Updates in Clinical Dermatology
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Dae Hun Suh *Editor*

Acne

Current Concepts and Management

Springer

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Preface

Acne is one of the most common skin diseases. It was in 1996 when I started researching acne and opened an acne special clinic, but until then, acne research was not actively conducted at the university level in Korea. This is probably related to the trend of taking acne lightly. People regard acne as a symbol of youth and dismiss it as a passing process. Sometimes, even doctors (excluding dermatologists) seem to have this thought. However, acne is definitely a notable chronic skin disease. It can occur not only during puberty, but also before adolescence, and often continues to last for a long time. Acne patients suffer considerably from active inflammatory/non-inflammatory lesions and scars, and there are cases of suicide attempts due to mental stress. Acne is a serious disorder and deserves meticulous attention. There tends to be a misunderstanding that acne is an "easy" disease, but there is still much to uncover about its pathophysiology, and thus research on it is increasingly active. Novel therapeutic drugs and methods are also being tried.

In 2000, I went to study in the United States with my family for a full-fledged acne research, where I could learn a lot from Prof. Thiboutot's laboratory. With the creation of the Asian Acne Board in 2005, I had the opportunity to exchange opinions with numerous acne researchers. After becoming a member of "Global Alliance to Improve Outcomes of Acne," a group of world-renowned acne researchers, I have had valuable opportunities to engage with famous scholars and hear their insights.

When Springer and Dr. Chee Leok Goh suggested I write a book about acne, I hesitated, knowing the difficulty of the task. However, the decision was made, as the collection of manuscripts written by acne researchers from around the globe should be of great help to dermatologists in the general hospital and private practice, dermatology residents, and medical students. I am grateful to the staff at Springer, including Ms. Asja Rehse and Ms. Maureen Alexander, for their efforts to complete my task. I'd also like to take this opportunity to thank my disciples and research associates for being a great help in my acne research. Last but not least, I express my gratitude to Prof. Jai Il Youn, Prof. Jouni Uitto, Prof. Joseph Gonnella, and Prof. Young Kauh for helping and encouraging me throughout my career.

The chapters' authors are all world-class acne masters, representing many regions. This combined knowledge has the advantage of being superior to the bulk of previously published books on acne. It is my great honor and glory to collaborate with these authors, and I deeply appreciate their kind and enormous work. These authors have laid out detailed and the most up-to-date

knowledge of acne pathophysiology, clinical features, differential diagnosis, treatment, and more. Pathophysiology, in particular, includes information on bacteria, immunity, endocrinologic factors, various deteriorating factors, and environmental factors. As for clinical features, adult acne, differences in clinical patterns by region and race, and acne fulminans are covered. Regarding treatment, the latest knowledge on existing treatments or treatment methods, new drugs, and core outcome measures are mentioned. The authors put forth their best efforts to bring state-of-the art knowledge to readers, sharing their expertise. I hope this book will function as an expert of acne, easily be approachable for those interested, physicians and researchers alike.

Finally, I dedicate this book to my beloved family, especially my wife and son who always remind me of the joy of life and offer me strong support. I also dedicate this book to my father and mother. My mother, who passed away in April last year due to an exacerbation of rheumatic disease, always loved her son with great pride in his communicating with world-class scholars and giving lectures around the world. Indeed, she would be most delighted with the publication of this book in heaven.

Seoul, South Korea Dae Hun Suh
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Update on *Cutibacterium acnes*

1

Marie-Ange Dagnelie, Stéphane Corvec, Amir Khammari, and Brigitte Dréno

Abbreviations

AMP	Antimicrobial peptide
CAMP	Christie-Atkins-Munch-Petersen (e.g. CAMP2, etc.)
CRISPR	Clustered regularly interspaced short palindromic repeats
D/PAMP	Damage-/pathogen-associated molecular pattern
EVs	Extracellular vesicles
hBD2	Human β-defensin 2
HYL-IA	Variant of hyaluronidase (HYL) found in phylotype IA
HYL-IB and II	Variant of hyaluronidase (HYL) found in phylotypes IB and II
IFN-γ	Interferon- γ
IL	Interleukin (e.g. IL-8, IL-6, etc.)
MMPs	Matrix metalloproteinases (e.g. MMP-9, MMP-13, etc.)
NK cells	Natural killer cells
NLRP3	NOD-like receptor family, pyrin domain containing 3
PAR-2	Protease-activated receptor-2
PCR	Polymerase chain reaction
QS	Quorum sensing
RIS-1/psoriasin	Retinoic acid-inducible skin-specific gene
RNA	Ribonucleic acid
RNases	Ribonucleases
SCORAD	Scoring atopic dermatitis
SLST	Single-locus sequence typing
TGF-β	Transforming growth factor-β
Th17/Th1	T helper 17/T helper 1 cells
TIMP-2	Tissue inhibitor of metalloproteinases (e.g. TIMP-2, TIMP-4, etc.)
TLRs	Toll-like receptors (e.g. TLR-2, TLR-4, etc.)
TNF-α	Tumour necrosis factor-α

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Introduction

This book chapter focuses on *Cutibacterium acnes*, which is a commensal bacterium of the cutaneous microbiome, playing a crucial role in acne development [1–4]. This chapter will first precisely describe the identity passport of this bacterium and then focus on the interactions existing

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between *C. acnes* and the other microorganisms' resident of the human skin, mainly *Staphylococcus epidermidis*. This chapter will then describe the interactions existing between *C. acnes* and the innate immune system of the skin and finally will open on the future potential treatments that will be developed in the next years, to treat acne.

Cutibacterium acnes (Ex – *Propionibacterium acnes*) Identity Passport

The skin represents a complex ecosystem [5]. A large and diverse community of microorganisms is present on the body. Depending on the ecological niches, the bacterial distribution can vary [6]. Thus, in a lipidic area, *Actinobacteria* are more represented, and *Cutibacterium acnes* can represent until 70% [7]. This anaerobic-aerotolerant Gram-positive bacteria is a skin commensal, and its ecological niche is represented by the sebaceous follicles [8–10].

Bacteriological Description

Initially, *C. acnes* was classified as a *Corynebacterium* [11]. According to the recent literature, the microscopy morphology can be diverse leading to different subtypes [12–14]. By direct microscopy examination, the historical phylotypes I, II and III are somehow different [12, 15, 16]. New insights from integration of population community's analysis, genomic studies and biochemical and host-microorganism interactions lead to a better knowledge of this bacterium involved in inflammatory process [17, 18].

Ecological Niches

C. acnes is a major resident of the normal human skin microbiota and dominates in the pilosebaceous units which can be explained by production of different enzymes [19–21]. It can interact with other microorganisms, especially *Staphylococcus epidermidis* playing an important role in the skin health, educating the innate immune system and maintaining the skin homeostasis [22]. *S. epidermidis* could be a partner in the pathogenesis of acne, producing antimicrobial substances (bacteriocins) active against *C. acnes* leading to a disruption (dysbiosis) of the normal skin homeostasis equilibrium [23]. Its involvement in skin disorder, especially acne, has been described, but we also can recover isolates from mouth, gastrointestinal tract, prostate and device-related infections [14].

Taxonomy Modification

Following its discovery in a patient with acne, *P. acnes*, henceforth *C. acnes*, underwent a series of taxonomic changes. It was successively placed in the genus *Bacillus*, followed by *Corynebacterium* [11]. However, in 1946, Douglas and Gunter were able to demonstrate that this microorganism was more closely related to the *Propionibacterium* genus members since, like other species of this genus, it ferments lactose to propionic acid in an anaerobic atmosphere maintaining an acid pH on the skin surface and limiting pathogen development [24, 25]. Recently, a significant taxonomic revision was proposed by Scholz et al., placing all *Propionibacterium* species from the skin microbiota within this new genus *Cutibacterium* [25]. Henceforth, the main actor of the sebaceous follicles should be named *Cutibacterium acnes*. Recently, according to the three main phylotypes described at the beginning, subspecies have been proposed. Thus, phylotype I corresponds to the subspecies *C. acnes* subsp. *acnes* [26], phylotype II corresponds to the subspecies *C. acnes* subsp. *defendens* [27] (due to the presence of a CRISPR system limiting gene transfer or acquisition) [28] and phylotype III corresponds to subspecies *C. acnes* subsp. *elongatum* according to its microscopy morphology [26].

Phylogeny

Since 2005, different groups have developed molecular tools to identify if possible clusters or

lineages are more involved in different specific diseases. At the beginning, the role of specific *C. acnes* subgroups in the physiopathology of these diseases was conducted with antibodies [15]. Using different targets such as *tly* or *recA* genes, several groups developed different molecular typing methods [29]. Thereafter, phylotype multiplex PCR, different multi-locus sequence typing schemes and a useful single-locus sequence typing method which can be performed directly from samples have been proposed [30–33]. Nevertheless, to compare the phylogeny of clinical isolates recovered during different diseases, we proposed a consensus with an algorithm to identify subtypes of *C. acnes* by molecular typing methods [34]. Thus, in moderate to severe acne, different studies have proven to have highly prevalence in skin inflammatory swab specimens of phylotype IA_1 [35–41]. At the opposite, for example, another skin disease is linked to an overrepresentation of phylotype III: progressive macular hypomelanosis [42, 43].

Growth Culture Conditions

Conventional microbial culture of *C. acnes* from skin samples requires some attention, but in a well-trained microbiology laboratory, it remains easy. Different media can be used, sometimes with supplementation with tween, for example [14]. Schaedler agar, Brucella agar, or chocolate agar plates can be seeded and incubated anaerobically for at least 7–10 days at 37 °C [13]. In acne lesions, different colony aspects can be observed regarding colour and haemolysis [44].

