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INVITED REVIEW

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A molecule solves psoriasis? Systemic therapies for psoriasis inducing interleukin 4 and Th2 responses

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Abstract Psoriasis is an autoimmune disease affecting 2–4% of the Caucasian population. Inflammatory processes induce the migration of interferon (IFN) γ producing Th1 lymphocytes into the skin. These play a key role in the pathogenesis of psoriasis. These Th1 lymphocytes are responsible for the pathological reactions in psoriatic skin leading to keratinocyte hyperproliferation, small vessel proliferation and neutrophilic infiltration. Antigen-presenting cells activate dermal $CD4^+$ T lymphocytes, and various signals can support the polarization of Th1 responses. The main signal for Th1 development is interleukin (IL) 12. After binding to their receptors both IL-12 and IFN-γ promote intracellular IFN-γ production by activating signal transducer and activator of transcription (STAT) 4 or 1. STAT1 activation by IFN-γ is followed by T-bet activation, a master transcription factor for Th1 lymphocytes. In experimental models of Th1-mediated autoimmune diseases immune deviation of polarized autoreactive Th1 into anti-inflammatory Th2 responses generally improves the disease. Therefore new therapeutic approaches based on immunomodulating molecules have been developed for psoriasis, a prototypical Th1-mediated autoimmune disorder. Recently IL-4, the most effective Th2-inducing cytokine, has been shown to be safe and efficient for treating psoriasis. Improvement was associated with the induction of a Th2 phenotype of skin infiltrating lymphocytes. This review summarizes the IL-4 inducing potential of various conventional and newer systemic therapies for psoriasis. Many of these were thought to be primarily immunosuppressive. A review of the literature reveals that most of them can induce IL-4 and Th2, and that Th2 induction may be an underestimated mode of action in the therapy of Th1-mediated autoimmune disease. Further studies are needed to determine the central role of IL-4 in the control of Th1-induced autoimmune disease, namely psoriasis.

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Abbreviations *APC:* Antigen-presenting cells · *DC:* Dendritic cells · *EAE:* Autoimmune encephalomyelitis · *FAE:* Fumaric acid ester · *IFN:* Interferon · *IL:* Interleukin · *IκB:* Inhibitor protein of nuclear transcription factor κB · *MHF:* Methylhydrogen fumarate · *NF:* Nuclear factor ·

NFAT: Nuclear factor of activated T cells · *PASI:* Psoriasis Area and Severity Index · *STAT:* Signal transducer and activator of transcription · *Th:* T helper cell · *TNF:* Tumor necrosis factor

Introduction

Psoriasis is an inflammatory autoimmune disease induced by autoreactive interferon (IFN) γ producing T helper cell (Th) 1 lymphocytes which orchestrate other cellular reactions, resulting in hyperproliferation of keratinocytes, concomitant inflammation, and dermal proliferation of small vessels (Fig. 1) [1]. This autoimmune disease of the skin and joints affects 2–4% of the population in Europe and the United States [2]. Disease development requires the conjunction of genetic and environmental factors leading to proinflammatory signals and differentiation of Th1 lymphocytes. Genetic predisposition for psoriasis includes linkage with certain human leukocyte antigens such as HLA-Cw6 and HLA-DR7, "psoriasis susceptibility" gene loci termed as PSORS 1–7, and gene polymorphisms of cytokines such as tumor necrosis factor (TNF) [3, 4]. In addition to genetic predisposition, environmental trigger-factors are required for the manifestation of psoriasis, such as streptococcal infections, "stress," and certain drugs [3]. Pivotal findings in the fields of cellular immunology and molecular biology have elucidated the role of lymphocytes and cytokines in the pathogenesis of psoriasis. The abnormal proliferation of keratinocytes was long considered to be the sole major event in the pathogenesis of psoriasis. Advances in cellular and molecular biology have drawn attention to the role of lymphocytes and the involvement of the immune system in the pathogenesis of psoriasis. This new orientation is based on several important observations. Predisposition to develop psoriasis or psoriasis arthritis is inherited and is associated with the expression of certain HLA molecules [5]. Histology reveals that activated T lymphocytes are the prominent infiltrating cell population in early stages of psoriasis. Coincidently, cyclosporine was found to clear psoriasis [6]. As, in addition, immunosuppressive agents are known to be effective in the therapy of psoriasis, antibody therapies using anti-CD3, anti-CD4 or administration of immunotoxins selective for T lymphocytes was tested in psoriasis. All these T cell-targeting treatments improve psoriasis [7, 8, 9, 10, 11]. The critical role of T lymphocytes in the pathogenesis of psoriasis was further underlined by the observation that psoriasis may heal following allogenic bone marrow transplantation for hematological malignancies. Conversely, this lymphocyte-mediated autoimmune disease can develop in patients without any history of psoriasis after bone marrow transplantation from psoriatic donors, which further substantiates the central role of T lymphocytes in the pathogenesis of psoriasis [12, 13].

