard ratio (HR) of non-fatal CVD and non-fatal MI was 1.55 (95 % CI, 1.04–2.31) and 1.70 (95 % CI, 1.01–2.84) respectively [103].

## Evidence Against an Association Between CVD and Psoriasis

In contrast to this Wakkee et al. presented data for a cohort of 15,820 psoriasis patients compared with 27,577 controls extracted from a database utilising Dutch health records which failed to demonstrate a significant increase in CV mortality when adjusted for established confounders [104]. Adjusted hazard ratios of 1.05 (85 % CI, 0.95–1.17) and 0.94 (95 % CI, 0.80–1.11) were reported for ischaemic heart disease and acute MI respectively [104]. The authors selected patients who were definitely diagnosed with psoriasis using an algorithm which included a criteria that the patient must have been prescribed either psoralen, calcipotriol, calcitriol, dithranol, fumaric acid or efalizumab. Whilst this is likely to select the majority of patients with psoriasis the authors acknowledged that patients with severe psoriasis managed with other systemic therapies may be omitted from this analysis (e.g. methotrexate and cyclosporine). Further evidence suggesting that psoriasis may not be an independent risk factor for CVD has been reported in a longitudinal study of 1,376 patients with severe psoriasis (treated with psoralens and ultraviolet-A therapy (PUVA) followed up for 30 years). This report indicated an increased all cause mortality but no increased risk of CVD [105, 106]. This has proven a contentious area with on going discussion in the published literature [107–109].

Given the strength of evidence in support of an independent risk of CVD in several large population cohort studies two consensus statements have been supportive of the position that psoriasis is an independent risk factor for CVD [43, 110].

## Effect of Treatment of Psoriasis on CVD Risk

Patients with psoriasis are at an increased risk of CVD, the aetiology of which is complicated by numerous confounder variables. A significant outstanding question relates to the effect of anti-psoriatic therapy on CV risk. Prodanovich et al. retrospectively examined vascular disease in a cohort of outpatients with psoriasis (n = 7,615) and rheumatoid arthritis (n = 6,707) [26]. In patients treated with methotrexate the relative risk of vascular disease was 0.73 (95 % CI 0.55–0.98) and 0.83 (95 % CI 0.71–0.96) for psoriasis and rheumatoid arthritis respectively. Smaller prospective studies have demonstrated amelioration of adverse markers of CVD with use of systemic anti-psoriatic therapies [111]. This research is further supported by growing evidence that TNFα (alpha) inhibitors reduce CVD risk in patients with rheumatoid arthritis [27]. A recent study of 24,081 patients with psoriasis and psoriatic arthritis suggested that in the cohort of patients treated with TNFα (alpha) inhibitors (n = 1,877) the hazard ratio for MI in the psoriasis-only group (n = 971) was 0.264 (95 % CI, 0.12–0.59; p = 0.0012) compared with those who received oral therapy or phototherapy [28]. No

**Table 21.7** Summary of risk factors undiagnosed or untreated in patients with moderate to severe psoriasis (PASI ≥12) in phase III clinical trials for ustekinumab (n = 2,899) [15]

| Cardiovascular risk factor | Undiagnosed (%) | Untreated (%) |
|---|---|---|
| Diabetes | 2.3 | 19.1 |
| Hypertension | 9.1 | 21.8 |
| Hyperlipidaemia | 4.9 | 38.6 |

**Table 21.8** Adjusted odds ratio for development of atrial fibrillation and stroke for psoriasis patients with mild and severe psoriasis, divided by age < or ≥50 years [98]

| | | Adjusted rate ratios (95 % confidence interval) | |
|---|---|---|---|
| | | Atrial fibrillation | Stroke |
| Mild psoriasis | <50 years | 1.50 (1.21–1.86) | 1.97 (1.66–2.34) |
| | ≥50 years | 1.16 (1.08–1.24) | 1.13 (1.04–1.21) |
| Severe psoriasis | <50 years | 2.98 (1.80–4.92) | 2.80 (1.81–4.34) |
| | ≥50 years | 1.29 (1.01–1.65) | 1.34 (1.04–1.71) |

risk reduction was observed in patients with psoriasis and psoriatic arthritis (n = 750); hazard ratio for MI 0.957 (95 % CI, 0.60–1.53; p = 0.855).

The need for primary intervention for CVD risk factors has been highlighted in a recent review summarising the comorbidities in patient with psoriasis who are participating in phase III clinical trials of ustekinumab (n = 2,899) which indicated that participants were frequently undiagnosed and untreated for diabetes, hypertension and hyperlipidaemia (Table 21.7) [15].

In summary it would appear that psoriasis may be an independent risk factor for CVD. Given that the prevalence of CVD and traditional risk factors are elevated in patients with psoriasis the dermatologist must be engaged in detection, management and primary prevention of these complications.

## Stroke and Atrial Fibrillation

Evidence to support a more generalised impact on vascular function was presented recently indicating that patients with psoriasis are at an increased risk of stroke and atrial fibrillation (AF) [98]. A cohort study of the Danish population compared 36,765 patients with mild psoriasis, 2,793 patients with severe psoriasis and 4,478,926 controls between 1997 and 2006 [98]. The rate ratios for AF and stroke are summarised in Table 21.8. It is interesting to note that this evidence indicates the greatest risk of AF and stroke is in young individuals with the most severe disease, consistent with CVD risk reported by Gelfand et al. [44].

This evidence is supportive of the hypothesis that chronic inflammatory burden associated with psoriasis has an impact on systemic vascular health. The reduction in risk observed in older patients is likely to reflect concomitant disease and adverse risk factors which cumulatively dilute the adjusted rate ratios of psoriasis.

Contrary to the evidence of Ahlehoff et al., Yang et al. has recently reported evidence of no increased risk of stroke in a cohort of 1,685 patients with psoriasis and 5,055 controls following interrogation of Taiwan's National Health Insurance (NHI) programme. In this study prevalence of stroke was 6.5 % (n = 109) for patients with psoriasis and 6.0 % (n = 304) in the control group (p = 0.728) [41]. However, stroke in Caucasian populations typically result from extracranial large artery atherosclerosis whilst in Chinese populations intracranial small vessel disease is more common [41]. The authors acknowledge that ischaemic stroke is mechanistically different in Chinese and Caucasian populations and may therefore not be comparable.

## Cancer and Lymphoma

An association between psoriasis and malignancy has been suggested in a number of studies and remains an area of uncertainty, complicated by the additional influence of phototherapy and immunosuppressive therapy which may increase malignancy risk.

## Skin Cancer

Studies examining the risk of primary skin malignancy have not demonstrated an increased risk

conferred by psoriasis. However, it is well established that treatment for psoriasis may confer substantial risk of primary skin malignancy. It has previously been reported that PUVA therapy may increase the risk of squamous cell carcinoma (SCC) 14-fold [112]. Use of any cyclosporine in patients with psoriasis previously treated with >200 treatments of PUVA demonstrated an additional risk of SCC with an adjusted incidence rate ratio of 3.1 (95 % CI, 2.6–3.7) [113].

### Lymphoma

Using the UK GPRD 153,197 patients with psoriasis (149,203 mild, 3,994 severe) were studied alongside a control group of 765,950 individuals [114]. Adjusted odds ratio for lymphoma were 1.34 (95 % CI, 1.16–1.54) and 1.59 (95 % CI, 0.88–2.89) for patients with mild and severe psoriasis respectively. This is consistent with the work of Brauchli et al. discussed below [115]. Sub analysis of the data reported by Gelfand et al. suggested that the greatest risk of lymphoma was conferred for Cutaneous T Cell Lymphoma (CTCL) [114]. Given the potential for clinical mis-diagnosis of CTCL and psoriasis one must be cautious in the interpretation of this latter association.

### General Cancer Risk

A further analysis of the UK GPRD performed by Brauchli et al. in 36,702 patients with psoriasis and 36,702 matched controls demonstrated an increased overall odds ratio for cancer of 1.50 (95 % CI, 1.30–1.74) for patients with psoriasis ≥4 years [115]. This odds ratio is controlled for age, sex, BMI and smoking status. The relative risk was greatest for lymphohaematopoietic malignancy. For patients who have not received systemic therapy the odds ratio for cancer development was 1.59 (95 % CI, 1.01–2.50) for <2 years psoriasis duration and 2.12 (95 % CI, 1.45–3.10) for ≥2 years psoriasis duration. This study controlled for age, gender and years on the GPRD but did not control for smoking, alcohol intake or family history of cancer.

Additional support for an association between psoriasis and cancer has been reported in a Taiwan based study. Utilising the National Health Insurance Research Database (NHIRD) between 1996 and 2000 3,686 patients with psoriasis were compared with 200,000 control patients [116]. Chen et al. calculated an adjusted hazard ratio for developing a cancer of 1.66 (95 % CI, 1.38–2.00) with significant associations including urinary, skin, oropharynx/larynx, liver/gall bladder and colon/rectum. A significant limitation of this study was that these ratios were not adjusted for smoking, alcohol intake or family history.

A study of the Iowa Women's Health Study compared 719 psoriasis patients with 32,191 non-psoriatic patients between 1991 and 2004 [117]. An adjusted hazard ratio (adjusted for age, smoking, BMI, education, physical activity, hormone therapy use) was reported for colon cancer in patients with psoriasis; HR 1.6 (95 % CI, 1.0–2.4) [117].