Virulence Factors

C. acnes is able to produce numerous virulence factors [45]. Thus, it produces short-chain fatty acids (leading to a local inflammation); thiopeptides; bacteriocins [46]; degradative enzyme such as lipases [20], endoglyceramidases, sialidase and hyaluronidase [21]; and other molecules with inhibitory properties against pathogens such as *Staphylococcus aureus* or *Streptococcus pyogenes*. *C. acnes* is able to trigger innate immune system via Toll-like receptor 2 (TLR-2) activation. Different TLR-2 ligands can be involved in this immune stimulation: lipoteichoic acids and peptidoglycan fragments [45] but also cell surface proteins like Christie-Atkins-Munch-Petersen (CAMP) factors which have co-haemolytic activity and cytotoxin properties [47, 48]. *C. acnes* lipase has a crucial role in hydrolysing triglycerides of sebum leading to the release of irritating fatty acids within pilosebaceous follicles which partly explain acne pathogenesis [13]. Interestingly, phylotype IA_1 recovered in 80% of acne lesion produces more lipase than other phylotypes [49].

Hyaluronidase is another extracellular enzyme implicated in the bacterial pathogenesis (involvement in penetrating the extracellular matrix) leading to total hyaluronic acid degradation for HYL-IB/II variant versus a partial degradation for the HLY-IA variant [13, 21, 50]. Certain *C. acnes* strains, especially those involved in acne, belonging to phylotype I can produce haemolysins with cytotoxin properties. Valanne et al. demonstrated the presence of the five CAMP factors in the different *C. acnes* subgroups. However, the *camp2* gene seems to be the most relevant and active co-haemolytic factor but in the IA phylotype *C. acnes* genetic background [13, 44, 47]. At last, the ability of *C. acnes* clinical strains to produce biofilm has been largely investigated, especially in device-related infections [51, 52]. In acne field, in 2008, Coenye et al. suggested the impact in acne of sessile *C. acnes* cells either highly resistant to antimicrobial agents or tolerant to with potential increased production of virulence factors and quorum sensing molecule regulation [53]. In biofilm condition, lipase has a greater extracellular activity [8]. In 2012, the presence of *C. acnes* macrocolonies within the pilosebaceous follicles has been described. Interestingly, different phylotypes were contained and coexisted [54]. Recently, Kuehnast et al. suggested that biofilm formation correlates with the phylotype, rather than the anatomical isolation site. In their model, phylotype IA_1 (SLST types A1 and A2) demonstrated higher biofilm production [55].

Resistance in Acne Context

C. acnes is susceptible to a large range of antibiotics [14]. Nevertheless, in acne context, antibiotics should be used for a short treatment period. Indeed, from 1979, the first resistant strains have been reported [56]. Henceforth, erythromycin resistance is largely higher than tetracycline one [57, 58]. According to antibiotic treatment habits, the epidemiological resistance of *C. acnes* is different: topical or systemic treatment, doses, combination, duration, etc. Thus, macrolide resistance rate can vary from less than 25% in Columbia to almost 90% in Spain [57]. The tetracycline situation is better with less than 10% in France to almost 50% in India [57]. The mechanism involved in these resistances is systematically point mutation in the chromosomal gene targets: 23S encoding gene and to a lesser extent L4 or L22 proteins for macrolides and 16S encoding genes for tetracycline [14]. Recently, in Japan, the impact of fluoroquinolone topical use has been reported with the emergence of resistant *C. acnes* strains [59] but also a worrying problem linked to the collateral damages with the impact on resistance in the microbiota and therefore *Staphylococcus epidermidis* fluoroquinolone selection [60].

Acne in the Genomic Era

As the skin ecosystem is a dynamic and evolving environment with numerous bacterial interactions, genomic, transcriptomic and metabolomic approaches will help us better understand the role of these specific bacterial communities in acne pathogenesis and inflammation (Table 1.1).

Table 1.1 Summary of nomenclatures of *Cutibacterium acnes* phylotypes and clonal complexes based on the two main MLST schemes and the SLST typing methods

Typing based on multiplex PCR	MLST9Aarhus scheme156 ST	MLST8Belfast scheme152 ST	SLST142 types
IA_1	CC18	CC1	A1-45
	CC3	CC3	C1-6
	CC28		D1-5
	CC31	CC4	E1-11
IA_2	CC28	CC2	F1-18
IB	CC36	CC5	H1-10
IC	Singletons	CC107	G1
II	CC53	CC6	K1-27
	CC60	CC72	
III	CC43	CC77	L1-10

Note that Aarhus MLST scheme can detect CC28 in IA_1 and IA_2 clades
CC clonal complex, *MLST* multi-locus sequence typing, *SLST* single-locus sequence typing, *ST* sequence type
Last update MLST9: September 22, 2019
Last update MLST8: September 22, 2019
Last update SLST: September 22, 2019

Cutibacterium acnes and Cutaneous Microbiome Interactions

The human skin microbiome is a unique and complex mixture of different groups of microorganisms. Human skin harbours bacteria (anaerobic, aerotolerant, or facultative anaerobic), virus, fungi and bacteriophages. Interspecies cross talks exist between these cutaneous microbial communities. These interactions take place through different ways, notably growth regulation, quorum sensing, biofilm synthesis regulation and extracellular vesicles exchanges. This fragile balance between growth and inhibition of each cutaneous species is the guarantor of skin homeostasis and functional skin barrier.

First of all, growth regulation is possible through the production of certain type of bioactive molecules able to kill and/or inhibit the growth of certain bacteria. To illustrate this phenomenon, Christensen et al. showed that *Staphylococcus epidermidis* strains possess an arsenal of mechanisms to inhibit *C. acnes* growth. These growth regulations result from the production of bioactive molecules called bacteriocins, such as the epidermin produced by *S. epidermidis* in that case [22]. These molecules act on the cytoplasmic membrane of Gram-positive bacteria. Another example of bioactive molecule is gallidermin. This molecule was successfully tested in a topical formulation on rat skin showing antibacterial potential against *C. acnes* and *S. aureus* [61]. Another example was reported by Wang et al. concerning

the inhibitory potential of *C. acnes* on the growth of methicillin-resistant *Staphylococcus aureus*, using an in vitro model [62].

Secondly, quorum sensing (QS) is a way to communicate between bacteria enabling the regulation of bacterial gene expression in response to changes in cell density. It permits them to sense bacterial numbers among their population (cell density), integrate and process the environmental parameters and synchronously alter their behaviour by expressing specific target genes [63, 64]. Nowadays, more and more evidences relate interspecies, inter-genera and inter-kingdom communications using largely diffusible small molecules named "quoromones" or "autoinducers" [65]. In Gram-positive bacteria such as *Cutibacterium acnes*, these molecules are often oligopeptides [65]. On the clinical point of view, it was recently suggested that QS mutants of human pathogens were attenuated for virulence [66, 67] quickly leading to the concept of using QS inhibitors to control some diseases [63]. Then, QS appears as a way to regulate microbial populations among skin microbiome, as previously suggested [68], and even more could be involved in the physiopathology of dermatoses such as acne [69].

Then, interspecies interactions are also described through biofilm synthesis regulation. This kind of mechanism was previously reported between *Staphylococcus aureus* and *C. acnes* [70]. In this study, authors demonstrated that *C. acnes* may have an effect on the behaviour of *S. aureus*. This study suggests that *C. acnes* may produce a factor or provide a promoting environment for staphylococcal biofilm formation. Since coproporphyrin III is known to induce *S. aureus* aggregation in cutaneous isolates, it is possible that this molecule could also induce biofilm formation or there may be a different mechanism currently not described [71].

Finally, extracellular vesicle (EV) exchanges are nowadays considered as a crucial player in bacteria communications [72]. All bacteria are capable of producing this type of natural messenger, including Gram-positive ones [73]. Recently, *C. acnes* was described as able to produce EVs [74]. These bacterial EVs enable the communication between bacteria themselves but also between them and host cells such as keratinocytes in cutaneous context, notably via TLR2-mediated signalling pathways [75]. Indeed, Choi et al. described that the entry of *C. acnes*-derived EVs into keratinocytes is mediated by clathrin-dependent endocytosis, and this way, the internal cargo of these EVs can be delivered into keratinocytes. In this example, Choi et al. demonstrated that *C. acnes*-derived EVs were able to induce an acne-like phenotype in keratinocytes and confirmed their results in a reconstituted human epidermis model. In addition, one specific study reports the possible regulation between bacterial populations from different microbiotas using EV pathway, to protect the skin from inflammation induced by a pathogen. Indeed, it was previously reported that EVs from *Lactobacillus plantarum*, which is a commensal found in digestive tract, were able to protect from atopic dermatitis induced by *S. aureus*-derived EVs. Clinical applications are then suggested using *L. plantarum*-derived EVs, based on their modulation potential towards cutaneous pathogens like *S. aureus*. Another clinical outlook was suggested in the literature, based on the inhibition of the release of EVs from *C. acnes* to avoid inflammatory cytokine releases from keratinocytes and acne phenotype occurrence [75].

Taken together, these elements of the literature underline the importance of appropriate interspecies cross talks. Indeed, an imbalance in these microbial interactions could potentially jeopardize the relationships between skin microbiota and host cells and may result in skin inflammatory diseases where dysbiosis is often cited as a potent actor.

Skin microbiota appears as a complex and multifactorial organ part of the skin, for which modulation is nowadays thought to be able to treat inflammatory dermatoses, as recently suggested in acne context [76]. Indeed, as antibiotic resistance is an increasing phenomenon especially in acne disease [77, 78], probiotic solutions are nowadays considered as an interesting alternative to antibiotic treatments and also a new option added to the current therapeutic arsenal of clinicians (Fig. 1.1).