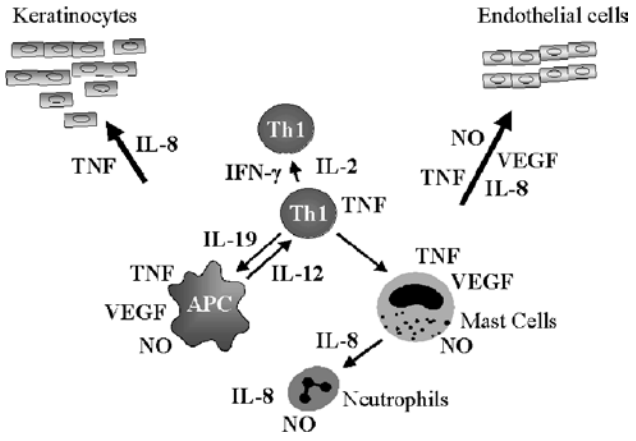

Fig. 1 Central role of IFN-γ producing T helper cell 1 (*Th1*) lymphocytes in the immunopathogenesis of psoriasis. Autoreactive Th1 lymphocytes interact with dermal cells, especially antigen-presenting cells (*APC*), mast cells, or endothelial cells and with keratinocytes in the epidermis through the release of soluble mediators or direct cell-cell interaction. *VEGF* Vascular endothelial growth factor; *NO* nitric oxide

Cellular and molecular events in the pathogenesis of psoriasis

Initiation of psoriasis is associated with production of the classical proinflammatory cytokines such as interleukin (IL) 1β, IL-6, TNF and the keratinocyte-derived Th1-inducing cytokine IL-18 [3]. Neutralization of TNF bioactivity abolishes the clinical manifestation of psoriasis [14, 15]. All these cytokines are overexpressed in psoriatic plaques. Furthermore, IL-19 and IL-8 also demonstrate elevated levels in lesional psoriasis skin. IL-19, a recently described cytokine, belongs to the IL-10 family and induces IL-6 and TNF production in monocytes. The chemotactic factor IL-8, which attracts neutrophils into the site of inflammation, was first isolated from psoriatic scales more than 15 years ago (Fig. 1) [16]. These cytokines are released not only into the skin, since patients with active psoriasis have elevated serum levels of IL-1β, IL-2 receptor, IL-6, IL-8, IL-18, TNF, and intercellular adhesion molecule 1 [17, 18]. Together this increase in proinflammatory cytokines in skin and in the peripheral blood suggests a generalized inflammation.

Bacterial infections such as streptococcal throat infection are the main factors triggering the release of proinflammatory molecules and affecting antigen-presenting cells (APC) to activate autoreactive Th lymphocytes [19, 20]. In the presence of IL-12 APC differentiate these Th lymphocytes into a Th1 phenotype (Fig. 1) [21]. Immunohistochemistry and flow cytometry have shown a predominance of IFN-γ producing Th1 lymphocytes in plaques and blood of psoriasis patients. IL-4-producing Th2 cells seem to be strongly diminished [1, 22]. Administration of IFN-α, a Th1-inducing cytokine used in the therapy of chronic hepatitis and tumors, can exacerbate psoriasis and other Th1-associated autoimmune dis-

eases [23]. T cells infiltrating psoriatic plaques express a restricted T cell receptor repertoire, confirming that psoriasis plaque-infiltrating T cells are oligoclonal [24, 25]. In a single individual the same T cell receptor pattern is found in psoriasis plaques at different body localizations and in subsequently occurring psoriasis plaques. $CD4^+$ and $CD8^+$ T lymphocytes infiltrate psoriatic lesions, but most investigations suggest that $CD4^+$ T lymphocytes are the main disease-inducing population. Thus anti-CD4 but not anti-CD8 antibodies improve psoriasis [10]. The critical role of $CD4^+$ cells is supported by skin grafts in SCID mice, with xenografts from patients with psoriasis. In these grafts the injection of autologous $CD4^+$ T lymphocytes induces psoriasis, but not injection of $CD8^+$ T lymphocytes [26]. Furthermore, reconstitution of SCID mice with minor histocompatibility antigen mismatched $CD4^+$ T lymphocytes induces psoriasislike reactions in recipient mice, while $CD8^+$ do not transfer the disease [27].