In summary it would appear that psoriasis may confer an increased risk of malignancy, particularly lymphoproliferative disease. Further studies are required to more clearly evaluate the impact of adverse confounder variables observed more frequently in patients with psoriasis than the background population (such as family history, diet, exercise, smoking and alcohol). Primary prevention and risk assessment of all patients with psoriasis is of great importance in early detection and management and in reducing risk in patients being considered for immunosuppressive systemic therapies.

## Autoimmune Disease

Understanding of the genetics and pathogenesis of psoriasis has moved forward dramatically in the past 20 years and afforded a valuable opportunity to further understand associations between psoriasis and diseases affecting the immune system including; inflammatory bowel disease (Crohns disease and ulcerative colitis), multiple sclerosis, coeliac disease, Type 1 diabetes mellitus, and Graves disease [65, 118, 119]. More recently this has included the identification of an

association with rheumatoid arthritis, alopecia areata, systemic sclerosis, Sjogren's syndrome, vitiligo, chronic urticaria, systemic lupus erythematosus, giant cell arteritis and chronic glomerulonephritis [120].

The relationship between psoriasis and inflammatory bowel disease has been suggested for over 30 years. Case-control studies suggest that 7–11 % of patients with Crohns disease also have psoriasis [121–123]. Numerous genetic susceptibility loci are common to both psoriasis and Crohns disease and this provides further evidence to support this observation [124, 125]. The pathogenesis of both diseases are significantly similar and recent evidence has implicated IL-4, −13 and −23 as key cytokines for both psoriasis and Crohns disease [126, 127]. This is supported by a recent large-scale genome wide association scan which identified seven novel and four previously identified shared susceptibility loci between the two diseases [28].

The link between psoriasis and autoimmune disease is compelling and suggests both shared genetic factors and potentially overlapping pathogenesis. Increasing access to genetic studies (such as genome wide association scans) and large scale databases offer a number of methodologies to evaluate such associations. This will provide increasingly valuable insight into disease pathogenesis.

## Psychiatric Illness

Psoriasis is highly visible and consequently has a significant social stigma which may result in maladaptive coping mechanisms and increased stress. This negative impact on quality of life is comparable to many major medical conditions including heart disease and diabetes [128]. Several studies have reported an increased prevalence of depression and mood disorders in association with psoriasis. A questionnaire of 2,391 patients by Esposito et al. reported depressive symptoms in 62 % of patients with psoriasis who responded [129]. This is consistent with a questionnaire of 6,194 patients with severe psoriasis which demonstrated that 79 % considered that their psoriasis had a negative impact on their quality of life [130]. The severity of this negative impact on quality of life is emphasised by a study of 138 patients in which 7.2 % reported thoughts of suicidal ideation [131].

A study using the Taiwan National Health Insurance (NHI) claims database compared 51,800 psoriasis patients with a control group of 997,771, reporting a prevalence of depression in 2.13 % (1,103) of subjects compared to 1.52 % (3,152) in controls ($P<0.0001$) [40]. This conferred an adjusted relative risk of 1.50 (95 % CI, 1.39–1.61) [40]. Further support of an association between psoriasis and psychiatric comorbidity is provided from an Israeli population based study of 10,669 patients with psoriasis compared with 22,996 control patients [39]. The prevalence of psychiatric comorbidity was 15.8 % (1,685) for patients with psoriasis and 13.1 % (3,019) for the control group ($p<0.001$).

However, a recent publication examining comorbid disease in Taiwan failed to demonstrate such an association in a population based study of 1,685 patients with psoriasis and 5,055 control subjects [41]. Depression was recorded in 3.7 % ($n=62$) of patients with psoriasis and 3.0 % (151) of the comparison group ($p=0.188$).

Given the impact of psoriasis on quality of life an association between psoriasis and depression appears intuitive. Whilst depression is a contraindication to inclusion in clinical trials, symptoms of depression are frequently observed to improve over the period of treatment as measured by quality of life indices [132–134].

A common pathogenic pathway for psoriasis and depression may involve IL-12 which is elevated in depression and is also a key cytokine established in the pathogenesis of psoriasis [135, 136].

Support for abnormal cognitive function in patients with psoriasis has been reported in a small cohort ($n=13$) examined for functional brain activity in response to disgust, measured by functional magnetic resonance imaging (fMRI) [137]. The insular cortex is activated in individuals who experience disgust or see others demonstrating facial expressions of disgust. In this cohort a significantly reduced response in the

insular cortex was reported in patients with psoriasis when compared with controls. The authors suggest that this is a coping mechanism related to social stigma of disease [137].

Psoriasis has a dramatic and negative impact on mental health. The increasingly routine use of the Dermatology Life Quality Index (DLQI) as a means to evaluate the impact of psoriasis on quality of life reflects the recognition of this in dermatological practice [138]. Large scale studies have provided supportive evidence that psoriasis is associated with depression. It remains to be established the nature of this relationship. Recent discovery of the IL-12 pathway, common to both psoriasis and depression, provide a theoretical link of a shared pathogenesis. Further research is indicated to better evaluate this association and allow a more rigorous approach to comorbid psychiatric disease.

## Conclusions

Emerging data from large-scale epidemiological studies and genome wide association studies are providing evidence that psoriasis is a multisystem disorder with multiple comorbidities.

Patients with psoriasis are at an increased risk of CVD and several CVD risk factors (obesity, dyslipidaemia, hypertension, diabetes, NAFLD and the metabolic syndrome). The aetiology of this remains to be fully elucidated. It is clear that patients with psoriasis demonstrate a number of adverse lifestyle choices (e.g. smoking, poor diet) which undoubtedly contribute to CVD and CVD risk factors.

In developed societies obesity and the metabolic syndrome are highly prevalent. This epidemic has enormous implications to delivery of healthcare. The acceptance of psoriasis as a multisystem disease associated with obesity and potentially metabolic syndrome raises significant questions about the future prevalence and severity of psoriasis in the general population.

Current evidence provides compelling support for a central role of inflammation linking psoriasis and CVD and CVD risk factors, particularly obesity. It remains to be established if control of inflammation associated with psoriasis will result in reversal, or stabilisation, of CVD or CVD risk factors. Evidence in support of this has been suggested in preliminary work in patients with psoriasis, rheumatoid arthritis and systemic lupus erythematosus and reduced incidence of MI in individuals treated with methotrexate and TNFα (alpha) inhibitors. This is of significant importance for the clinician as an additional factor to consider when evaluating treatment options for a patient with moderate to severe psoriasis.

Psoriasis appears to confer an additional risk of malignancy. This would appear to be greatest for lymphomas. Many of the studies evaluating this relationship are limited by the inability to control for significant confounders (e.g. family history, smoking) and require further evaluation. This data should serve to inform the clinician of an increased prevalence of malignancy in this patient cohort. This is particularly pertinent when considering systemic immunosuppressive therapies and the need for baseline evaluations and monitoring (e.g. cervical smear testing, mammography).

Evidence in support of an association between psoriasis and a broad range of autoimmune disease is increasingly robust. Many of these associations are linked through shared genetic loci. It remains to be determined if therapies for diseases with shared genetic loci are responsive to common therapeutic regimens.

The association between psoriasis and psychiatric disease is well recognised. Choice of therapy is driven in large part by patient demand (related to the negative impact of psoriasis on quality of life). The impact psoriasis has on mental health should not be under estimated and requires continuous evaluation as part of any management plan. Recognition of overlapping pathogenesis provides new insight into the relationship between psoriasis and psychiatric disease, especially depression, and may provide further opportunity to improve patient outcomes.

Patient and physician education are of the utmost importance. Psoriasis is increasingly recognised as a multisystem disease that requires a multimodal approach to holistic patient-centred care. For the patient increased awareness of comorbid disease will allow greater opportunity for lifestyle modification to reduce disease burden and improve morbidity and mortality. For the clinician, recognition of psoriasis as a systemic disease should prompt a broader approach to clinical practice and utilisation of primary and secondary prevention strategies to improve morbidity and mortality in this patient group.

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# Summary of Published Treatment Guidelines

22

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**Abstract**

The treatment of psoriasis can be challenging with multiple therapeutic modalities from which to choose. Various organizations around the world have developed treatment guidelines to help with these challenges with recommendations intended to assist clinicians in their decision-making. While some of these guidelines are detailed in their treatment recommendations providing comprehensive options including the multiple topical and systemic medications available, as well as phototherapy, others offer very limited recommendations. Additionally, the use of biologics has been incorporated into many, but not all, treatment guidelines. Most of the published guidelines were established using evidence based medicine and the consensus of expert panels. The treatment of psoriasis ultimately needs to be individualized to patients' needs and preferences, but guidelines are available to aid clinicians as they formulate personalized treatment plans from the many existing therapeutic options and to influence better treatment outcomes.