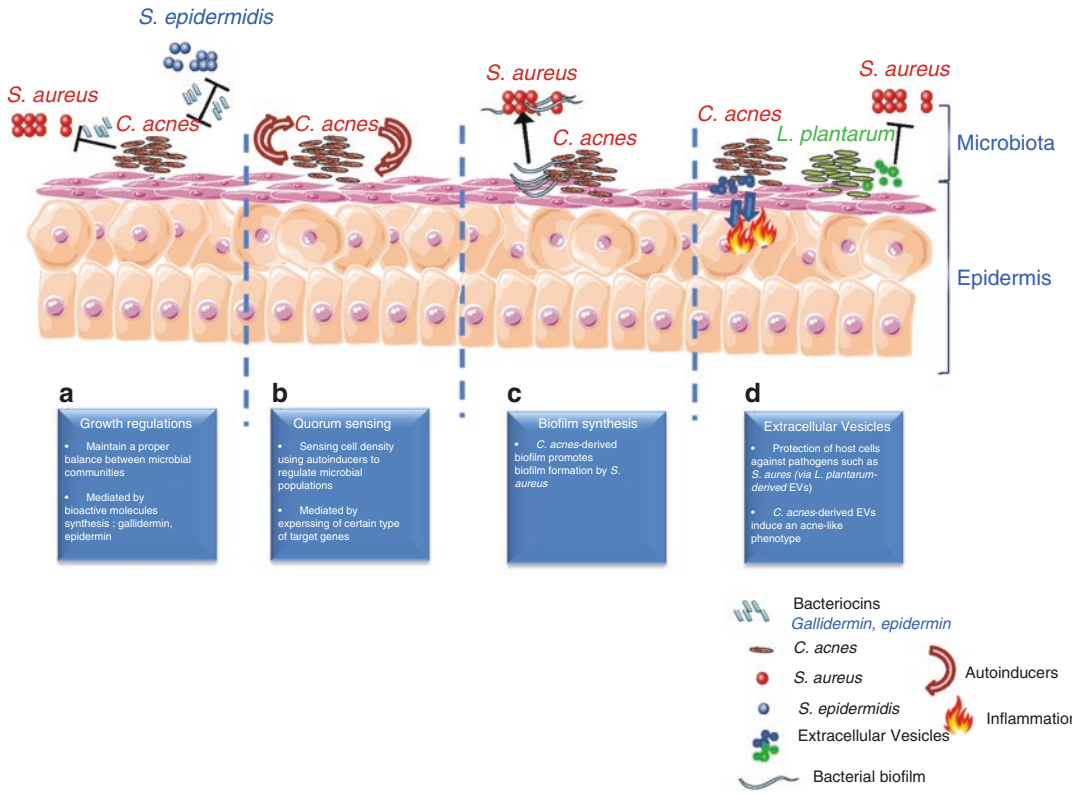

Fig. 1.1 *Cutibacterium acnes* and cutaneous microbiome interactions. Summary of the different interactions existing between *C. acnes* and the different skin microbial communities. (**a**) Growth regulations are mediated through different bioactive molecules (epidermin, gallidermin). (**b**) Quorum sensing is one of the pathways possible for interaction between bacteria. (**c**) Interactions between *C. acnes* and skin microbiota also take place through biofilm synthesis. Indeed, recent studies reported that *C. acnes*-derived biofilm was able to promote biofilm synthesis by *S. aureus*. (**d**) Extracellular vesicles are able to carry signals promoting interspecies communications and also host/microbiota communications

Cutibacterium acnes and Innate Immunity

The skin with its microbiome develops a wide range of innate immune responses to protect the body against infection. In contrast to the gut microbiome that is physically separated from the epithelium by a dense mucus layer in the colon, the skin microbiome is in close contact with the epidermis. It is important that the immune response is primed to recognize and tailored to respond to an appropriate threat, as any immune reaction towards commensal agents could lead to chronic disease. Keratinocytes and sebocytes are the main cell types of the epidermis and actively participate in innate immunity, as a source of antimicrobial peptides and cytokines that trigger inflammation when the epithelium is exposed to damage-/pathogen-associated molecular patterns (D/PAMP), mainly represented by Toll-like receptor 2, 4 and 6 (TLR) ligands and protease-activated receptor (PAR)-2 ligands that link with the corresponding receptors expressed on/in the keratinocytes and sebocytes [79]. The activation of innate immunity seems different according to the type of the skin and phylotype of *C. acnes*. In one study, type IC isolated in the normal skin would induce higher secretion of IL-8 in keratinocytes than type IA [80]. In contrast, types IA and IB of *C. acnes* were found to induce greater levels of the human β-defensin 2 (hBD2) from cultured sebocytes than a type II isolate [81, 82]

which demonstrated that *C. acnes* type III had the highest pro-inflammatory potential by upregulating the expression of PAR-2, TNF-alpha, MMP-13 and TIMP-2, whereas *Cutibacterium avidum* had the weakest by upregulating only MMP-13 and TIMP-2 [82].

C. acnes can induce IFN-γ from NK cells by mechanism involving the release of RNA and an innate pathway dependent on activation of TLR8 and the secretion of IL-12p40 and IL18 [83]. In addition of IL-8, in the process of inflammation triggered by *C. acnes*, secretion of IL-1β by monocytes and sebocytes throughout the activation of the key inflammasome gene NLRP3 has been observed [84]. This mechanism is regulated by proteases and reactive oxygen species. Moreover, *C. acnes* promotes mixed Th17/Th1 responses by inducing the concomitant secretion of IL-17A and IFN-γ from specific CD4+T cells in vitro. Therefore, the presence of IL-17A-positive T cells and the activation of Th17-related cytokines in acne lesions indicate that the Th17 pathway may play a pivotal role in the disease process, possibly offering new targets of therapy [85]. Recently it has been shown that IL-17 was increased in the serum of acne patients [86]. In addition of cytokines, antimicrobial peptides (AMPs) are important modulator of cutaneous inflammation and belong to the innate immunity. There is strong evidence that AMP plays a role in the pathogenesis of inflammatory acne lesions. Skin-derived AMPs comprise the family of β-defensins, S100 proteins, RNases and the cathelicidin LL-37. While some AMPs are constitutively secreted, hBD-2 and hBD-3 and LL-37 are upregulated in acne lesions and induced by culture supernatants of *C. acnes* in vitro both in keratinocytes [48] and in sebocytes [87]. RIS-1/psoriasin is an epithelial antimicrobial peptide, whose expression is upregulated in inflammatory skin diseases including acne and is induced by retinoids. Inflammation modifies the compartmentation of RIS-1/psoriasin in sebaceous glands and the follicular root sheaths with an increase of its expression, thus making this AMP a new target of acne treatments [88].

Acne is associated with scar development in many patients. Recently, we showed that in the skin of acne patients prone to scars versus not prone to scars, TLR-4, IL-2, IL-10, TIMP-2 and JUN were significantly overexpressed and the MMP-9 protein level was decreased. Similar results were obtained in inflammatory papules, except for TLR-4. Thus, these results suggest a link between the early events of inflammation with levels of activation of innate immunity in the normal epidermis of acne patients and the development of scars showing how crucial it is to treat inflammation in acne to prevent the development of scars [89]. TGF-β1 could also play a role in the development of scars as it is strongly elevated in lesions of acne patients who were prone to scars [90].

A crucial question in the microbiome field is why do cells switch from a state of immunological tolerance to a chronic inflammatory state in the absence of an infection. In the case of acne development, a dynamic shift in the microenvironment of the follicle induced by hyperseborrhea can trigger a different transcriptional response of the microbiome. Thus, culturing *C. acnes* in a lipid-rich, hypoxic environment similar to that of an occluded hair follicle promotes anaerobic fermentation and production of short-chain fatty acids that activate an epigenetic mechanism to enhance the TLR2-mediated production of IL-6, IL-8 and TNFα in human keratinocytes [91] (Fig. 1.2).

What Alternatives in the Future?

The development of new treatments against pathology requires a good and strong knowledge of the physiopathology and the pathways involved in order to better target the factors involved in the pathology and by inducing few side effects. Currently, the exact pathophysiological mechanisms of acne are only partially known. The predominant involvement of *C. acnes* is questionable since the latest knowledge shows that acne state and induced inflammation are governed by complex association of multiple factors. These factors mainly depend on the microbiological microenvironment, gender, age and individual intrinsic factors.