Th1 lymphocytes are characterized by a high IFN-γ to IL-4 ratio and expression of the chemokine receptors CCR5 and CXCR3 [28]. The Th1-promoting cytokines IFN-γ and IL-12 bind to specific receptors. IFN-γ signaling activates signal transducer and activator of transcription (STAT) 1 and T-bet, while IL-12 induces STAT 4. Activation of this cascade results in strong IFN-γ production and suppression of IL-4 [29]. In contrast, Th2 lymphocytes produce only low levels of IFN-γ but high amounts of IL-4, IL-5, IL-10, and IL-13 and express preferentially CCR4 [28]. In Th2 lymphocytes STAT6, GATA-3, or *c-maf* can be involved in the IL-4 signaling cascade [29]. Recognition of the strong association with Th1 responses led to the development of new antipsoriasis strategies based on molecules inhibiting cell adhesion or activation, those inducing immunosuppression, or most specifically those that divert Th1 into Th2 responses [30, 31, 32, 33, 34, 35]. The most efficient signal-inducing Th2 differentiation is IL-4 itself [36, 37]. In vivo the potential therapeutic efficacy of IL-4 in the treatment of inflammatory autoimmune disease was first shown in mice with experimental autoimmune encephalomyelitis (EAE). Meanwhile the efficacy of IL-4 therapy has been established for many other experimental models of Th1-mediated autoimmune diseases, including autoimmune diabetes and collagen-induced arthritis [38, 39]. IL-4 is the only cytokine known that is capable of directly inducing a Th2 phenotype in activated T cells. Therefore IL-4 also induces a Th2 phenotype in autoreactive T cells and thus abolishes their capacity to induce inflammatory autoimmune disease [40, 41]. IL-10 protects against encephalomyelitis when administered to mice [42]. However, IL-10 or transforming growth factor β, the other immunosuppressive cytokine, do not directly induce IL-4-producing Th2 cells. Presumably these cytokines act primarily on APC. IL-10 may also induce regulatory T cells; the strength of the IL-10 signal on the generation of IL-10 producing Th2 cells is enhanced by IL-4 [43].

These data have recently been extended to the treatment of humans with psoriasis [33, 34, 35, 37, 38, 39, 40, 41]. Similar to the therapeutic use of IL-4 in mice with EAE, an experimental model for multiple sclerosis, continuous subcutaneous administration of IL-4 significantly improved psoriasis in humans and induced Th2 responses [34].

Established systemic therapies of psoriasis

Patients with severe relapsing psoriasis or psoriasis arthritis must be treated by systemic therapy. The existing therapeutic repertoire includes immunosuppressive drugs that were developed mainly for transplantation medicine, such as cyclosporine and methotrexate [7, 8]. Alternatively, phototherapies with selected UV spectra are used, either as UVB broadband phototherapy, UVB 311 nm as narrow band, or as photo-chemotherapy with 8-methoxypsoralen as photosensitizer and UVA [44]. More recent data reveal that some derivatives of vitamin A or vitamin D_3 also improve psoriasis [45, 46]. In this context it is interesting that systemic administration of these vitamin A or D_3 derivatives can efficiently improve Th1-mediated inflammatory autoimmune diseases in mice.

Cyclosporine

Based on the original observation that cyclosporine improves psoriasis this agent was investigated for the therapy of severe psoriasis [7, 47]. Cyclosporine inhibits calcineurin phosphatase, an intracellular signaling pathway, thus blocking transcription of genes involved in T lymphocyte activation. Activated calcineurin is responsible for the dephosphorylation of cytoplasmic nuclear factor of activated T cells (NFAT) proteins and thus the translocation of dephosphorylated NFAT into the nucleus. The orchestrated activation of several calcium-regulated transcriptions factors NFAT, activator protein 1, and other transcription factors activates defined sets of promoter units. These include genes regulating cytokines such as IL-2, IL-4, IFN-γ, and transforming growth factor β and the IL-2 receptor [48, 49]. Since psoriasis is maintained by activated $CD4^+$ T lymphocytes, the major effect of cyclosporine seems to be prevention of T cell activation and inhibition of proinflammatory cytokines induced via the intracellular calcineurin pathway. New topically applied immunosuppressive macrolides such as tacrolimus and pimecrolimus also act by inhibiting calcineurin-dependent dephosphorylation of NFAT and seem not to affect Th differentiation [50].