**Keywords**

Psoriasis • Treatment guidelines • Evidence based recommendations • Biologics • Cyclosporine • Methotrexate

A 2003 consensus statement from the American Academy of Dermatology stated that the goal of treating psoriasis is to create lasting improvement in symptoms while minimizing any adverse events that might result from treatment [1]. There are a plethora of medications for psoriasis, and therapeutic regimens can be based upon traditional dogma, scientific evidence, or the experiences of the physician. To assist clinicians with the management of psoriasis, there are guidelines for treatment from various organizations

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**Table 22.1** Overview of published guidelines reviewed

| | Therapies discussed | Evidence-based | Year of publication |
|---|---|---|---|
| American Academy of Dermatology | Topicals, phototherapy, systemics, biologics | Yes | 2008–2011 |
| Psoriasis Process of Care Consensus Panel | Topicals | Yes | 2010 |
| Dermatology Society of South Africa | Topicals, phototherapy, systemics | Yes | 2010 |
| German Society of Dermatology | Topicals, systemics, biologics | Yes | 2007 |
| European Association of Dermatology and Venereology | Systemics | Yes | 2009 |
| American National Psoriasis Foundation | Cyclosporine | Yes | 2008 |
| Spanish Academy of Dermatology and Venereology | Methotrexate | Yes | 2010 |
| Germany Consensus Conference | Fumaric acid esters | Yes | 1997, updated 2007 |
| National Psoriasis Foundation Medical Board | Systemics, biologics | Yes | 2012 |
| Canadian Dermatologic Association | Topicals, phototherapy, systemics biologics | Yes | 2009 |
| National Psoriasis Foundation Medical Board | Systemics, biologics, phototherapy | Yes | 2012 |

in many different countries. These guidelines incorporate information drawn from both clinical expertise as well as data from trials, which have provided evidence-based information regarding efficacy and safety. Ultimately, there is a consensus that treatment of psoriasis must be addressed on an individual basis and that personalized regimens to which the patient's symptoms respond and with which the patient is willing to be compliant are key. This chapter will summarize the more recent published treatment guidelines by giving a description of the published guidelines themselves, as well as a review of the therapeutic options available (Table 22.1).

## Overview of Treatment Guidelines

Many published guidelines address the treatment of psoriasis. A frequently used measure efficacy of medications is the Psoriasis Area and Severity Index (PASI) and the time period it takes patients to report a 75 % improvement in their symptoms, which is called a PASI-75 [2, 3]. In 2010, a group of expert clinicians and researchers came together to form the Psoriasis Process of Care Consensus Panel and produced a set of guidelines regarding the use of topical medications [4]. This document communicates the practices and recommendations of these experts on everything from choosing an appropriate medication to building rapport with patients and evaluating their compliance. It includes specific recommendations for anatomic locations that can be difficult to treat, including the scalp, nails, or intertriginous areas. Treatment recommendations are based upon large scale trials and evidence based medicine wherever possible.

The *British Journal of Dermatology* published a systematic review of the literature regarding the use of topical medications in 2008 and recommended further investigation with longer term trials for topical medication to determine their relative efficacies [5].

The Dermatological Society of South Africa published a set of guidelines addressing topicals, phototherapy and systemics in 2010 that was intended for use by all levels of healthcare providers. A group of eight South African dermatologists comprised the working group that created this document, which was an adaptation of the contemporary guidelines published by organizations in the United States and in Europe. Levels of evidence for various trials and therapies were discussed where applicable [6].

The American Academy of Dermatology put forth a series of six articles in a series published

between 2008 and 2011. They address the use of topicals, systemics, phototherapy, biologics for psoriasis and psoriatic arthritis. These articles are strongly evidence based in their recommendations wherever possible and defer to consensus opinions of experts if definitive data is not available [7–12].

The German Society of Dermatology published a set of guidelines in 2007 with the expressed goal of creating an evidence based tool for clinicians to use in the treatment of psoriasis [13]. This paper addresses topicals, systemics and biologics and was created by a panel of experts after an extensive and systematic review of the literature.

The Canadian guidelines for the management of plaque psoriasis were published in 2009 [14]. This set of guidelines is very lengthy and thorough, is evidence based, and addresses the use of topicals, systemics, phototherapy and biologics. It also devotes individual focus to population subsets that may be more complex to treat, such as patients who are pregnant or who have chronic illnesses or malignancies. In 2012, the National Psoriasis Foundation Medical Board reviewed and updated these Canadian guidelines for the management of plaque psoriasis. This update is strongly evidence based, includes new data available regarding medications and their efficacy, and again addresses specific population subsets [15].

In 2009, the European Association of Dermatology and Venereology published a set of guidelines on the treatment of psoriasis vulgaris with systemic medications. This was intended for use by medical specialists, particularly dermatologists, as well as those involved in making policy [2]. This set of guidelines is strongly evidence based. It included a thorough review of the literature with evaluation of both levels of evidence as well as efficacy. Maintenance therapy was not addressed in these recommendations. Therapeutic recommendations for systemic medications were made based upon this combination of factors. In 2008, the American National Psoriasis Foundation published a consensus statement on the use of cyclosporine to treat psoriasis [16]. This document was founded on a review of the literature and is strongly evidence based.

In 2010 the psoriasis group of the Spanish Academy of Dermatology and Venereology published a paper establishing guidelines for the use of methotrexate for the treatment of psoriasis [17]. This document is based on the agreement of experts in this field. In 1997, a consensus conference was held in Germany to create recommendations for the use of fumaric acid esters. This document was updated in 2007 and is based on both the experiences and evidence obtained from studies [18].

## Topicals

Traditional dogma dictated that patients with 10 % or less total body surface area involvement might simply be treated with topical medications. Once the percentage of involved skin exceeded 10 %, treatment shifted towards ultraviolet (UV) light or systemic medications [10]. More recently, it has been appreciated that even very limited body surface area involvement may greatly affect a patient's quality of life, particularly if areas such as the scalp or palms are involved [4, 10]. Additionally, lesions may be refractory to topical therapies [4]. Therefore, present guidelines for the treatment of psoriasis agree that patients with smaller percentages body surface area involvement may be still considered candidates for phototherapy or systemic medications based on their symptoms. Patients with less severe symptoms may be given a trial with topical medications first. Topical treatments for psoriasis may be used intermittently or chronically and may be administered as immunotherapy or used in conjunction with other agents [9]. Typically, topical treatments are relatively safe and may be efficacious in the treatment of mild to moderate psoriasis [19]. As monotherapy, topicals are not usually effective for more severe disease but may be very useful in conjunction with other medications as part of a customized treatment regimen. The vehicle by which the medication is delivered is crucial as it may affect both penetration of the medication as well as patient adherence [4, 9].

Basic therapy is the treatment of psoriasis with either non-medicated emollients or these vehicles infused with topical keratolytic agents such as salicylic acid [13]. Non-medicated emollients are typically applied once to three times daily [13]. There are no known contraindications to the use of emollients and they are considered safe for use in pediatric and pregnant or nursing patient populations [9]. Although incorporating the use of emollients is widely accepted as part of a multi-agent treatment regimen, there have not been any large clinical trials to support the efficacy of basic therapy as a monotherapy treatment [13]. Keratolytic agents such as salicylic acid are typically applied daily [9]. There are no specific indications for the use of topical keratolytic agents alone but it is known that use of keratolytics in conjunction with other topical medications results in increased efficacy and increased toxicity of the other medications due to increased absorption associated with the keratolysis [4, 6, 9]. Salicylic acid should not be used in patients with hepatic or renal dysfunction or in patients who are taking other salicylate drugs [9]. It is thought safe for use in pregnant and nursing patients but should be avoided in the pediatric population [9].

The corticosteroids are an important group of topical medications. This group includes everything from low strength formulations that may be purchased over the counter to potent prescription medications that may only be used for limited amounts of time on certain areas of the body [6, 13]. Efficacy and side effects of topical steroids are widely variable and are dependant on many factors including potency, vehicle, occlusion and patient compliance [9]. Corticosteroids are specifically indicated for plaque-type psoriasis and are usually applied one to two times daily [9]. High potency agents are more efficacious than lower potency agents, but in order to minimize adverse effects, typically the strength of the topical corticosteroid is decreased after the psoriasis symptoms start to improve [13]. There is little data regarding long-term usage of corticosteroids, as most clinical trials are short in duration. Local toxicities include skin atrophy, striae, purpura, rosacea, telangiectasias, and contact dermatitis [4, 9]. Systemic adverse effects include glaucoma, cataracts, and suppression of the hypothalamic-pituitary-adrenal axis [4, 9]. There is no baseline monitoring necessary to initiate treatment with a topical corticosteroid, but patients should be regularly examined for signs of local toxicities [9]. Topical corticosteroids are considered to be Category C for pregnant patients and their safety in nursing patients is unknown at this time [9]. They are acceptable for use in pediatric population with the knowledge that due to larger proportion of body surface area to body mass, their absorption and therefore risk of systemic side effects is increased [9].

Coal tar has a long history in the treatment of psoriasis. There are a plethora of formulations of coal tar, so standardization of this treatment is difficult [9]. Adverse effects include irritation and photosensitivity [9]. Additionally, coal tar has often been poorly tolerated by patients due to odor and staining, particularly in scalp use in patients with lighter hair. A foam vehicle is now available and lessens these cosmetic concerns [4]. Its use in pregnancy and in nursing mothers for short periods of time is approved, but caution is recommended in the pediatric population [9].

Anthralin, which is also known as dithranol, has a long history in the treatment of psoriasis but has seen a decline in use in recent years [9, 13]. It is applied to psoriatic lesions twice daily for 20 or 30 min at a time, and it is most frequently used in the inpatient population [9]. This medication is not recommended for long term maintenance but may also be used for 1–2 months on an outpatient basis [6]. The starting concentration is low at either 0.5 % if used for long term therapy or 1 % for short term therapy, and is then increased as tolerated [9]. Adverse effects include local irritation and discoloration of skin and clothing and there are no noted systemic toxicities [4, 6]. It is considered to be pregnancy category C and is caution is recommended in the pediatric population [9]. It is contraindicated in pustular and erythrodermic psoriasis [9].