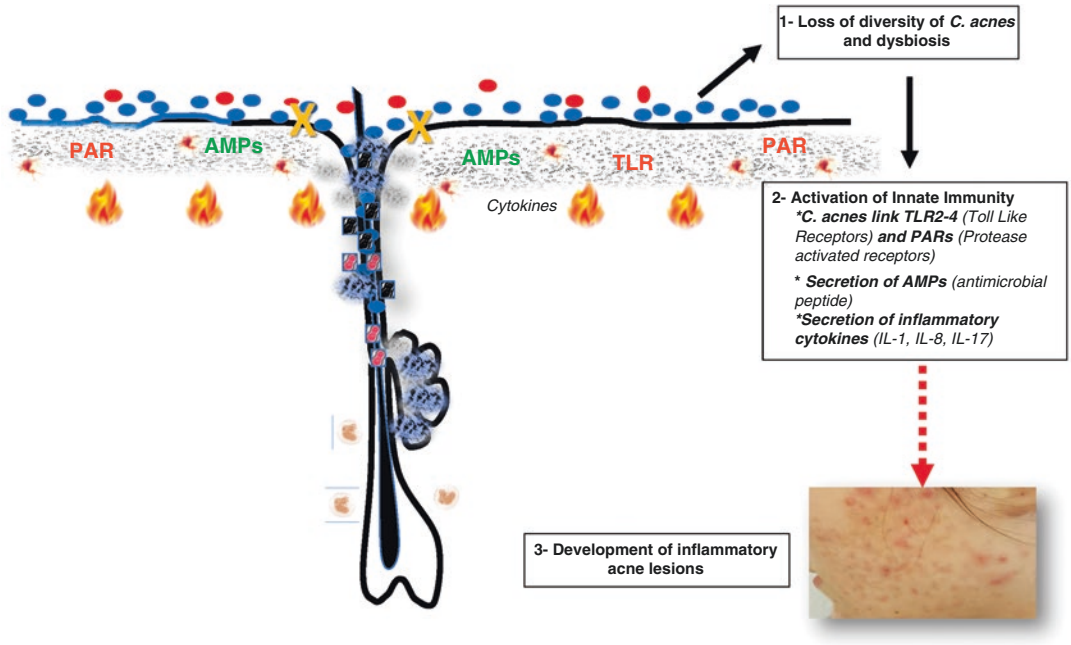

Fig. 1.2 *C. acnes* cross talks with the cutaneous innate immunity

In the current therapeutic arsenal, the management of acne varies mainly according to acne severity. Management algorithms are published [92] including topical treatments (antibiotics, retinoids, benzoyl peroxide and salicylic/azelaic acids) and systemic treatments (antibiotics, retinoids, zinc) [93]. Some studies pointed that the main research goal of acne treatment is to target *C. acnes* and the induced inflammatory status, the sebum hypersecretion and hyperkeratinization [94]. In parallel, antibiotics modulate *C. acnes* and have an anti-inflammatory effect [95]. Benzoyl peroxide and azelaic acid inhibit *C. acnes* colonization and have comedolytic and anti-inflammatory/antibacterial effects [96–98]. Oral retinoids or isotretinoin are more likely used to treat severe acne. These molecules impact on sebum production and regulate *C. acnes*/TLR-2-mediated innate immune response [99]. Systemic retinoids might indirectly regulate skin microbes and reduce the number of *C. acnes*, inducing changes in microbial diversity [93, 100].

Despite some proven efficacy of current treatments, cutaneous side effects of topical products, systemic effects as for isotretinoin, antibiotic-induced bacterial resistance and acne chronicity encourage the research to explore targeted therapies, respecting the microbiome diversity and inducing fewer side effects. Currently, there are four main axes in development: probiotics, vaccines, phages and antimicrobial peptide therapies.

Microbiome and Probiotics Approach

The use of antibiotic therapy to eliminate, as a priority, *C. acnes* considered for a long time as major acne agent is less and less recommended especially in oral monotherapy [92] for at least two major reasons: development of resistance to antibiotics and disruption of the skin and gut microbiome (bacterial diversity loss) which is a crucial condition in normal healthy status. Furthermore, it is known that phylotype IA1 is overrepresented and involved in moderate to severe acne [37–39]. In parallel, dysbiosis in acne patient is associated with a decreased number of *S. epidermidis* which is able to control *C. acnes* proliferation via releasing of succinic acid and fatty acid fermentation product [23]; this way, the systematic eradication of *C. acnes* no

longer seems a relevant strategy. In consequence, it will now be necessary to take into account the other types of bacteria that constitute the skin microbiome. The steady state of the microbiome and its preservation is complex and little known. Recently, data from a clinical study showed that *Propionibacteriaceae* and *Staphylococcaceae* family were significantly overrepresented respectively in healthy controls and acne patient [101].

Without targeting only *C. acnes*, the new research orientations aim at the development new per os treatments or topical formulations based on probiotics. These innovative approaches aim to restore skin microbiome diversity and eliminate pathogenic species and induced inflammation in acne and other inflammatory diseases [79, 93, 102].

Recent knowledge demonstrated that microbial dysbiosis in the skin and the gut was implicated in many chronic inflammatory diseases. The improvement of dysbiosis and restoration of a normal skin microbiome are promising therapeutic strategies that have been tested in intestinal dysbiosis by oral administration of probiotics, living microorganisms that are beneficial to the host's health or by faecal transplantation with a pill which encapsulates stool of a healthy donor containing its intestinal microbiota. Faecal transplantation has been used in *Clostridium difficile* infections, in the irritable bowel syndrome or in inflammatory colitis. The faecal microbiome transplants have been demonstrated to be safe and effective for patients with *Clostridium difficile* infections [103].

The therapeutic approach for cutaneous dysbiosis is currently poorly developed, and some trials have been conducted in inflammatory conditions such as atopic dermatitis, psoriasis and acne [76, 104]. Topical treatment consisting of the commensal bacterium *Vitreoscilla filiformis* used in patients with atopic dermatitis showed significant clinical improvement with decreasing SCORAD (scoring atopic dermatitis) score and pruritus [104]. Moreover, the approach based on specific bacterial strains selected from the skin microbiome to treat atopic dermatitis patients has been shown to eliminate *S. aureus* and restore a balanced microbiome [105].

Some data have shown that probiotics could induce *C. acnes* inhibition with antimicrobial proteins such as *Streptococcus salivarius* which suppresses the growth of *C. acnes* by secreting a bacteriocin-like inhibitory substance [106]. Topical treatment with cream containing *Streptococcus thermophiles* was shown to display antimicrobial activity against *C. acnes* by ceramide production [107]. Probiotics could also act on immune response by inhibiting pro-inflammatory cytokine IL-8 from keratinocytes [108], by suppression of substance P-induced skin inflammation [109].

Some clinical trials have been conducted in acne patients to investigate the clinical benefit of probiotics [93]. Topical *Enterococcus faecalis* treatment has shown significant reduction of inflammatory acne lesions versus placebo [110]. *Lactobacillus plantarum* treatment also induces a decrease of acne severity and associated erythema [111]. Interestingly, association of freeze-dried *Bifidobacterium bifidum* and *L. acidophilus* used as a supplement to acne treatment showed greater resolution of acne compared with the non-supplemented group [112].

The new concept in acne drug development, despite *C. acnes* implication in acne, takes into account that *C. acnes* might also play a protective role in the skin by preserving a permanent low level of innate immunity activation, and thus therapeutic options that respect *C. acnes* equilibrium are an adequate alternative to treat acne [94]. An ongoing clinical study investigates the role of the skin microbiome and the potential use of a topical probiotic cream (YUN ACN cream) for acne treatment [113].

Recently some data postulated the beneficial effect of *S. epidermidis* in the physiopathology of acne by limiting *C. acnes*-induced colonization of the skin and inflammation [23]. However, overexpression of *S. epidermidis* could induce nosocomial infections. Therefore, to respect the balanced skin homeostasis, future treatments may be based on probiotics derived from *S. epidermidis* to allow a restoration of the normal skin microbiota and to target the regulation of the host's AMP mediators, without increasing *S. epidermidis* population [23].

Phage Therapy Approach

The development of phage therapy in acne would be suitable to target the specific *C. acnes* strain implicated in acne and preserve microbiome diversity profile of the healthy skin. This is based on the fact that in acne patients, skin *C. acnes* phages are more present than in the skin from healthy patients [18] and that an increase amount of phage with increasing age would be related to disappearance of acne in older individuals. Bacteriophages, the least understood component of the human microbiome, are viruses that can infect and kill bacteria. Interestingly it has been shown that type I strains of *C. acnes* appear to be more susceptible to phage infections compared to those from the type II phylogroup [114]. This interesting effect of phage on *C. acnes* type I has recently been confirmed and more detailed by Liu et al. who challenged genetically distinct *C. acnes* strains with 15 different phages and found that strains from types IA_1 and IA_2 phylogroups were more sensitive to infection, while those from types IB, II and III phylogroups appeared to be more resistant [18].

These data suggest that antiviral strategies based on certain strains of *C. acnes* could normalize the cutaneous microbiota and allow a potential personalized therapy based on a well-selected phage. While this approach seems to be attractive, few data are available on phage treatments essentially in acne.

Vaccine Approach

C. acnes is able to produce many virulence factors which are either secreted or anchored in the cell wall and which stimulate adjacent host cells, triggering inflammation and cell damages. Among them is the CAMP factor, a secretory virulence factor that constitutes an essential source of inflammation in acne physiopathology [115].

The various *C. acnes* phylotypes release various CAMP factors which could explain the pathogenic potential of the different phylotypes. The genome of *C. acnes* contains five genes encoding five CAMP homologs including CAMP factor 2, a major active co-haemolytic factor of *C. acnes* [116].

It has been shown that *C. acnes* CAMP factor is immunogenic [117] and that mice vaccinated by CAMP factor overexpressed in *Escherichia coli* experienced therapeutic protection against *C. acnes* [117–119]. Furthermore, the mutation of CAMP factor leads to a less effect on the inflammation induced by *C. acnes* in mice, demonstrating the essential role of CAMP factor in the cytotoxicity of *C. acnes* [115]. Incubation of ex vivo acne explants with an antibody targeting CAMP factor has shown to decrease IL-8 and IL-1β, usually expressed at higher levels in acne lesions. It has also been published that vaccination approach by using surface sialidase [120] or heat-killed *C. acnes* [121] as an antigen significantly decreases the inflammation induced by *C. acnes*.

All these data bring a valuable rational to consider the vaccination using *C. acnes* CAMP factor as a promising target for acne immunotherapy. As *C. acnes* phylotype IA_1 is widely known to be associated with acne, in parallel, higher expression of CAMP2 was detected in phylotype IA compared with other phylotypes, CAMP2 seems to be the best eligible and the most effective virulence factor to be targeted by the vaccine strategy.