Methotrexate

It has been thought that a similar "immunosuppressive" effect underlies the mode of action of the folic acid antagonist methotrexate that inhibits dihydrofolate reductase and the conversion of dihydrofolate to tetrahydrofolate. This conversion affects de novo synthesis of purines

and pyrimidines, formation of polyamines, and transmethylation of DNA, RNA, phospholipids, and proteins. Other enzymes such as thymidylate synthase and 5-aminoimidazole-4-carboxamide ribonucleotide transformylase are also affected by methotrexate [51, 52]. High-dose methotrexate has strong antiproliferative effects. It was originally used in tumor therapy. Inhibition of proliferation and cytotoxic effects on lymphocytes are not prominent at the low-dose methotrexate applications used in psoriasis or rheumatoid arthritis. Methotrexate-induced accumulation of 5-aminoimidazole-4-carboxamide ribonucleotide is associated with an intracellular increase in adenosine. In vitro and in vivo investigations have shown that excessive adenosine inhibits proinflammatory cytokines in various cell types [51, 52]. The effect of methotrexate on Th cell-cytokine production has also been investigated. Methotrexate induces a significant increase in IL-10 and IL-4 gene expression in mitogen activated peripheral blood lymphocytes in vitro [53]. Both cytokines are promoters of Th2 development. A recent work focused on cytokine production by $CD4^+$ and $CD8^+$ lymphocytes in patients with rheumatoid arthritis before and during methotrexate therapy. Prior to therapy $CD4^+$ and $CD8^+$ lymphocytes of patients with rheumatoid arthritis produced increased amounts of Th1 cytokines. After 12 months of therapy the Th1/Th2 cytokine balance was within the normal range. In vitro analysis suggests that methorexate directly promotes Th2 development, further suggesting that the in vivo effects of methotrexate on Th1-mediated autoimmune diseases is due to a rebalancing of an aberrant Th1 differentiation [54].

Studies on skin infiltrating T lymphocytes in psoriasis show not only that both cyclosporine and methotrexate reduce the number of skin infiltrating T cells, but that reduction in the Psoriasis Area and Severity Index (PASI) is associated with a reduction in the IFN-γ to IL-4 ratio at least in some of the patients [55]. This is supported by analysis of lesional cytokine mRNA analysis during psoriasis therapy. In two patients responding to cyclosporine IL-4 mRNA increased and IFN-γ mRNA decreased concomitantly while no change in the IFN-γ to IL-4 ratio was found in a patient not responding to the treatment [35].

Vitamin D_3 and analogs

The human skin contains the precursor 7-dehydrocholesterol which is converted to vitamin D_3 by UV irradiation. 1,25-Dihydroxy vitamin D_3 and its analogues are used as topical therapy for psoriasis. Upon activation the nuclear vitamin D_3 receptor binds to vitamin D responsive elements in various promoter regions. Vitamin D_3 also affects the activity of transcription factors such as NFAT and nuclear factor (NF) κB [56]. Under experimental conditions systemic administration of vitamin D_3 is strongly immunosuppressive and improves various Th1-induced diseases including EAE and autoimmune diabetes in mice and psoriasis in humans; vitamin D_3 may even prevent rejection of allografts. In experimental animals therapeutic improvement was associated with the induction of IL-4 producing Th2 cells [57, 58]. The underlying mode of action seems to be complex as vitamin D_3 affects several components of the immune system. When exposed to human dendritic cells (DC) during differentiation and maturation, vitamin D_3 suppresses MHC class II expression and costimulatory molecules so that cells keep a rather immature status [59]. Vitamin D_3 further suppresses secretion of proinflammatory cytokines, including IL-12 production by macrophages and DC, probably by downregulation of NF-κB and suppression of transcriptional activation of the IL-12 p35 and p40 genes [60]. In addition to its negative effect on the most important Th1-inducing cytokines, vitamin D_3 also seems directly to promote Th2 differentiation in Th cells. Thus vitamin D_3 promotes the development of a Th2 phenotype with augmented production of IL4, IL-5, and IL-10 and reduced production of IFN-γ in antigen-stimulated and CD3/CD28 stimulated $CD4^+$ lymphocytes. Vitamin D_3 stimulated lymphocytes express enhanced levels of the Th2 driving transcription factors c-*maf* and GATA-3, which explains the strong Th2-driving effects [61]. In vitro vitamin D_3 also abolishes the pathogenicity of autoreactive Th1-cells as injection of activated lymphocytes exposed to vitamin D_3 have a significantly impaired capacity to induce psoriasis in a skin xenograft model of psoriasis [62]. In agreement with these findings, topical application of vitamin D_3 analogs may not only improve psoriasis but increase IL-10 producing and decrease IL-8 producing cells [63]. Together these observations suggest that vitamin D_3 derivatives are effective in the therapy of Th1-mediated diseases by promoting IL-4 production and Th2 development. The systemic use of vitamin D_3 is currently limited due to its risk of dysregulating calcium homeostasis. Therefore derivatives with immune modulating properties are needed that lack an effect on calcium/phosphate metabolism [64].