Vitamin D analogues are recommended for the treatment of mild to moderately severe psoriasis and particularly for plaque-type psoriasis [9, 13]. Currently, in the United States, vitamin D

analogues are only commercially available as combination preparations with topical corticosteroids [9]. They are applied to lesions two times each day [9]. They may be used as monotherapy for lesions on the face or in intertriginous areas [4]. They are considered to be Category C in pregnant patients and are safe for use in pediatric patients [9]. There is no data regarding their use in nursing mothers. Some sources report that they can result in temporary and reversible elevation of serum calcium levels [9]. Other sources report that there is no effect on serum calcium levels with therapy extending up to a full year [4]. They can result in photosensitivity and local irritation [9, 13]. A systematic review of the literature regarding calcipotriol, a vitamin D analogue, in 2000 showed that although there was a high incidence of local irritation, very rarely did the medication have to be discontinued for this reason. It also showed that calcipotriol was as effective as high potency topical steroids at 8 weeks of therapy [20].

Pimecrolimus and tacrolimus are topical calcineurin inhibitors that are used off-label to treat facial and intertriginous psoriatic lesions due to the fact that they do not cause as much local irritation as many of the other topical medications [4, 13]. They are usually applied twice daily to the lesions, and there are no recommended durations on the length of treatment with these medications [9]. They are considered safe for use in pediatric patients at least 2 years of age. They are considered to be pregnancy category C [9]. Breakdown products of these medications are found in human breast milk, so they are therefore not recommended for use in nursing mothers [9]. The most common adverse effects include self-limited pruritis and/or burning sensation at the site of application, and there is a specific "black box warning" by the FDA against the use of these medications in patients with lymphoma [4, 9].

Topical retinoids are typically applied once each day to affected areas and are indicated for the treatment of plaque psoriasis [9]. They are considered to be pregnancy category X and are not recommended for use in nursing patients [4, 9]. These medications are approved for use in children 12 years and older for the treatment of acne but there is no data for their use in the treatment of pediatric psoriasis [9]. These medications work best when used together with topical vitamin D analogues or topical steroids and can even prevent local steroid atrophy [4, 9]. Common adverse effects include local inflammation and photosensitization [9]. They should not be used in intertriginous areas due to this propensity to cause local irritation [4].

## Phototherapy

Phototherapy and photochemotherapy have a long history in the treatment of dermatologic disorders, including psoriasis. Treatment with ultraviolet (UV) light produces good results and is very cost effective [10]. Before initiating therapy with UV light, patients should be thoroughly examined and an extensive history should be obtained [13]. UV therapy should be strictly avoided in patients with lupus erythematosus and xeroderma pigmentosum [13]. Patients with a history of or risk factors for cutaneous malignancy, including previous arsenic intake or exposure to ionizing radiation, should be carefully examined for lesions, and all patients should be well-educated [10, 13]. Skin types should be taken into consideration, and those with types I and II treated cautiously [10]. If patients are utilizing any photosensitizing mediations, care must be taken with the dosing of the medication as well as the dosing of the UV light [13]. Topical therapies such as coal tar and dithranol that result in photosensitivity may be intentionally administered in conjunction with phototherapy, but this practice lacks formal data and is mainly based upon expert recommendation [6]. All patients receiving UV therapy should have meticulous records with recordings of the cumulative UV dosages and total number of treatments they have received [6].

Phototherapy may consist of either UVA or UVB wavelengths. UVB light can be administered as broad band or narrow band therapy and is indicated for generalized psoriasis and guttate psoriasis [10]. For broad band UVB light therapy, patients tend to note amelioration of their

symptoms within 4 weeks of beginning therapy [14]. One course of therapy consists of 20–25 light sessions, and this is generally a sufficient amount to induce clearance [10]. Five percent of patients see remission after a year with broad band UVB light treatment and maintenance therapy can extend remission [10]. Narrow band UVB is more effective than broad band UVB [15]. For narrow band therapy, patients begin to see improvement in symptoms after eight to ten treatments. One course of therapy consists of 15–20 sessions and this is the average number of treatments required to induce clearance [10]. Acute adverse affects of UVB light include itching, burning and erythema. Chronic UVB exposure results in photoaging, carcinogenesis, solar lentigines and telangiectasias. Patients must wear eye protection during treatments to avoid risks of cataracts [14]. UVB light therapy is thought to be the safest treatment for both pregnant patients [14]. While experts feel that it is likely safe and preferable to utilizing more toxic systemic agents, there are not adequate studies in pediatric patient populations, so phototherapy should be used with caution in patients under the age of 18 [14].

Targeted phototherapy allows for the treatment of psoriatic lesions while sparing normal skin, which reduces the overall UV radiation exposure [10, 15]. The excimer laser is a device that delivers UVB radiation at 308 nm and is the primary mechanism for delivering this therapy [6]. Targeted phototherapy is indicated in patients with mild, moderate or severe psoriasis with <10 % of the total body surface area involved in the disease process [10]. One course of therapy generally consists of 10–12 treatments that are usually given a few times per week [10]. The average remission time for targeted phototherapy is 3.5–6 months and patients see improvement after just a few weeks of treatment [10]. Adverse effects include temporary hyperpigmentation and erythema [15]. While there have been no adequate studies performed in the pediatric patient population or in pregnant or nursing patients, experts agree that targeted phototherapy is safe in these populations [10, 14].

UVA light is more effective in the treatment of psoriasis than UVB light but has greater risks of carcinogenesis and photoaging [6]. It is typically administered in conjunction with photosensitizing compounds known as psoralens and so may be referred to as photochemotherapy or "PUVA." The psoralens may be administered topically or orally [14]. Oral psoralen plus UVA light is referred to as systemic PUVA and is indicated for generalized disease in adults who have been nonresponsive to topical therapy [10]. A single course of systemic PUVA consists of 20–25 treatments, which are usually administered between two and three times per week [10]. Improvement can be seen as soon as within a month of initiating the therapy with clearance within months [10]. PUVA may be used long term as maintenance therapy [10]. Remission times typically range between 3 and 12 months [6]. Contraindications to systemic PUVA include porphyria, lupus erythematosus and xeroderma pigmentosum [14]. Liver dysfunction can lead to the accumulation of dangerously high levels of psoralen, and other acute adverse effects include nausea and vomiting, dizziness, headache, itching, erythema, and blistering [10]. Chronic treatment may result in adverse effects, which include carcinogenesis, photoaging and lentigines. Prior to treatment initiation all patients should undergo a thorough skin exam to evaluate for malignancies and an eye exam [14]. If the patient history suggests the possibility of liver dysfunction or the possibility of an autoimmune disease, then liver enzymes or ANA panels may be indicated as well [10]. While undergoing PUVA therapy, patients should have regular full skin examinations [6]. If patients are not compliant with eye protection during treatments, they should also undergo a yearly eye examination as well [10]. Systemic PUVA is considered to be pregnancy category C [14]. Nursing is contraindicated for 24 hours after taking oral psoralen [10]. There are no studies in patients under the age of 18 for systemic PUVA, so this therapy should only be used with great caution in the pediatric patient population [14].

UVA therapy may also be given in conjunction with psoralens applied topically in emollients or as a bath. Topical PUVA is indicated for palmoplantar psoriasis and generalized psoriasis [10]. A single course of topical PUVA consists of 30–40

treatments, and it can be used to get control of episodic flares or may be used chronically as maintenance therapy [10]. Contraindications include porphyria, lupus erythematosus and xeroderma pigmentosum [14]. Acute adverse effects include hyperpigmentation, blistering and redness. In contrast to other forms of phototherapy, however, there has been no shown increased risk of skin cancer [10]. There are no drug interactions associated with this therapy and there is no indication for any baseline monitoring parameters [10]. For patients undergoing therapy, follow up is recommended to assess improvement in the disease symptoms as well as to monitor for erythema. Topical PUVA is considered to be pregnancy category C, and experts agree it can be used in pregnant patients with great caution [14, 15]. There have been no studies in nursing patients. It is felt safe for use in pediatric populations but there have not been any studies to look at rates of or effects of systemic absorption of psoralen in patients under the age of 18 years [10].

## Traditional Systemics

Methotrexate is indicated for generalized pustular psoriasis, moderate to severe plaque psoriasis, psoriatic arthritis, and disease that has not responded to other therapies [17]. It is an oral medication that is taken once weekly. Patients are typically given a test dose between 2.5 and 5 mg. The dose tapered up slowly until the patient has a good response to the medication but should not be greater than 30 mg/week [11]. The patient should be maintained on the lowest possible dose that will provide adequate relief from symptoms [11]. Thirty six percent of patients treated with methotrexate were able to achieve PASI-75 after 16 weeks of therapy [11]. This medication may be administered long term so long as the patient does not develop any adverse effects. The major adverse effects are hepatotoxicity, myelosuppression, and pulmonary toxicity [17]. Before initiation of this medication, patients should undergo a complete blood count (CBC), liver function tests (LFTs), a renal panel, and a full history and physical exam [13]. Women with childbearing potential should have a pregnancy test as this medication is pregnancy category X [14]. Patients with a history of liver disease should undergo a liver biopsy prior to methotrexate therapy, and patients with pulmonary disease should have a chest x-ray. Purified protein derivate (PPD) testing for tuberculosis and human immunodeficiency virus (HIV) screening should be considered as well. Patients typically are given concurrent treatment with folic acid, which is taken orally each day of the week except for the day that they take their methotrexate [17]. Patients taking methotrexate should have complete blood count every 2–4 weeks for the first several months that they are using the medication and then every 2–3 [2]. LFTs should be checked every month and renal function every 2–3 months [2]. After lifetime doses of 3.5–4 g, either patients should be switched to a different medication or liver biopsies should be considered [11]. It is approved for use in the pediatric population for juvenile rheumatoid arthritis and is considered safe for the treatment of psoriasis in children under the age of 18 [17]. Methotrexate does interact with a number of other medications so it is important to evaluate other treatments a patient may be receiving concurrently. Patients who are nursing should not use this medication [14].