It has been suggested that as CAMP2 is expressed by all other strains, it also might be important for the normal existence of the commensals that vaccination targeting CAMP2 may also affect *C. acnes* strains involved in the skin homeostasis and could induce colonization by pathogenic agents. Consequently, the ideal vaccination targets should be highly specific to avoid unwanted side effects due to the elimination of the needed bacteria. Although it is currently admitted that *C. acnes* phylotype IA_1 is highly associated with acne, recently our group demonstrated that acne severity would rather be dependent on the basal level of active innate immunity in patients prone to severe acne [36, 89]. Moreover, recent studies reported that severe acne was associated with an important *C. acnes* phylotype diversity loss and that this diversity loss was capable of inducing a cutaneous inflam-

matory response [37, 122]. Considering these data, it may be more suitable and relevant to target secreted virulence factors than focusing on vaccination strategy aiming to eradicate *C. acnes* or targeting a surface antigen. The specific inhibition of secreted virulence factors should limit the risk of unwanted targeting of nonpathogenic bacteria and overcome a possible selection of resistant bacteria [116].

Although CAMP2 vaccination approach seems to be attractive, complementary studies are needed to investigate the effects of such vaccination on the microbiota and also to demonstrate that such approach will not induce bacterial dysbiosis, leading to cutaneous pathologies.

Conclusion

In the last 3 years, a lot of new data have been associated with *C. acnes* deeply changing the pathophysiology of acne. First, it changed the name from *P. acnes* to *C. acnes*. Its role as commensal bacteria is more and more well-known. In addition, at the same time, its role in the pathophysiology of acne has also evolved. *C. acnes* is now well recognized as able to produce numerous virulence factors and thus to be one of the most pro-inflammatory bacteria of the skin. Moreover, the six main different phylotypes of *C. acnes* are able to activate differently the innate immunity which continually interacts with *C. acnes* through cytokines, antimicrobial peptides and specific receptors expressed by keratinocytes and other skin cells (TLR, PAR). Until recently, the severity of inflammatory lesions in acne was considered directly related to the proliferation of the bacteria. But now, the inflammation is considered in link with the severity of the dysbiosis of the microbiome with a diversity loss of the phylotypes of *C. acnes* combined with the overrepresentation of the phylotype IA_1. At the therapeutic level, the consequences are crucial as the objective of innovative treatments is not to eradicate *C. acnes* but to rebalance the microbiome to make it as close as possible of the microbiome of a normal skin. Consequently, new approaches with vaccines, antimicrobial peptides, probiotics, and phage therapy are developed in acne.

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Updates in Isotretinoin

2

Katherine A. Berry, Katherine K. Hallock, and Diane Thiboutot

Abbreviations

AAD	American Academy of Dermatology
ASDS	American Society for Dermatologic Surgery
CBC	Complete blood count
FDA	Food and Drug Administration
JAMA	*The Journal of the American Medical Association*
LFTs	Liver function tests

Introduction

Isotretinoin was first approved by the US Food and Drug Administration (FDA) in 1982 for the treatment of acne [1], and since that time, it has been the most effective treatment available for recalcitrant nodulocystic acne [2]. Although isotretinoin demonstrates unparalleled efficacy in clinical practice, few randomized controlled trials exist supporting its use, as was recently noted in the 2018 Cochrane review. The review looked at randomized clinical trials of patients with acne on isotretinoin compared to placebo, systemic and topical active therapies, and isotretinoin in different formulations, doses, and course duration. The quality of evidence both in breadth and study design was determined to be very poor, and the authors were unable to arrive at a definitive conclusion regarding its efficacy based on the limited number of randomized control trials available [3]. However, isotretinoin remains the standard of care for recalcitrant moderate to severe acne, and its efficacy in clinical practice remains unparalleled. Guidelines for the treatment of acne, including the use of isotretinoin, vary by country. The current consensus of the American Academy of Dermatology working group is that "the presence of moderate acne that is either treatment-resistant or that produces physical scarring or significant psychosocial distress, is an indication for treatment with oral isotretinoin" [4]. The European Directive states that isotretinoin should be reserved for patients with severe acne that has not or is not responding to antibiotic and topical treatments [5]. The Asian working group recommends isotretinoin for severe acne and as a second-line treatment for moderate acne that is unresponsive to other treatments [6]. A recent global working group recommended oral isotretinoin should be the first-line therapy for very severe acne and second-line for moderately severe to severe acne, but there remains significant variability in prescribing practices by country [7]. This chapter serves to

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highlight the most recent advances in isotretinoin treatment for acne found in the literature. In the past several years, there have been numerous studies with a focus on dosing, laboratory monitoring, depression, and timing of procedures in relation to isotretinoin treatment. This chapter will address the new data that was gleaned on isotretinoin over the past 5–10 years.

Dosing

Isotretinoin has a variety of dosing schedules, which have been explored in an effort to maintain efficacy while minimizing dose-dependent adverse side effects. Dermatitis is a common dose-dependent side effect. Elevations in liver enzymes and lipids were found to be dose dependent as well; however statistical significance was not reached [8]. The alternative dosing regimens that have been proposed include mini-dose, low-dose, alternate-day, and intermittent dosing. Mini-dosing comprises of up to 20 mg 2 days per week, while low-dose comprises of 0.25–0.5 mg/kg/day [9]. Alternate-day dosing is every other day, while intermittent dosing is 7–10 days per month. The increased tolerability of isotretinoin at these doses is significant, as a low daily-dose regimen showed a decrease in cheilitis and xerosis of 33% and 50%, respectively, in comparison to a higher daily-dose regimen (0.5–0.7 mg/kg/day) [9].

The widely recommended cumulative dose of 120–150 mg/kg of isotretinoin was based on two studies, the first of which noted a reduced rate of relapse when a threshold of 120 mg/kg was obtained [10]. The upper range of 150 mg/kg was suggested as no further therapeutic gain was noted after crossing this threshold [11]. However, more recent studies have demonstrated that cumulative doses exceeding 200 mg/kg are more effective at reducing the rate of relapse [12]. For example, a recent prospective study found a relapse rate of 26.9% in high-dose isotretinoin therapy (>220 mg/kg) in comparison to a relapse rate of 47.4% in a more traditional dosing regimen (170 mg/kg) [8]. Dosing does vary by population, and a recent study in Asia showed a low relapse rate despite low cumulative doses of isotretinoin (<100 mg/kg). The low dosing was tolerable, with only 6% of patients discontinuing use due to side effects, and side effects were less prevalent than one would expect at higher rates [13].

Isotretinoin is a lipophilic molecule with a half-life of 10–20 h. Twice-daily dosing is likely ideal due to the pharmacologic properties of isotretinoin. Studies have shown that daily dosing achieves a higher peak plasma concentration and has a less predictable pharmacokinetic profile than twice-daily dosing. This has led to concerns of an increased side effect profile. However, once-daily dosing is sometimes preferred by dermatologists due to improved patient adherence. Whether there are truly any differences between the clinical response and side effects of once-daily or twice-daily dosing is yet to be elucidated, and further studies are warranted.

Although there is controversy over the appropriate dosing regimen, there are accepted risk factors for relapse after isotretinoin treatment. A large nested case-control study evaluated 17,351 first-time isotretinoin users, and 26% of those treated required a second course of isotretinoin. Being male, under 16 years of age, and living in an urban area, all were significantly associated with requiring a second course. Receiving a cumulative dose greater than 2450 mg as well as isotretinoin treatment longer than 121 days was protective from relapse [14], which is consistent with other data. As the follow-up length for this study was up to 20 years, this likely reflects the true relapse rate.

Due to the many variations in studies, including the heterogeneity of outcomes, inconsistencies in dosing regimens, and differences in acne grading, there is an inability to perform a meta-analysis of the data. Furthermore, there is a lack of high-quality data. However, when comparing multiple doses of isotretinoin within the same study, it has been consistently shown that higher cumulative doses result in a lower relapse rate.

Laboratory Monitoring

Until recently there has been no consensus on laboratory monitoring during isotretinoin treatment, including the frequency and type of monitoring. Per the package insert, it is recommended to monitor lipid levels and liver functions tests (LFTs) at weekly or biweekly intervals until a response to isotretinoin has been established [15]. There is a significant variation between providers with respect to monitoring, which was highlighted in a survey study in the *Journal of Drugs in Dermatology*. This study revealed that greater than 60% of providers checked a baseline complete blood count (CBC), LFTs, and lipid panel, while 74% check a monthly lipid panel and LFTs, and 57% check a monthly CBC. When asked how these practices were developed, the majority of responders stated from residency training or personal experience. Only 13% stated that they used evidence-based guidelines. Despite monitoring, there was very rarely a change in patient management [16].

Laboratory monitoring is performed due to a concern about rare side effects of isotretinoin. Hepatotoxicity due to isotretinoin therapy has been reported [17], but over the decades of isotretinoin use, there have been no long-term hepatic sequelae [18]. Approximately 15–20% of patients do develop an increase in LFTs; however the majority are insignificant and resolve spontaneously despite continued treatment. Very rarely are the elevations greater than three times the upper limit of normal [16], which is ground for discontinuation of any medication or therapy in medical practice. Fatty liver, supplement use, and alcohol intake can affect liver enzymes, so screening for these conditions may be prudent prior to initiation of isotretinoin [19].

Lipid aberrations are the most common laboratory abnormality in isotretinoin users affecting up to 44% of patients [20], although they are very rarely high enough that pancreatitis becomes a concern. In a systematic review, it was found that only 4 of 25 cases of pancreatitis associated with isotretinoin use were associated with hypertriglyceridemia, while the others were idiosyncratic [21]. The mean increase in triglyceride levels from the baseline is 45.3 mg/dL at 8 weeks of treatment, and this does not significantly change at week 20, indicating there is no substantial late effect of isotretinoin therapy on triglyceride levels [22]. Furthermore, many providers do not require fasting prior to laboratory testing, and normal postprandial elevations in triglyceride levels may be the culprit [19]. It has also been shown that more frequent elevations are seen in patients with baseline triglyceride abnormalities, which may prompt an altered screening protocol [23]. However, normal baseline levels do not preclude the development of severe abnormalities [24].