Retinoids

Vitamin A derivatives or retinoids are also used in topical and systemic therapy of psoriasis. Acitretin and etretinate have been shown to be effective in the therapy of psoriasis in selected patients. A multicenter study showed a mean improvement in PASI of 47% with etretinate [65]. Retinoids affect cell differentiation, proliferation, and apoptosis. These retinoids act through nuclear receptors, the retinoic acid receptors, and retinoid X receptors. In addition to action through retinoic acid-responsive elements in promoter regions of target genes, vitamin A derivatives may antagonize transcription factor activator protein 1 [46]. Retinoids affect lymphocyte differentiation and the course of inflammatory autoimmune disease. This was first shown in EAE, where treatment with all-*trans*-retinoic acid improved the disease, increased IL-4 mRNA in myelin basic protein specific lymphocytes, and decreased IL-2, TNF, and IFN-γ

mRNA [66]. In vitro such an IL-4 inducing effect has also been shown for human autoreactive myelin basic protein specific T cell lines [67]. In addition, certain retinoid X receptors agonists can induce Th2 differentiation in naive T cell receptor transgenic Th lymphocytes during stimulation with APC and the specific peptide. In this model induction of IL-4 and IL-5 and suppression of INF-γ are associated with an increase in the Th2-associated transcription factors GATA-3 and c-*maf* [68].

It is important to emphasize that not all vitamin A-derivatives exert the same effect on Th1-/Th2-differentiation and the regulation of the IFN-γ/IL-4 production. Moreover, as explicitly shown for the cytokine IL-4, the biological effects of a given reagent depend not only on its biochemical structure but also on the target cell upon which the molecule acts. For example, IL-4 itself induces a Th2 phenotype when acting on T cells during their proliferation while it promotes Th1 development when acting on dendritic APC, where it promotes development of an IL-12 producing DC phenotype [69].

Phototherapy

Treatment of psoriasis with various modes of ultraviolet irradiation, such as broadband UVB (290–320 nm), narrowband UVB (310–315 nm), and psoralen plus UVA (320–400 nm), is a highly effective therapy [44, 70]. Phototherapies act differently on lymphocytes and keratinocytes. In lymphocytes phototherapy has been shown to induce apoptosis, alteration in surface molecules, inhibition of proliferation, and induction of immunosuppressive cytokines such as IL-10 and α- melanocyte-stimulating hormone [71, 72]. UV irradiation reduces the antigen-presenting capacity of APC by reducing the expression of MHC class II and adhesion and costimulatory molecules. Moreover, APC from UV-irradiated mice secrete enhanced levels of IL-12p40 homodimer, a natural antagonist of biologically active IL-12, thus preventing the development of IFN-γ producing Th1 cells [73]. IFN-γ production can also be reduced by UVB through direct inhibition of STAT1 phosphorylation [74]. UVB therapy of psoriasis induces an especially strong reduction in epidermal lymphocytes producing IFN-γ, IL-2, or TNF-while IL-4 mRNA increases, showing that the best established antipsoriatic therapies induce not only apoptosis and immunosuppressive cytokines such as IL-10 but also divert the skin-infiltrating lymphocytes towards an IL-4 producing Th2 phenotype [75].