Different guidelines give different indications for the use of cyclosporine in the treatment of psoriasis. By some guidelines cyclosporine is indicated for the treatment of patients with severe, recalcitrant psoriasis. Others indicate that it should be used for the treatment of moderate to severe psoriasis. It is generally used in short intervals to achieve clearance for patients who cannot tolerate or have failed other systemic medications. Long term maintenance using this medication is not recommended due to its adverse effects, primarily including renal dysfunction and hypertension [11]. Because of these toxicities, which are associated with long term use of this medication, in the US, it is recommended for use for only up to one year of continual treatment. In other countries it is approved for up to 2 years of continual use, but use for longer than 1 year is not recommended [11, 16]. Patients should have

a full history and physical exam including two blood pressure checks, two renal function panels with electrolytes, a urinalysis, LFTs, a CBC, a lipid panel, and uric acid level [16]. Tuberculosis screening should be considered as well prior to therapy. During the initial 3 months of treatment, patients should have blood pressure and renal function checks every other week. Subsequently these parameters should be checked monthly along with a CBC, LFTs, a lipid panel, electrolytes, and uric acid levels [16]. Women of child bearing potential should have a pregnancy test before initiating therapy with repeat testing throughout the course of treatment and be educated regarding the risks of becoming pregnant while taking cyclosporine. It is considered to be pregnancy category C. In transplant patients, it has been associated with low birth weights and shorter gestational periods, but this may be due to complications with the transplants themselves as opposed to this medication [16]. It has been noted that symptoms of psoriasis tend to lessen in pregnant patients, so in general it is recommended that patients be tapered off systemic agents during pregnancy [16, 21]. If it is necessary to continue an oral medication during pregnancy, cyclosporine is the only of the traditional systemic agents that should even be considered [16]. Breast feeding mothers should not use cyclosporine [14]. Dosing is weight based at 2.5–5.0 mg/kg/day divided BID. Sixty five percent of patients reported that their symptoms were cleared or very nearly cleared after just 8 weeks of therapy with 5 mg/kg/day. Up to 70 % reached a PASI 75 at 16 weeks [11]. Specific contraindications for cyclosporine are renal dysfunction, malignancies, current use of PUVA or UVB, methotrexate, immunosuppressive therapies, or coal tar [11]. Patients who have previously received radiation or more than 200 PUVA treatments in the past also should not use cyclosporine [16]. There are a number of medications that interact with cyclosporine, so the patient's medications must be thoroughly reviewed and the patient educated prior to therapy [16]. This medication is used safely in the pediatric transplant population but has not been formally studied in children with psoriasis [14].

Acitretin is indicated for the treatment of plaque type psoriasis in adults [11]. It can be administered with or without concurrent phototherapy. This medication is taken as orally once each day at doses between 10 and 50 mg [11]. There are not any studies that directly define the short or long term efficacy of this medication, and it is not recommended for routine use, but it is known that acitretin is more effective when given in combination with phototherapy [13]. If given concurrently with light therapy, the dose of the UV light should be decreased as well [13]. Prior to initiating therapy patients should have a complete history and physical exam, a lipid panel, CBC, LFTs, and renal function tests [11]. Patients with childbearing potential should undergo a pregnancy test before starting the medication and serially thereafter while taking the medication as acitretin is considered pregnancy category X [14]. LFTs and lipid profiles should be evaluated every 2 weeks for the first 8 weeks of therapy and then every 6 weeks to 3 months thereafter. A CBC and renal panel should be checked every 3 months while the patient continues the medication [11]. Adverse effects of this medication include GI symptoms like nausea and vomiting as well as CNS symptoms such as headache, pseudotumor cerebri, and paresthesias. This medication has not been studied in the pediatric population for the treatment of psoriasis. Prolonged use of acitretin in children for the treatment of other disorders has been associated with adverse musculoskeletal effects [11].

## Second Tier Systemic Agents

There are quite a few other oral medications that are used primarily in the treatment of other medical issues, such as transplant rejection prophylaxis or for inflammatory joint or bowel disease, which have been used off-label for the treatment of psoriasis. These include hydroxyurea, azathioprine, 6-thioguanine, fumaric acid esters, leflunomide, mycophenolate mofetil, tacrolimus and sulfasalazine [11]. Because these medications are used less frequently for psoriasis, there is not as much data regarding their use for this illness, and

they are not as frequently included in the treatment guidelines for psoriasis as the other medications discussed in this chapter. Both the South African guidelines and the guidelines published by the American Academy of Dermatology (AAD) discuss hydroxyurea and sulfasalazine, and the use of fumaric acid esters is included in the various publications out of Europe, where this medication is available. The remainder of these treatments are only discussed thoroughly in the guidelines published by the AAD in the section devoted to treatment of psoriasis with systemic therapies.

Hydroxyurea is an immunosuppressive agent that has been used for decades in the treatment of hematologic disorders and is used off label for psoriasis [11]. Typically 500 mg is taken by mouth twice daily, and this is eventually increased up to 3 g/day [6]. Short term results are unclear, but by 16 months, 60 % of patients treated with hydroxyurea near or total resolution of their symptoms [6]. Prior to taking this medicine, patients should have a full history and physical exam, and a CBC [11]. Women of childbearing potential should have a pregnancy test prior to therapy and serially thereafter while taking the medication as it is considered to be pregnancy category D [6]. Patients should have a monthly CBC and twice-yearly physical exams focusing on the skin and lymph nodes due to potential for bone marrow suppression and development of cutaneous squamous cell carcinomas [11].

Azathioprine is an oral immunosuppressant that is taken daily. Patient suitability for therapy with this medication is ultimately dependent on the patient's expression of the enzyme thiopurine methyltransferase (TPMT) as deficiencies of TPMT lead to myelotoxicity and cytopenia with azathioprine. Either the patient's level of TPMT must be measured before initiating the medication with dosing based on TPMT expression, or the medication is started very low at 0.5 mg/kg/day and the patient is monitored for cytopenia. For the latter, if the patient develops no adverse effects in the first 2 months of treatment, then the dose is increased every month by 0.5 mg/kg/day to a maximum of 75–150 mg/day. Monitoring involves testing for tuberculosis and hepatitis plus following CBCs and LFTs. At least twice a year patients should have a focused exam of skin and lymph nodes due to increased risk of cutaneous squamous cell carcinomas and lymphoproliferative disorders with this medication.

6-Thioguanine is a breakdown product of azathioprine that has been noted to be more efficacious than azathioprine itself. Dosing begins at 80 mg orally two times per week. It is typically increased by 20 mg either biweekly or monthly to a maximum of 160 mg orally three times per week. Screening and monitoring is similar to that for azathioprine. Contraindications include liver disease, immunosuppression, malignancy and hematologic abnormalities such as anemia, leucopenia, or thrombocytopenia as myelosuppression and hepatic dysfunction are potential side effects. This medication is pregnancy category D, so patients with childbearing potential should have a pregnancy test prior to therapy and serially while taking the medication. If patients become pregnant, they should discontinue the medication immediately. Males taking this medication should use contraceptives and this medicine should not be taken by nursing patients [11].

Fumaric acid esters are commonly used in Europe but are not officially FDA approved in the United States for the treatment of psoriasis [11]. Fumaderm is a brand name fumaric acid ester that contains 120 mg of dimethylfumarate, 87 mg of calcium monoethylfumarate and 3 mg of zinc monoethylfumarate per tablet [11]. Dosing typically begins with 1 tablet daily and can be increased up to 6 tablets daily, and is usually escalated slowly over 8 weeks [11]. Overall, patients reported about a PASI-50 after treatment for both 9 weeks and 16 weeks [11]. Although further investigations should be conducted, case series have demonstrated no increased incidence of malignancies or infections in patients on maintenance fumaric acid ester therapy [18]. Patients should undergo a full history and physical exam, a CBC with platelets, serum chemistry, and a urinalysis prior to initiating therapy with fumaric esters [11]. Patients should have a CBC with platelets, serum chemistry, and urinalysis every other week for the first 8 weeks and then every 4 weeks for the next 4 months and then every 2

months thereafter [11]. Adverse effects include fatigue, malaise, GI complaints, and hematologic abnormalities such as lymphopenia, eosinophilia, and leucopenia. Hepatotoxicity, abnormalities in renal function and abnormal lipid profiles also may occur, so this medication is contraindicated in patients with severe or chronic liver, kidney of gastrointestinal diseases [18]. If these adverse effects occur, the medication may be stopped suddenly without concern for rebound [18]. This medication should not be used by pregnant or nursing mothers or in patients with a history of malignancy or hematologic abnormalities [18]. It should not be used in conjunction with phototherapy for longer than 4 weeks [18]. There is no data regarding use in children under than age of 18 and minimal evidence to support its efficacy in the treatment of psoriatic arthritis [18].