Complete blood counts have been monitored due to case reports indicating possible thrombocytopenia and leukopenia [25, 26]. However, monitoring is not warranted, as abnormal values tend to resolve or remain stable during treatment [19, 22, 27] and severe blood dyscrasias are not substantiated by the literature.

Recent recommendations have been published that support less frequent laboratory monitoring. A standardized protocol for isotretinoin has been proposed [19]:

- Documentation of family and personal history of lipid, liver, or blood count abnormalities.
- Elimination of CBC monitoring, unless known abnormality or risk factor is identified.
- Baseline liver function and lipid panel.
- If baseline study results are normal, repeat liver function and lipid panel in 2 months (after the peak dose is attained). If repeated study findings in 2 months are normal, then no more laboratory monitoring is required.
- If baseline study findings, or study findings at month 2 are abnormal, or if there is a known lipid abnormality, then more frequent monitoring is required. If new medications or supplements are added during isotretinoin therapy, repeated laboratory testing should be considered.
- All female patients of childbearing potential receive monthly urine pregnancy tests according to iPLEDGE guidelines.

These guidelines reduce healthcare cost and variability while enhancing patient experience and maintaining safety. This was recognized as a pivotal study by the American Academy of Dermatology (AAD), suggesting that we are over-monitoring patients on isotretinoin and clinical practice should change [28].

Depression

An association between depression and isotretinoin use was first noted in 1983 [29]. In 1998 the FDA issued a warning stating that isotretinoin use may cause depression, psychosis, suicidal ideation, and suicide [30]. In 2005, a black box warning was added for these side effects. Several studies, including a case crossover [31] and systematic review [32], concluded that there is an association between isotretinoin and depression and suicide in some individuals.

Acne itself has been associated with depression and suicidality, which was explored in a cross-sectional study of 3375 patients. It was found that those with substantial acne in comparison to those with little or no acne had a two- to threefold increased risk for suicidal ideation (girls and boys, respectively). The association between acne and low attachment to friends, not thriving at school, and never having a romantic relationship or sexual intercourse was also found [33]. Depression and suicidal ideation that have been associated with isotretinoin may reflect the burden of severe acne rather than an effect of the medication.

Numerous studies demonstrate that depression improves after isotretinoin treatment [34–40]. A 2017 systematic review found that the change in depression scores from the baseline was not significantly different between patients receiving isotretinoin treatment and those receiving an alternative treatment [41]. Furthermore, the prevalence of depression after isotretinoin treatment significantly declined, and mean depression scores significantly decreased from the baseline [41]. Additionally, a recent meta-analysis showed a significant association between isotretinoin and improved depressive symptoms in comparison to the baseline [42]. It is also interesting to note a relationship between isotretinoin and depressive symptoms was found in retrospective studies, but no relationship was noted when analyzing prospective studies [42]. This highlights the complexity of confounding psychosocial and clinical factors.

However, the AAD acne guidelines state that "given the prevalence of depression, anxiety and suicidal ideation/suicide in the general population, and especially the adolescent population who may be candidates for isotretinoin therapy, the prescribing physician should continue to monitor for these symptoms and make therapeutic decisions within the context of each individual patient" [43].

Procedures

Scarring is a known significant complication of acne that can cause a large psychological toll. Until recently, the prevailing recommendation has been that scar revision and resurfacing procedures should be delayed for at least 6 months following isotretinoin therapy due to reports of abnormal wound healing and scarring [44–46]. The mechanism was thought to be due to the isotretinoin's effect on the pilosebaceous unit through causing apoptosis and an impaired regenerative capacity of the epidermis [47]. This standard of care has recently been revisited due to the increasing awareness that it was based on several small case studies and the growing volume of contradictory data documenting safety and efficacy of concomitant and recent isotretinoin use. Furthermore, the original case reports described procedures which are no longer commonly used that are much more invasive than the newer procedures utilized currently. One recent prospective study [48] and three systematic reviews [49–51] culminating in evidence-based recommendations have served to support a low rate of adverse outcomes and a lack of evidence to delay cutaneous procedures in the context of isotretinoin therapy.

In a prospective study monitoring adverse events in 503 procedures including laser, micro-

Table 2.1 Combined ASDS and JAMA consensus guidelines for procedures while on isotretinoin or within 6 months of isotretinoin use[a]

Procedural intervention	Consistency of evidence	Recommendation	Strength of recommendation
Mechanical dermabrasion with rotary devices	Inconsistent	Not recommended as it may be associated with adverse events in some patients	B/D
Manual dermabrasion and microdermabrasion	Consistent	There is insufficient evidence to delay manual or microdermabrasion	B
Chemical peel	Consistent	There is insufficient evidence to delay superficial chemical peels	B
		There is insufficient evidence on the use of medium or deep-depth chemical peels to make a recommendation	D
Cutaneous surgery	Inconsistent	There is insufficient evidence to delay or make recommendations for timing of cutaneous surgery	D
LASIK surgery	Inconsistent	Isotretinoin should be stopped before LASIK surgery	D
Laser hair removal	Consistent	There is insufficient evidence to delay laser hair removal	B
Vascular lasers	Consistent	There is insufficient evidence to delay vascular lasers	B
Fractional ablative/ nonablative laser	Consistent	There is insufficient evidence to delay fractional ablative or nonablative laser procedures	B
Fully ablative lasers	Consistent	Fully ablative laser procedures are not recommended	C

[a]Adapted from Waldman et al. [49] and Spring et al. [50]

dermabrasion, and incision involving 183 patients, only two cases of keloid formation were documented, and common side effects were transient, such as erythema and hyperpigmentation [52]. Another recent retrospective review looked at complications in the perioperative period involving surgery in which a skin incision was made in patients exposed versus unexposed to isotretinoin. They found that the complication rate was similar, 2.6% versus 2.4%, for those exposed versus unexposed, respectively [53]. A randomized split-face controlled study evaluated 18 patients receiving 10 mg of isotretinoin daily who also received three sessions of nonablative fractional laser on one half of the face. There were mild, transient adverse effects including erythema and edema. Both comedones and the appearance of atrophic boxcar scars were significantly improved on the treated side [54].

Such studies support the new guidelines to not delay procedures after isotretinoin use and suggest a low likelihood of permanent adverse effects, including scarring [47].

Although the American Society for Dermatologic Surgery (ASDS) guidelines and *The Journal of the American Medical Association (JAMA) Dermatology* consensus statements have been changed to reflect the most recent literature on procedures post isotretinoin treatment, the iPLEDGE, and isotretinoin manufacturers, recommendations have not been updated and still advise a 6-month waiting period [15, 55, 56]. Specific recommendations from the ASDA and the *JAMA Dermatology* consensus statements are found in Table 2.1.

Conclusion

Over the past 5 years, a new research has improved our understanding of isotretinoin and leads to several substantial clinical changes. Due to the heterogeneity of studies, the optimal dosing for isotretinoin therapy has yet to be elucidated. However, there is consistent data that supports higher doses are associated with a lower

rate of relapse. New evidence suggests that monthly laboratory monitoring may not be needed. Given the low rate of serious adverse effects, as well as the timing during which they occur, it is now recommended that lipid profile and liver function tests are completed at the baseline and after 2 months or when the maximum dose has been achieved. Further testing is only warranted for severe abnormalities and comorbid medical conditions. Although a causative effect between isotretinoin and depression has not been established, isotretinoin remains on the US FDA's list of top 10 drugs associated with depression and suicide. This in combination with acne itself being an established risk factor for depression makes it prudent to closely monitor this patient population. Finally, according to a panel of national experts who published a systematic review and consensus statement in *JAMA Dermatology* and the ASDS consensus statement, it is no longer recommended to wait for 6 months post isotretinoin treatment to undergo scar revision and resurfacing procedures [48, 49]. Despite the recent advances in isotretinoin, there remains an ongoing need for further high-quality research for better understanding and optimal use of this drug.

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3 Developing a Core Outcome Set for Acne Clinical Trials: Towards Standardization and Harmonization

Jerry Tan, Diane Thiboutot, Alison Layton, and Maegan Miklas

Why Perform Interventional Clinical Trials?

The underlying reason for undertaking clinical interventional trials in medicine is humanistic and patient centred – to reduce pain and suffering in patients with disease. These trials are performed to address uncertainties with treatment including the following: Does it work? How well does it work? What are the risks?

Concepts central to trials start with the intent of treatment – to affect pathophysiology of disease or reduce the impact on the patient's illness. Disease has been used to refer to abnormal structure or function of organs as evaluated by medical experts and/or laboratory testing and is thus based on either anatomical or physiological dysfunction. Illness, however, refers to the spectrum of aspects of being unwell subjectively reported by those affected patients [1].

Efficacy is the determination of whether a treatment can work for a certain disease under experimental controlled conditions of highly selected homogeneous patient populations as in clinical trials. Furthermore, there is enforced and monitored utilization of interventions and exclusion of other medical conditions and concurrent medications/treatments that could interfere with evaluations of benefit and risk [2, 3]. In clinical trials, primary endpoints are those selected to provide pivotal evidence to support an indication for the treatment of a specific disease. Measures that are not pivotal but supportive are called secondary or tertiary endpoints. Endpoints and their measures are predefined in trial protocols and are negotiated between sponsors and regulatory authorities [4].

Measurement Issues in Clinical Trials

The results of clinical trials on efficacy should be provided in metrics that can be of greatest value to patients and their clinicians in answering the questions: Does it work? How well does it work?