Fumaric acid esters

Dimethylfumarate and its main metabolite methylhydrogen fumarate (MHF) are the biologically active components of the mixture of fumaric acid esters (FAE), currently registered in Germany for the treatment of severe psoriasis [76]. After showing a significant efficacy of FAE in a multicenter double-blind, placebo-controlled study a further multicenter study revealed a mean PASI reduction of 80% in 70 patients after 4 months of FAE treatment [77, 78]. The exact mode of action and the intracellular signaling pathways are not fully understood. Dimethylfumarate prevents the nuclear entry of NF-κB and inhibits cytokine-induced expression of E-selectin, vascular cell adhesion molecule 1 and intercellular adhesion molecule 1 in human endothelial cell lines in vitro [79, 80]. A decrease in peripheral T lymphocyte numbers during FAE therapy has also been reported, and in vitro FAE induces lymphocyte and DC apoptosis in a dose-dependent manner [76, 81]. The main target of FAE seems to be immune cells since FAE has been shown to provide immunosuppressive effects in an experimental organ transplant model [82]. However, the exact relationship between these biological effects of FAE, the immune system, and the improvement in psoriasis remain elusive. FAE can induce IL-10 production by monocytes [83]. The main effect seems to be the induction of Th2 differentiation by peripheral blood lymphocytes in vitro and obviously also in vivo [84, 85]. An in vitro study analyzed the effect of MHF on T cell cytokine production in detail and found that in purified T cells stimulated with anti-CD2/anti-CD28 or anti-CD3/anti-CD28 MHF induces a strong production of the Th2 cytokines IL-4 and IL-5 without effecting IL-2 or IFN-γ production. The stimulating effect of MHF on IL-4 and IL-5 production has also been shown for various $CD4^+$ T cell clones [84].

Based on previous data showing that such a switch from a Th1 to a Th2 phenotype abolishes the pathogenicity of autoreactive T cells in vitro, we analyzed the effects of FAE on the pathogenicity of autoreactive T cells in vivo. Using an animal model for a Th1-induced autoimmune disease we confirmed that FAE not only induces a Th2 phenotype in autoreactive T cells but indeed abolishes their capacity to induce autoimmune disease in vivo (Deng et al., manuscript submitted). In vivo induction of an IL-4 producing Th2-phenotype in autoreactive T cells abolished their capacity to cause disease. This strongly suggests that IL-4 plays a key role in establishing protection against Th1-mediated autoimmune diseases.

Cytokine and anticytokine therapies

Based on the experience that organ-specific autoimmune diseases are mediated by Th1 cells, and that TNF is a critical intermediate in the induction of Th1-mediated tissue damage, various immunotherapies with cytokines or anticytokine antibodies have been developed that block TNF bioactivity either to paralyze Th1 responses or to alter Th1 to Th2 responses (Fig. 2). The most important approaches include IL-10, IL-11, and IL-4 itself as well as anti-TNF [14, 15, 33, 34, 35]. All these approaches improve psoriasis, at least in a significant number of patients.

TNF is considered to be the main effector cytokine for the transmission of Th1-mediated inflammation, in-

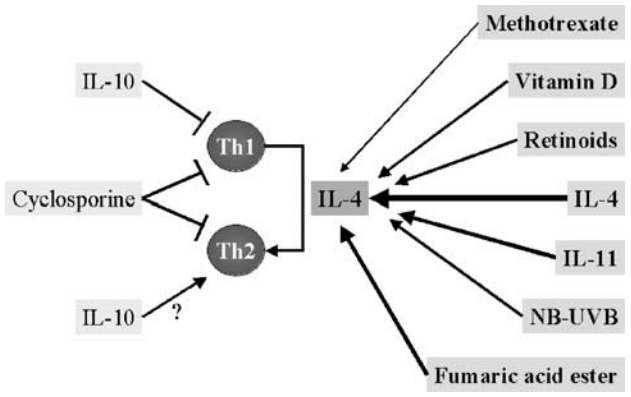

Fig. 2 Interleukin 4 inducing potency of different therapies shown to be efficient in psoriasis such as immunosuppressive or immunomodulating drugs, cytokines, vitamin analogues, or phototherapy. Most therapies seem to alter disease-inducing Th1 lymphocytes to a Th2 phenotype. *NB* Narrowband