Leflunomide is a medication for rheumatoid arthritis that has more recently been examined for off label use as a treatment of psoriatic arthritis and psoriasis [11]. This medication is dosed at 100 mg for the first 3 days followed by 20 mg/day thereafter. No long term results have been reported thus far and short term trial showed that 17 % of patients were able to achieve a PASI-75 after 24 weeks of therapy. CBCs and LFTs should be checked before and trended throughout therapy. As the medication is pregnancy category X testing is indicated for women of childbearing potential prior to and throughout therapy [11].

Mycophenolate mofetil is another immunosuppressive medication that is also used off label to treat psoriasis. While there is no long term efficacy data, patients saw an average of 47 % PASI reduction after 6 weeks and 12 weeks of therapy [11]. Complete metabolic panels and LFTs should be trended throughout therapy. This medication is pregnancy category D, so patients with childbearing potential should have a pregnancy test prior to therapy and serially while taking the medication. Males taking this medication should use contraceptives [11].

Tacrolimus is a calcineurin inhibitor often used in transplant patients to prevent rejection that has also been used off label for the treatment of psoriasis. One study showed a statistically significant improvement in PASI after 9 weeks of therapy, but in general, efficacy rates have not been well defined [11]. While on this medication patients should have routine checks of CBCs, LFTs, and their blood pressures should be followed as well [11]. This medication is pregnancy category C. Toxicities include abnormal renal function, hypertension and hepatotoxicity [11].

Sulfasalazine is an anti-inflammatory medication most frequently used to treat inflammatory bowel disease and rheumatoid arthritis [6]. It is used off label to treat psoriasis. Dosing starts at 500 mg orally twice daily and is escalated to up to 3 or 4 g/day [6]. There is not much data regarding efficacy rates, but the medication may be used long term without any additional issues. CBCs and LFTs should be evaluated before and throughout the duration of the use of this medication. It is pregnancy category D, so patients with childbearing potential should have a pregnancy test prior to therapy and serially while taking the medication. There is no data for use of this medicine in the pediatric population. In one study for the treatment of psoriatic arthritis, 45 % of patients treated with sulfasalazine achieved response criteria [11].

## Biologics

Six medications for the treatment of psoriasis fall into the category known as the biologics. These medications are either recombinant DNA products or are purified from animals. Alefacept and efalizumab target T cells while infliximab, adalimumab and etanercept inhibit tumor necrosis factor (TNF). Efalizumab has been taken off of the market due to safety concerns [7]. Ustekinumab is a newer medication that targets IL-12 [15].

Alefacept is indicated for the treatment of moderate to severe psoriasis. It is administered weekly with either 15 mg intramuscular or 7.5 mg intravenous injection [6]. One treatment course consists of 24 weeks. For the first 12 weeks, patients receive the weekly injections followed by 12 weeks without injections [6]. Approximately 1/5 of patients will see improvement at week 14 [7]. This medication is indicated

only for intermittent use and treatment courses can be repeated only twice per year [15]. For baseline monitoring, a CD4 count is checked [7]. While undergoing therapy, patients must have a CD4 count checked every 2 weeks. If the CD4 count dips below 250, this medication should be held and stopped completely if it remains this low for greater than 4 weeks [6]. Alefacept is considered to be pregnancy category B [7]. The major contraindication is HIV infection [7]. In 2011 the manufacturer of alefacept also withdrew the drug from the market, although due to business needs not due to a re-assessment of safety or efficacy.

Efalizumab is a recombinant human monoclonal antibody that was initially approved for moderate to severe psoriasis [7]. Due to patients developing severe infections, including several cases of progressive multifocal leukoencephalopathy, this medication has been taken off the market [6].

All three of the TNF inhibitors are approved for the treatment of moderate to severe psoriatic arthritis, moderate to severe psoriasis, adult rheumatoid arthritis and ankylosing spondylitis. Adalimumab and Etanercept are also approved for the treatment of juvenile rheumatoid arthritis in patients as young as 4 years old [7]. Both adalimumab and infliximab are approved for the treatment of Crohns disease, and infliximab is also approved for treatment of ulcerative colitis [7]. All three medications require screening for tuberculosis, liver function tests, and complete blood counts prior to initiation of therapy [7]. If using adalimumab or infliximab, patients should also undergo a hepatitis profile. Both hepatitis B and tuberculosis reactivation have been noted in patients treated with anti-TNF medications [13]. All patients using TNF inhibitors should have yearly tuberculosis screening, periodic history and physical examinations, CBCs, and LFTs [13]. All three medications are considered to be pregnancy category B [13].

The TNF inhibitors have been linked to demyelinating diseases and so should not be used in patients who have a history of or risk factors for such disorders [15]. In general, TNF inhibitors are contraindicated in patients who have ongoing infections [13]. Additionally, there has been an association with anti-TNF medications and congestive heart failure (CHF) [7]. Patients have experienced both new-onset and worsening of this chronic medical condition so caution should be exercised when treating patients with CHF [7]. There have also been a few reports of malignancies associated with treatment with these medications. Infliximab was specifically associated with hepatosplenic T-cell lymphoma in the pediatric population [7].

Adalimumab is a human monoclonal antibody to TNF-α. It is not a weight based dosing and all patients are given 80 mg subcutaneously in the first week followed by 40 mg the second week. Thereafter, patients are given 40 mg by subcutaneous injection every other week [15]. There have been reports of painful injection site reactions. 80 % of patients treated with this medication are able to achieve PASI-75 by 12 weeks of treatment [7].

Etanercept is a recombinant human TNF-α inhibitor. Like adalimumab, etanercept is also not dosed based on patient weight. Either 25 or 50 mg is administered by subcutaneous injection twice weekly for the first 3 months [14]. If the patient has responded by 24 weeks, then the dose subsequently reduced to 50 mg/week [7]. If the patient has not responded by 24 weeks, then experts believe the clinician should consider continuing the 50 mg twice-weekly dosing schedule [15]. There have been reports of mild pruritis at the site of medication injection [7]. After 12 weeks of therapy, at least a third of patients achieved a PASI-75 [14]. Although caution must be exercised with this medication in patients with medical conditions or risks previously mentioned for all anti-TNF medications, the only specific contraindication to utilizing etanercept is sepsis [7]

Infliximab is a chimeric monoclonal anti-TNF antibody made from murine and human DNA [13]. This medication utilizes a weight based dosing schedule with 5 mg/kg intravenous infusions. The second dose is given 2 weeks after the first dose, the third dose 4 weeks after the second dose. Thereafter it is usually administered every 6–8 weeks but this interval may be tailored to

individual patient responses and needs [7]. By 10 weeks of treatment, 80 % of patients had achieved a PASI-75 and 61 % of patients had a PASI-75 at 50 weeks of treatment [7]. There are reported instances of people developing infusion reactions or serum sickness with this medication [7].

Ustekinumab is a newer human monoclonal antibody that inhibits IL-12 an IL-23 [15].

For patients weighing less than 100 kg, 45 mg is injected subcutaneously in the first week and again in the fourth week. It is thereafter administered every 12 weeks. If the patient weighs more than 100 kg, the dosing is doubled at 90 mg [15]. Up to 80 % of patients achieved a PASI-75 with prolonged use and although longer term studies are lacking, there were no initial concerns for increased risk of infection or malignancy with the preliminary data [15, 22, 23].

### Conclusion

There are a multitude of treatments for psoriasis and no shortage of recommendations on how to utilize them. This chapter has reviewed some of the guidelines published by the most respected dermatologic organizations in various countries. Certainly, this is by no means an exhaustive review of the published literature, but hopefully, it will provide an insight into what is available regarding the treatment of psoriasis.

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# Appendix 1

## TREATMENT COMPARISON

National Psoriasis Foundation
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*getinfo@psoriasis.org* | *www.psoriasis.org*