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What are the risks? Outcome measures are means to evaluate the effect of treatments both in benefit and in risk or adverse events. Depending on the source of evaluation, these may be clinician or patient reported. A third aspect, based on laboratory testing or instrumentation, may also be included [4]. Determination of clinical trial efficacy endpoints is critical in clinical trial design. If a physiological or morphological outcome is the primary endpoint, then relevant measures should be applied. In acne, these include acne lesion counts and global assessments. However, patient-reported outcomes, as secondary endpoints, can support the primary physiological endpoints if the latter achieve success. Alternatively, a patient-reported outcome can be selected as a primary endpoint if used to establish an indication for treatment of that construct (e.g. pain of acne lesions). Patient-reported outcomes are those reported directly by patients, without an intermediary, to reflect their experience. These can include signs, symptoms and varying aspects of function and adaptation. Relevant concepts or domains can be established a priori. Instruments for these domains developed by appropriate psychometric methodology and subsequently validated can then be used in clinical trials. Adequacy of these measures to support medical product labelling claims depends on satisfying criteria based on intrinsic characteristics (examples include number of items, framework, population of interest, administration and data collection methodology, response range, recall period, scoring, weighting, format, respondent burden and appropriate translation and adaptation as necessary), content validity and clinimetric properties [4].

However, across all fields of medicine, there has been a legacy of inadequate external validity of outcome measures in clinical trials, limiting their generalizability and confounding comparative effectiveness research (CER). There is unnecessary waste in the conduct of clinical trials – inefficient use of available resources and inadequate generation of useful data to inform healthcare utilization including CER. In the United States, recognition of this shortcoming led to allocation of US$1.1 billion for 2 years of CER under the American Recovery and Reinvestment Act. In 2010, the Patient-Centered Outcomes Research Institute was established to organize federally funded CER [5].

Issue with Acne Clinical Trials

Pathophysiological manifestations of acne involve follicular and perifollicular inflammation and its manifestations. Primary acne lesions include micro-comedones, comedones, papules, pustules, nodules and cysts. The secondary lesions of acne include macular erythema, macular pigmentation, atrophic scars and hypertrophic/keloidal scars. These are derived from visual examination and can be clinician or imaging based but can also reflect patient-based reporting of appearance. The impact of acne may involve psychological, sociological, occupational, adaptational and symptomatic aspects. Other relevant impacts of treatment may be appropriate to evaluate in clinical trials including satisfaction which can only be gleaned by specific interrogation of patients. These are best evaluated by direct reports from patients.

In acne, as in other healthcare conditions, decisions on treatment options should be based on the same outcomes, measured similarly. However, there are multiple treatments with outcomes measured in different ways. As consumers of healthcare research, we are faced with the dilemma of differing outcome measures for different interventions where there may be concerns about reporting bias and inability to compare the relative benefit of different interventions. Furthermore, most outcome measures were developed without input from patients [6–8].

In 2002, a retrospective analysis of 270 acne trials over the preceding five decades demonstrated multiple methodological weaknesses and a multiplicity of measures: 1237 of them. There were at least 25 methods of acne severity grading and 19 for lesion counting [7]. Ten years later, a systematic search of randomized acne trials published over the course of 1 year demonstrated persistent variability in outcome measurements used [9]. There have been more recent efforts to

advance global acne grading towards a standard. A Delphi consensus survey of expert dermatologists for important criteria for acne severity grading identified essential clinical components (defined as content-related items) and features (defined as scale-related properties). Components included determination of primary acne lesions, their quantity and extent and sites of involvement including extrafacial sites, while features included clinimetric properties (validity, reproducibility, responsivity, discriminant capacity) and adequate categorization of severity, efficiency and acceptance [10]. Recognizing the initial importance of the component criteria, a follow-up study evaluating extant acne severity grading scales showed four scales to rank in the highest quartile, including two previously used as Investigator Global Assessments (IGA) in prior acne trials for regulatory approval [11–14]. These scales could provide a pathway to development of an ideal acne global grading standard [15]. Nevertheless, the goal of a standardized system for acne severity assessment has not yet been achieved [16].

Regulatory Guidance

In 2018, the US Food and Drug Administration (FDA) published a final guidance document for establishing effectiveness of drugs in acne vulgaris. While a wide variety of outcome measures have been used in prior acne research, the de facto standard for acne clinical trials over the past two decades has increasingly been based on recommendations from this regulatory body. This document states that efficacy is to be based both on lesion counts (termed as noninflammatory and inflammatory by the FDA) and on the Investigator Global Assessment (IGA). Recognizing that there is no single standardized grading system for acne, the FDA encourages discussion of trial design and scales proposed by sponsors.

IGA is recommended as a qualitative static evaluation (obtained at time of examination and without reference to a prior time such as baseline) based on an ordinal scale with approximately five severity grades representing *clear*, *almost clear*, *mild*, *moderate* and *severe*. Each category is to be defined by clinically distinct definitions and should not include ranges of lesion counts. Furthermore, success on IGA is to be based on a *clinically meaningful metric* – defined as achievement of *clear* and *almost clear* and a two-category improvement from baseline. A caveat is that it does not address systemic retinoids where development programs, inclusive of outcome measures, are to be reviewed with the agency before trial initiation. Specific instructions on lesion counting are also provided including separate counting of inflammatory and noninflammatory counts. All facial areas are to be evaluated including the nose.

Treatment efficacy is to be established both on lesion count changes and IGA success to provide complementary quantitative and qualitative outcome measures. Acne lesion counting is considered a quantitative measure of acne severity with statistical potency due to the continuous nature of the measured variables. In contrast, global acne grading is qualitative but considered more clinically relevant as an indicator of acne severity [17].

Certain aspects of this guidance document deserve further consideration. While it posits that there are two types of acne lesions (noninflammatory and inflammatory), these only designate primary acne morphologies. Secondary ones include macular erythema, dyspigmentation and scars – hypertrophic and atrophic. Furthermore, while comedones may not have perceptible erythema, there is immunohistochemical evidence of increased expression of the pro-inflammatory cytokine interleukin 1 – alpha and histological evidence of inflammation [18, 19]. While the term IGA is used to designate the global scale used in pivotal acne trials in accord with US FDA terminology, it does not designate a singular unwavering scale. Acne IGA scales have varied over the past two decades with differences in categorical descriptions, number of categories and concepts included (area involved such as *less than half* and *almost all* versus text descriptions of numerosity such as *few* and *many*) [20]. Finally, the proposition that IGA success requires a clinically meaningful threshold is reasonable.

However, it has not been shown that a one- or two-grade reduction in IGA (but not achieving clear/almost clear) is not clinically meaningful [20]. There is thus a need to establish evidence for thresholds indicating clinically relevant differences in IGA categories.

Need for Standardization

Recognition of the need to standardize outcome measures in rheumatoid arthritis leads to establishment of the outcome measures in rheumatoid arthritis clinical trials (OMERACT) group. The success of this endeavour has transformed this initiative into an international collaboration with development of working groups in outcome measurements across the breadth of rheumatology treatment studies [21]. Aspects of the clinical condition relevant to measure in a clinical trial start with a framework of core concepts of life impact, pathophysiological manifestations and survival/death. Specific areas for these concepts include biological and physiological variables for pathophysiological manifestations and overall quality of life, general health perceptions and functional and symptoms status for life impact. Additionally, adverse events should be included in all clinical trials to provide a measure of risk within the context of risk-benefit analysis (see Fig. 3.1) [22].

What Are Core Outcome Sets?

If outcome measures for clinical trials were rationalized, standardized and harmonized for each disease, this would facilitate comparative effectiveness research and improve patient care. Furthermore, it would reduce wastage of resources in data collection for non-essential domains or with the use of outcome measures inadequately suited to purpose. Such a consensus-derived standardized minimal set of outcomes

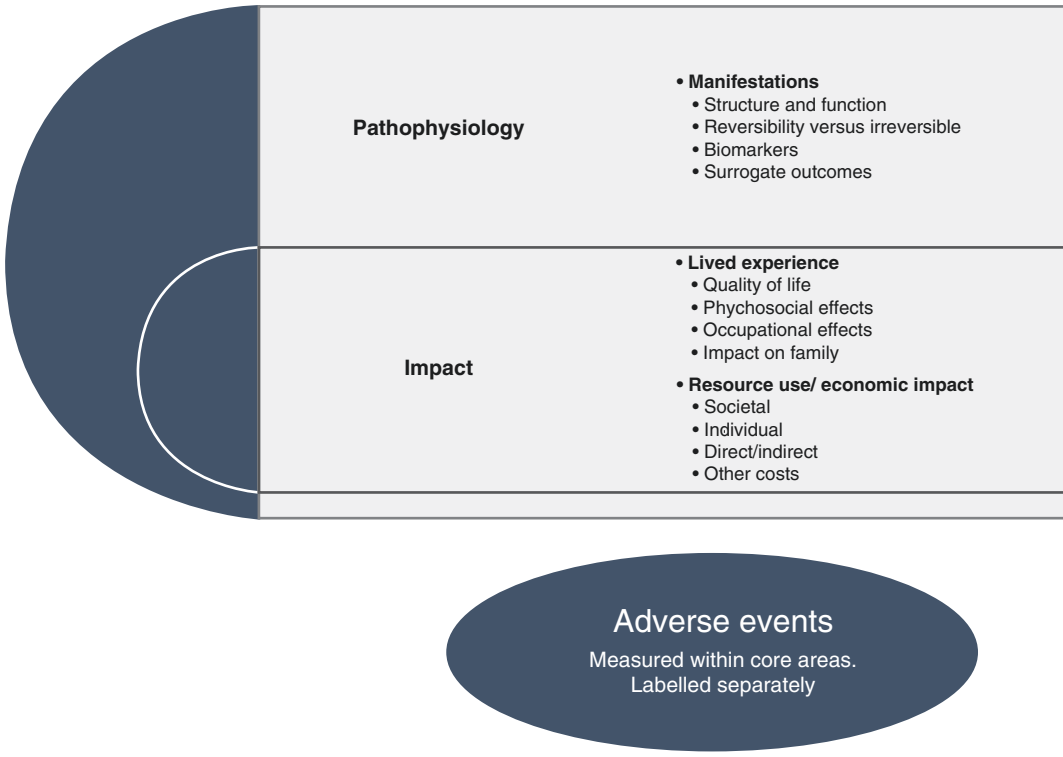

Fig. 3.1 Framework for developing core outcome sets based on disease concepts of pathophysiology and illness impact. (Modified with permission from Boers et al. [22])

which should be assessed and reported in all clinical trials of a target disease is termed a core outcome set (COS) [23]. A COS is a minimal standard and does not preclude additional or innovative measures in clinical trials. This is in recognition that ongoing innovation in objective, laboratory and imaging methodologies may supplant or coexist with current measures. This underscores the importance of periodic review of the COS with new developments. While some of the measures within the COS can serve as primary outcome measures for regulatory trials, it is not essential, and primary outcomes can be distinct from the COS.