cluding psoriasis. APC and mast cells secrete TNF when stimulated by Th1 cells [86]. Blocking TNF action by binding with soluble TNF receptor or anti-TNF antibodies improves psoriasis and other Th1-mediated diseases such as rheumatoid arthritis and psoriatic arthritis [14, 87, 88]. These findings underline the critical role of Th1-mediated inflammation in these diseases. A placebo-controlled randomized trial using the chimeric monoclonal anti-TNF antibody infliximab found that PASI was improved by 75% in more than 70% of patients. Two of 11 patients in the placebo group had a similar improvement [14]. In contrast, in only 26% of patients treated with the soluble receptor etanercept was the PASI improved by 75% [15]. However, since TNF is also crucial for beneficial Th1-mediated inflammation, such as defense against mycobacteria, it is questioned whether altering specifically the disease-inducing Th1 response into a Th2 phenotype would not be safer than long-term anti-TNF therapy. Therefore different cytokine therapies have been developed.

IL-11 was isolated from a bone marrow stromal cell line and has pleiotropic effects, including promotion of hematopoiesis, growth control of gastrointestinal epithelial cells, osteoclast development, and neurogenesis. Being an IL-6 type of cytokine, IL-11 activates cells through a receptor complex composed of IL-11 receptor α chain and glycoprotein 130, a signal transduction molecule. Activation of glycoprotein 130 by IL-11/IL-11 receptor α binding leads to activation of the Jak family of cytoplasmic tyrosine kinases and the subsequent phosphorylation of STAT3, which is involved in cytokine signal transduction. IL-11 increases intracellular levels of the inhibitor protein of NF-κB (IκB), a mechanism that seem to be involved in both the anti-inflammatory and the Th2-inducing effects of IL-11. This enhancement of IκB seems to reduce IL-1β, IL12, and TNF release by activated macrophages [89, 90]. In a mouse model of graft-vs. host disease induced by a minor antigen mismatch, IL-11 attenuated the disease and significantly prolonged survival of the mice due to TNF suppression and skewing of donor T lymphocytes to an IL-4 producing Th2 phenotype [91]. Based on this observation IL-11 was administered to patients with chronic psoriasis, and 11 of 12 patients improved between 20% and 80%. This first noncontrolled dose-escalation study confirmed that IL-11 reduces the IFN-γ to IL-4 ratio within the psoriatic lesions. This was associated with clinical improvement, a reduction in keratinocyte proliferation and the inflammatory infiltrate [35]. Recently IL-11 was shown directly to affect the differentiation of $CD4^+$ T cells. Purified naive human $CD4^+$ T lymphocytes stimulated in the absence of APC with anti-CD3/CD28 developed a strongly polarized Th2 phenotype when activated in the presence of IL-11 [92].

IL-10 has been reported to be a cytokine inhibiting activation and cytokine production of Th1 lymphocytes. Under most conditions, IL-10 silences a broad spectrum of immune cells, including macrophages, monocytes, T cells, and mast cells, while B cells are activated by IL-10. The IL-10 receptor is composed of α and β chains, both of which are members of the interferon receptor family. IL-10 inhibits NF-κB activation and thus the production of inflammatory cytokines such as IL-1β, IL-6, IL-12, and TNF and chemokines such as IL-8 and interferon-inducible protein 10. In addition, IL-10 downregulates surface expression of MHC class II and of costimulatory molecules on APC. Through these effects IL-10 seems to alter maturating DC towards a DC phenotype that either paralyzes T cells or generates suppressor T lymphocytes. However, IL-10 seems to suppress especially IL-12 production by DC and thus may promote Th2 development in vivo. Based on this concept IL-10 was given to patients with Th1-mediated autoimmune diseases [93]. Five independent trials showed that a significant number of psoriasis patients improve when treated with subcutaneous injections of IL-10 [33, 94, 95]. To date two double-blind, placebo-controlled studies with different treatment durations have been performed. In one trial IL-10 or placebo was administered for 12 weeks and showed a transient clinical improvement between weeks 6 and 8 of IL-10 therapy. Surprisingly, the clinical response was rapidly lost on continuing the therapy [95]. The second trial was performed to analyze the incidence of relapses in patients with chronic plaques psoriasis in remission. These patients received either placebo or IL-10 for up to 4 months. Less than one-third of IL-10 treated patients relapsed during the 4 months of observation, whereas in the placebo group 90% of the patients showed a relapse [96]. Functional analysis revealed little evidence of anergy induction; instead IL-10 shifted the dermal T cell infiltrate from a Th1-dominant to an IL-4-dominant Th2 phenotype after 7 weeks of IL-10 therapy. This was due to a significant increase in intralesional IL-4 mRNA expression [96, 97]. Interestingly, the IFN-γ to IL-4 ratio of peripheral blood $CD4^+$ T cells decreased significantly in IL-10 treated patients but not in the placebo group, suggesting that IL-10 promoted Th2-development in this study [95].