| TRADITIONAL SYSTEMIC TREATMENTS AND LIGHT THERAPY (SEE REVERSE FOR BIOLOGIC TREATMENTS) | | | | |
|---|---|---|---|---|
| **TREATMENT TYPE**<br>For moderate to severe psoriasis and psoriatic arthritis | **Light therapy** | **Methotrexate** | **Cyclosporine** | **Soriatane** |
| **INDICATION**<br>Which diseases the drug treats | **Psoriasis** | **Psoriasis**<br>**Psoriatic arthritis** | **Psoriasis** | **Psoriasis** |
| **METHOD OF DELIVERY**<br>How the drug is given or taken | Exposure to ultraviolet light B (UVB) or ultraviolet light A (UVA) in doctor's office or home setting | Orally via liquid or pill or by subcutaneous injection | Orally via liquid or capsule | Orally via capsule |
| **FREQUENCY**<br>How often the drug must be taken | Up to 3 times per week | Once per week; doses may be divided and taken three times over 24 hours | Daily | Daily |
| **DURATION**<br>How long the drug must be taken | Variable, averaging 12 weeks | Continuously to maintain results | Up to one year maximum | Continuously to maintain results |
| **COMMON SIDE EFFECTS**<br>A side effect is an undesirable secondary effect of a medication. Side effects may vary for each individual depending on disease state, age, weight, gender, ethnicity and general health. All medications have side effects. | • Itching<br>• Redness of the skin | • Nausea<br>• Tiredness<br>• Difficulty sleeping<br>• Light headedness<br>• Mouth ulcers<br>• Vomiting<br>• Headache<br>• Easy bruising<br>• Fever<br>• Chills | • Decreased kidney function<br>• Headache<br>• High blood pressure<br>• High cholesterol<br>• Skin sensitivity<br>• Flu-like symptoms<br>• Upset stomach<br>• Tiredness<br>• Musculoskeletal pain | • Hair loss<br>• Chapped lips<br>• Dry skin<br>• Bleeding gums<br>• Peeling fingertips<br>• Changes in blood-fat levels<br>• Depression<br>• Headache<br>• Joint pain |
| **POSSIBLE RISKS**<br>The possible risks listed include serious adverse events that have been reported in association with these medications during and after clinical trials. | • UVB: Skin burn, skin cancer<br>• PUVA (UVA with drug psoralen): Skin cancer<br>• Wrinkling<br>• Itching<br>• Nausea | • Liver damage<br>• Birth defects<br>• Reduced white blood cell count<br>• Increased toxicity in patients with poor kidney function | • Kidney damage<br>• Skin malignancies<br>• Hypertension<br>• Excessive hair growth<br>• Tremor | • Birth defects<br>• Elevated cholesterol<br>• Liver damage |
| **MONITORING**<br>Some adverse reactions can be detected by laboratory tests such as blood counts or liver function tests. | Monitoring for skin cancer | Complete blood count<br>Chem screen (liver, kidney function)<br>Occasional liver biopsies | Blood pressure monitoring<br>Kidney function monitoring | Liver enzyme testing<br>Cholesterol screening<br>Triglyceride monitoring |

J.M. Weinberg, M. Lebwohl (eds.), *Advances in Psoriasis*,
DOI 10.1007/978-1-4471-4432-8, © Springer-Verlag London 2014

| BIOLOGIC TREATMENTS (SEE REVERSE FOR TRADITIONAL SYSTEMIC TREATMENTS AND LIGHT THERAPY) | | | | | | |
|---|---|---|---|---|---|---|
| **TREATMENT TYPE**<br>For moderate to severe psoriasis and psoriatic arthritis | **Cimzia**<br>*Certolizumab pegol* | **Enbrel**<br>*Etanercept* | **Humira**<br>*Adalimumab* | **Remicade**<br>*Infliximab* | **Simponi**<br>*Golimumab* | **Stelara**<br>*Ustekinumab* |
| **INDICATION**<br>Which diseases the drug treats | Psoriatic arthritis | Psoriasis<br>Psoriatic arthritis | Psoriasis<br>Psoriatic arthritis | Psoriasis<br>Psoriatic arthritis | Psoriatic arthritis | Psoriasis<br>Psoriatic arthritis |
| **METHOD OF DELIVERY**<br>How the drug is given or taken | Subcutaneous injection by a health care professional, or self-injection | Subcutaneous self-injection | Subcutaneous self-injection | Intravenous infusion by health care professional | Subcutaneous self-injection | Subcutaneous injection by a health care professional, or self-injection |
| **FREQUENCY**<br>How often the drug must be taken | Week 0, week 4, then every 3 months | 1-2 times weekly | Every other week | 3 times in first 6 weeks, then every 8 weeks | Monthly | Week 0, week 4, then every 3 months |
| **DURATION**<br>How long the drug must be taken | Continuously to maintain results | Continuously to maintain results | Continuously to maintain results | Continuously to maintain results | Continuously to maintain results | Continuously to maintain results |
| **COMMON SIDE EFFECTS**<br>A side effect is an undesirable secondary effect of a medication. Side effects may vary for each individual depending on disease state, age, weight, gender, ethnicity and general health. All medications have side effects. | • Upper respiratory infections<br>• Rash<br>• Urinary tract infections<br>• Headache<br>• Fatigue<br>• Nausea | • Injection site reactions<br>• Upper respiratory infections<br>• Headaches | • Injection site reactions<br>• Upper respiratory infections<br>• Headaches<br>• Rash<br>• Nausea | • Respiratory infections<br>• Headache<br>• Rash<br>• Coughing<br>• Stomach pain | • Upper respiratory infection<br>• Nausea<br>• Abnormal liver tests<br>• Injection site reactions<br>• High blood pressure<br>• Bronchitis<br>• Dizziness<br>• Flu | • Upper respiratory infections<br>• Headache<br>• Tiredness<br>• Fatigue |
| **POSSIBLE RISKS**<br>The possible risks listed include serious adverse events that have been reported in association with these medications during and after clinical trials. | • Serious infection<br>• Nervous system problems<br>• New or worsening heart failure<br>• Allergic reactions<br>• Lupus-like syndrome<br>• Malignancies<br>• Hepatitis B reactivation | • Serious infection<br>• Nervous system problems<br>• New or worsening heart failure<br>• Allergic reactions<br>• Lupus-like syndrome<br>• Lymphoma<br>• Hepatitis B reactivation<br>• Skin cancer | • Serious infection<br>• Nervous system problems<br>• New or worsening heart failure<br>• Allergic reactions<br>• Lupus-like syndrome<br>• Lymphoma<br>• Hepatitis B reactivation<br>• Skin cancer | • Serious infection<br>• Nervous system problems<br>• New or worsening heart failure<br>• Allergic reactions<br>• Lupus-like syndrome<br>• Lymphoma<br>• Hepatitis B reactivation<br>• Skin cancer<br>• Anaphylaxis<br>• Liver enzyme abnormalities | • Hepatitis B reactivation<br>• New or worsening heart failure<br>• Nervous system problems<br>• Liver failure<br>• Low blood count<br>• Lupus-like symptoms<br>• Allergic reactions<br>• Lymphoma | • Increased risk of serious infections<br>• Reactivation of latent infections, including tuberculosis<br>• Reversible Posterior Leukoencephalopathy Syndrome<br>• Hypersensitivity reactions |
| **MONITORING**<br>Some adverse reactions can be detected by laboratory tests such as blood counts or liver function tests. | Tuberculosis screening<br>Annual blood count and liver function tests | Tuberculosis screening<br>Annual blood count and liver function tests | Tuberculosis screening<br>Annual blood count and liver function tests | Tuberculosis screening<br>Annual blood count and liver function tests | Tuberculosis screening<br>Annual blood count and liver function tests | Tuberculosis screening |



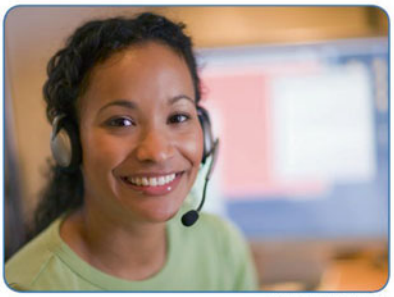
*Last updated October 2013*

# Appendix 2

NATIONAL PSORIASIS FOUNDATION®

FACT SHEET

## Financial Assistance



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There are many programs that provide financial assistance to help with accessing health care and treatment for psoriasis and psoriatic arthritis. The following list offers resources provided by pharmaceutical companies, government and nonprofit organizations. Start with the manufacturer of your drug, as the company may be able to offer the fastest assistance. If you do not find your medical treatment listed below or need more information, go to the National Psoriasis Foundation's website at: ***www.psoriasis.org/financial-assistance.***

### Pharmaceutical Patient Assistance Programs

**Cimzia** (UCB, Inc.)
*www.cimzia.com*
*866.424.6942*

**Enbrel** (Amgen)
*www.enbrel.com*
888.436.2735

**Humira** (AbbVie)
*www.humira.com*
800.448.6472

**Otezla** (Celgene Corporation)
*www.otezla.com*
844.468.3952

**Remicade** (Janssen Biotech, Inc.)
*www.remistart.com*
888.222.3771

**Simponi** (Janssen Biotech, Inc.)
*www.simponione.com*
866.317.2775

**Stelara** (Janssen Biotech, Inc.)
*www.stelarainfo.com*
877.783.5272

**Clobex** (Galderma USA)
*www.clobex.com*
855.431.3737 (uninsured)
877.264.2440 (coupon card)

**Gengraf Cyclosporine** (AbbVie)
*www.abbviepaf.org*
800.222.6885

**Neoral Cyclosporine**
**Sandimmune Cyclosporine** (Novartis)
*www.patientassistancenow.com*
800.277.2254

**Soriatane**
**Olux Foam** (GlaxoSmithKline)
*www.bridgestoaccess.com*
866.728.4368
*www.gsk-access.com* (Medicare only)
866.518.4357

**Taclonex Scalp Topical Suspension** (LEO Pharma)
*www.taclonex.com*
855.227.3536

**Tazorac** (Allergan)
*www.rxhope.com/allergan*
800.553.6783

**Vectical** (Galderma)
*https://galdermapap.cdfservices.net*
866.730.5074

## Discount Medication Access Programs

**NeedyMeds, Inc.**
*www.needymeds.org*
800.503.6897

**RxHope**
*www.rxhope.com*
8.267.0517

**Partnership for Prescription Assistance**
*www.pparx.org*
888.477.2669

**RxOutreach**
*www.rxoutreach.com*
800.769.3880

**Xubex**
*www.xubex.com*
866.699.8239
Medications are offered to qualified individuals at a discount rate. Will also offer help to those with Medicare Part D. An administrative fee is applied per prescription.

**Prescription Hope**
*www.prescriptionhope.com*
877.296.4673
Offers assistance to those who are underinsured or fall in the Medicare Donut Hole. There is a $20 annual fee. Most medications are $18 per prescription.