As IL-4 signaling during T cell stimulation is the most efficient signal for the induction of IL-4 producing Th2 cells, and as IL-4 induced immune alteration of Th1

to Th2 responses is highly efficient in either preventing or treating Th1-mediated autoimmune disease, we analyzed the therapeutic potential of IL-4 in psoriasis [37, 41]. Three subcutaneous injections of recombinant human IL-4 daily for 6 weeks led to a significant, dose-dependent improvement. In this prospective dose escalation study 19 of 20 patients improved by more than 50%, and PASI improved in 75% of the patients more than 68%. Skin biopsy specimens of psoriasis plaques have shown alteration of the strong, IFN-γ-dominated Th1 pattern to an IL-4 dominated Th2 pattern in the skin, but not in the blood. Induction of a Th2 phenotype inside the plaque was associated with a significant decrease in dermal infiltrating $CCR5^+$ Th1 cells and a reduction in IL-8 and IL-19 mRNA [34]. In this context IL-19 seems to be of special interest. IL-19 is a new member of the IL-10 family. IL-19 signals through the IL-20 receptors, which have been shown to be involved in signaling for abnormal keratinocyte differentiation and proliferation. Moreover, IL-19 induces IL-6 and TNF production by monocytes, the leading effector cytokines in the pathogenesis of psoriasis [3, 98, 99].

Conclusions

Psoriasis is a complex disease. Manifestation of psoriasis requires genetic predisposition that allows abnormal keratinocyte proliferation and differentiation. In addition, manifestation needs an initiating event that obviously involves TNF as key effector cytokine. Therefore the blocking of TNF improves psoriasis as well as most of the protective inflammatory responses against invading pathogens and perhaps also tumors. In view of this it seems to be more appropriate to antagonize the TNF-inducing psoriasis while leaving protective immune responses unaffected. In recent years IL-4 has been recognized as the most important, antigen-specific suppressor of Th1- or TNF-mediated immune responses. As IL-4 is mainly T cell-derived, it should be possible to prime for specific, anti-inflammatory, IL-4-producing T cells that interfere with the psoriasis-inducing TNF while leaving protective Th1 responses unaffected. Indeed, IL-4 is the common molecule known to be induced by most anti-immunosuppressive agents (Fig. 2), and a new study based selectively on the alteration of proinflammatory Th1 cells into a Th2-phenotype was highly efficient in the therapy of psoriasis. Importantly, clinical improvement in psoriasis induced by immune modulating therapies such as FAE and IL-4 is similar to that in the most efficient therapies published (Fig. 3). Moreover, these newer approaches show that improvement in psoriasis is closely associated with an alteration of the skin-infiltrating T cells from a Th1 to an IL-4-producing Th2-phenotype. Future research will show whether new concepts of vaccination designed to induce IL-4 producing, autoreactive Th2 lymphocytes can solve the severe problems associated with psoriasis and other Th1-mediated autoimmune diseases.

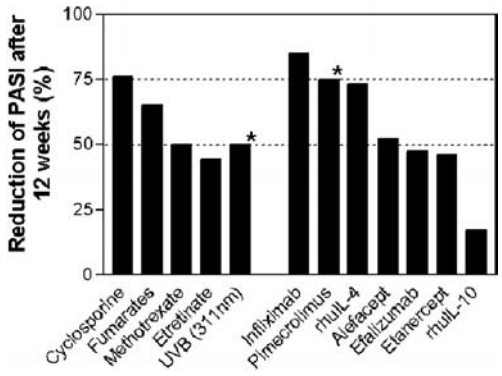

Fig. 3 Comparision of the overall efficacy of various treatment modalities for UV or systemic treatment of moderate to severe psoriasis. Results were obtained from representative studies and given as the mean reduction in PASI during a 12-week treatment course. *Asterisks* Treatment results after 4 weeks. (From [14, 15, 31, 32, 34, 47, 65, 70, 78, 92, 100]; methotrexate data from U. Mrowietz, personal communication)

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