## Co-Pay Assistance Programs

These programs offer help to insured patients who have exhausted company programs or who are on Medicare Part D. Availability of funding can vary so check with all of the programs periodically for the current funding status.

**Healthwell Foundation**
*www.healthwellfoundation.org*
800.675.8416

**Chronic Disease Fund**
*www.cdfund.org*
877.968.7233

**Patient Access Network Foundation**
*www.panfoundation.org*
866.316.7263

**Patient Advocate Foundation**
*www.copays.org*
866.512.3861

**The Assistance Fund**
*www.theassistancefund.org*
855.845.3663

## Other Resources

**Medicare and Medicaid**
*www.cms.hhs.gov*
800.772.1213

**State health insurance assistance programs**
*www.hapnetwork.org/ship-locator*
202.737.6340

**Resources for applying for disability**
*www.psoriasis.org/access-care/disability*

**Find a free or low-cost clinic:**
*www.freeclinics.us*
*www.needymeds.org*

**Access to help with housing, utilities, food:**
*www.211.org*
*www.eldercare.gov;* 800.677.1116

6600 SW 92nd Ave., Suite 300 · Portland, OR 97223 · 800.723.9166 · *education@psoriasis.org* · *www.psoriasis.org*

March 2014 – KC

# Appendix 3

**Sample letter to health plan on behalf of patient—home phototherapy**

**This letter is only an example**. Please edit the letter to suit your needs and replace **bold** sections.

[**Today's date**]

[**Name of medical director**]
[**Name of insurance company**]
[**Street address**]
[**City**] [**State**] [**ZIP code**]

Dear [**name of medical director**],

[**Name of patient** (**Insurance ID** #)] is under my care for **his/her** psoriasis. [**Name of patient**] has received [**name of light therapy used here**] with excellent response to this modality. In addition, **he/she** has an excellent response to natural UV sunlight. However, it is increasingly difficult for **him/her** to undergo out-patient phototherapy due to the frequency of prescribed treatments per week and the associated travel time.

I anticipate that this patient's need for on-going treatment with UVB light therapy will be continuous due to the chronic nature of this disease and due to the fact that **his/her** psoriasis flares when this therapy is interrupted. Therefore, I feel that **he/she** is an excellent candidate for a home UVB phototherapy unit. Allowing for this coverage will be more cost effective over the long term, as the continuation of light treatments in an out-patient setting will far exceed the initial cost of purchasing a home unit.

Although **he/she** also may be a potential candidate for alternative systemic therapies such as [**list systemic treatments here**], I feel that home phototherapy would offer the safest, most convenient and most cost-effective treatment option [**review patient's treatment history including treatment failure and contraindications to other therapies. Be sure to address how the patient meets any pre-authorization requirements or why an exception should be made**].

Psoriasis can have a significant negative impact on a patient's health. Lack of appropriate treatment for psoriasis can result in serious adverse impacts to functioning, including loss of mobility, pain, isolation and depression, and may contribute to comorbid conditions. There is an increased risk for psoriasis patients developing other serious conditions such as heart disease, stroke, hypertension and diabetes.[1] Research studies have established that the risk of premature death is 50 % higher for people with severe psoriasis and that these individuals die 4 years younger, on average, than those without psoriasis.[2] Access to treatment is important to prevent much of the disability and psychosocial impacts of the disease.

If you have additional questions regarding this patient, please do not hesitate to contact me.

[1] National Psoriasis Foundation. Psoriasis and comorbid conditions issue brief. 2012. http://www.psoriasis.org/document.doc?id=410.

[2] Gelfand JM, Troxel AB, Lewis JD, Kurd SK, Shin DB, Wang X, Margolis DJ, Strom BL. The risk of mortality in patients with psoriasis: results from a population-based study. Arch Dermatol. 2007;143(12):1493–9.

Sincerely,

**Physician name**
**Physician address**
**City**, **State ZIP code**
**Phone number**

CC: **Name of patient**
Leah Howard, Director of Government Relation and Advocacy, National Psoriasis Foundation

# Appendix 4

**Sample letter to health plan on behalf of patient—switching biologics**

**This letter is only an example**. Please edit the letter to suit your needs and replace **bold** sections.

[**Today's date**]

[**Name of medical director**]
[**Name of insurance company**]
[**Street address**]
[**City**] [**State**] [**ZIP code**]

Dear [**name of medical director**],

[**Name of patient** (**Insurance ID #**)] is under my care for **his/her** severe psoriasis. In the past **he/she** has been treated with numerous therapies including [**name of biologic**]. However, **he/she** was unable to tolerate [**name of biologic**] because [**list all contraindications**, **ineffectiveness or intolerances**, **here**]. Therefore I feel that [**name of patient**] is no longer a candidate for [**name of biologic**], and have recommended that **he/she** begin a course of [**name of biologic**]. [**Be sure to address how the patient meets any pre-authorization requirements or why an exception should be made**.]

It is not unusual for patients to cycle through different treatments for their psoriasis as medications work differently for different people and also may lose effectiveness over time.

Lack of appropriate treatment for psoriasis can result in serious adverse impacts to functioning, including loss of mobility, pain, isolation and depression, and may contribute to comorbid conditions. There is an increased risk for psoriasis patients developing other serious conditions such as heart disease, stroke, hypertension and diabetes.[3] Research studies have established that the risk of premature death is 50 % higher for people with severe psoriasis and that these individuals die 4 years younger, on average, than those without psoriasis.[4] Access to treatment is important to prevent much of the disability and psychosocial impacts of the disease.

I request that you review the recently published evidence-based guidelines of care for psoriasis and psoriatic arthritis produced by the American Academy of Dermatology and available at http://www.aad.org/research/guidelines/index.html. These guidelines touch on the points raised in this letter and provide an overview of treatment protocols for psoriasis and psoriatic arthritis.

If you have additional questions regarding this patient, please do not hesitate to contact me.

[3] National Psoriasis Foundation. Psoriasis and comorbid conditions issue brief. 2012. http://www.psoriasis.org/document.doc?id=410.

[4] Gelfand JM, Troxel AB, Lewis JD, Kurd SK, Shin DB, Wang X, Margolis DJ, Strom BL. The risk of mortality in patients with psoriasis: results from a population-based study. Arch Dermatol. 2007;143(12):1493–9.

Sincerely,

**Physician name**
**Physician address**
**City**, **State ZIP code**
**Phone number**

CC: **Name of patient**
Leah Howard, Director of Government Relations and Advocacy, National Psoriasis Foundation

# Appendix 5

**Sample letter to health plan on behalf of patient—appealing a denial**

This letter is only an example. Please edit the letter to suit your needs and replace **bold** sections.

[**Today's date**]

[**Name of medical director**]
[**Name of insurance company**]
[**Street address**]
[**City**] [**State**] [**ZIP code**]

Dear [**Name of medical director**],

I am contacting you on behalf of my patient, [**Name of patient** (**Insurance ID #**)]. [**Name of insurance company**] has denied **his/her** claim for name of [**therapy/drug**] for **his/her** psoriasis and/or psoriatic arthritis. Please consider this letter a formal, written appeal of your denial of this medically necessary therapy.

Psoriasis is a noncontagious, chronic, inflammatory, painful, disfiguring and disabling disease for which there is no cure. It is often accompanied by psoriatic arthritis, a specific form of arthritis that is painful and debilitating and causes joint damage. Psoriasis appears on the skin, most often as red, scaly patches that itch and may bleed, and it requires sophisticated medical care. Access to treatment is important to prevent much of the disability and psychosocial impacts of the disease.

Lack of appropriate treatment for psoriasis can result in serious adverse impacts to functioning, including loss of mobility, pain, isolation and depression, and may contribute to comorbid conditions. There is an increased risk for psoriasis patients developing other serious conditions such as heart disease, stroke, hypertension and diabetes.[5] Research studies have established that the risk of premature death is 50 % higher for people with severe psoriasis and that these individuals die 4 years younger, on average, than those without psoriasis.[6]

In view of [**Name of patient's**] signs, symptoms and history, I feel [**therapy/drug**] is medically necessary. [**Explain the benefit/efficacy of the therapy/drug to this specific patient**, **and review patient's treatment history including treatment failure and contraindications to other therapies. Be sure to address how the patient meets any pre-authorization requirements or why an exception should be made**.]

[5] National Psoriasis Foundation. Psoriasis and comorbid conditions issue brief. 2012. http://www.psoriasis.org/document.doc?id=410.

[6] Gelfand JM, Troxel AB, Lewis JD, Kurd SK, Shin DB, Wang X, Margolis DJ, Strom BL. The risk of mortality in patients with psoriasis: results from a population-based study. Arch Dermatol. 2007;143(12):1493–9.

I request that you review the recently published evidence-based guidelines of care for psoriasis and psoriatic arthritis produced by the American Academy of Dermatology and available at http://www.aad.org/research/guidelines/index.html. These guidelines touch on the points raised in this letter and provide an overview of treatment protocols for psoriasis and psoriatic arthritis.

If you have any further questions regarding this patient, please do not hesitate to contact me.

Sincerely,

**Physician name**
**Physician address**
**City**, **State ZIP code**
**Phone number**

CC: **State Insurance Commissioner**
**Name of patient**
Leah Howard, Director of Government Relations and Advocacy, National Psoriasis Foundation

# Index



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