A COS comprises all relevant outcomes (i.e. what to measure) and their respective measures (i.e. how to measure) to include in a clinical trial for the evaluation of treatment effects in a specific disease. Relevance is dependent on identifying the critical domains of disease from the concepts of pathophysiological manifestations, impact of illness and resource utilization. This determination should be consensus based involving a key stakeholder spectrum including patients, healthcare providers, journal editors and regulatory authorities where possible (see Fig. 3.2). Measures for these domains are then sought and evaluated for their utility and suitability for purpose. Determination of essential measures of these domains requires systematic literature search, risk of bias review and assessment of whether pre-existing measures are suitable or if a new one should be developed. The four major steps include conceptual considerations, systematic search, quality assessment and recommendations including selecting only one outcome

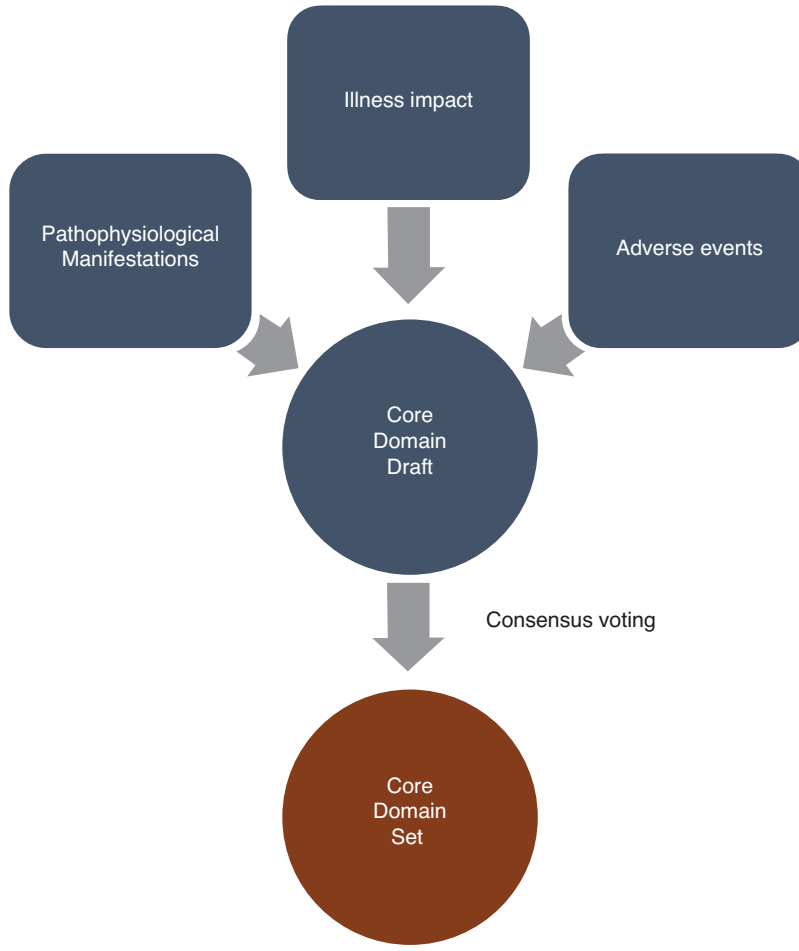

Fig. 3.2 Establishing core domain set. (Modified with permission from Boers et al. [22])

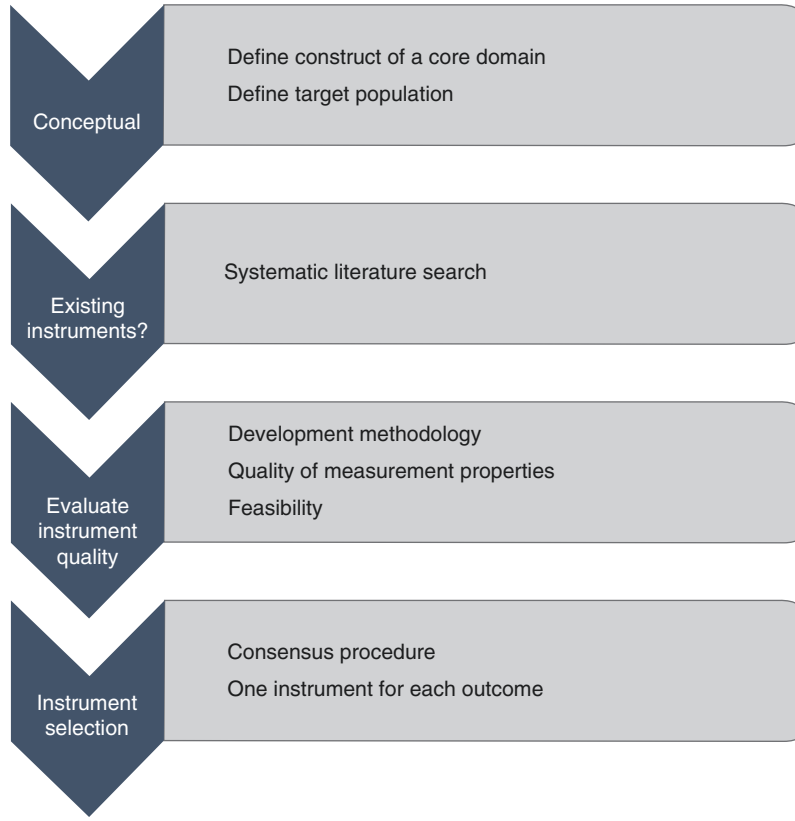

Fig. 3.3 The stepwise development for outcome measures from core domain set. (Modified from Prinsen et al. [25])

measurement instrument for each domain. Minimum requirements for including an outcome measurement instrument include high-quality evidence for content validity and internal consistency and consensus agreement (see Fig. 3.3).

The Core Outcome Measures in Effectiveness Trials (COMET) initiative, launched in 2010, was established to increase awareness of issues with clinical trial outcomes, encourage the development and uptake of evidence-based COS, promote involvement of patients, provide resources and prevent needless replication. Their handbook provides a detailed insightful account of logistical and developmental strategies to fulfil these objectives in development of COS. The process and operational aspects are crucial for groups looking to develop a COS. Resource allocation is not trivial – infrastructure should comprise a study management group, a study advisory group and a budget to incorporate staffing, software, websites, meetings, incentivization, publication and implementation [24]. A collaborative effort between the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) and Core Outcome Measures in Effectiveness Trials (COMET) initiatives provided further guidance in the selection of outcome measurement instruments [25].

Core Outcome Sets in Dermatology

In a systematic evaluation of efficacy outcomes in 10 randomly selected Cochrane Skin systematic reviews and the 220 dermatology trials included, the former did not include 742 (68%) of the 1086 trial outcomes. Furthermore, of 60 outcomes sought, 17 (28%) were not reported in any trial. Additionally, meta-analysis was not feasible for 11 of 23 (48%) primary review outcomes due to absent or inadequately reported trial outcomes. These findings suggest that der-

matology trials are not measuring the outcomes considered most important by patients and other stakeholders including clinicians, systematic reviewers and trialists [26].

Initiatives supporting the development of core outcome sets in dermatology include the International Dermatology Outcome Measures group (IDEOM) http://dermoutcomes.org/index.html and the *C*ochrane *S*kin – *C*ore *Ou*tcome *S*et *In*itiative (CS-COUSIN), part of the Cochrane Skin Group http://cs-cousin.org/. Efforts in atopic dermatitis have led to development of the Harmonized Outcome Measures for Eczema (HOME) roadmap. This provides a methodological framework for development of outcome measures in dermatology. In brief, this roadmap involves four steps: defining the scope and applicability of the core outcome set including population, intervention, setting, geographical scope and stakeholders; developing core set of outcome domains based on consensus involving representation from relevant stakeholders; development of a core outcome set measures; dissemination; and future revision of core outcome measures [27].

Process of Determining Acne Core Domains

Determination of *domains* relevant to a core outcome set is based on consensus determination by stakeholders regarding what is important to measure. Outcome *measurement instruments* provide the means of evaluating the domains of interest or how to measure [27].

The Acne Core Outcomes Research Network (ACORN) was established with a US National Institute of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases grant (1U01AR065109-01) to develop a core outcome set for acne clinical trials. Specific objectives are to deliver an acne COS based on accepted methodology, standardize reporting and measurement of key outcomes and facilitate acceptance by regulatory agencies including addressing their requirements and universal adoption in future acne trials. The challenges are manifold and include manpower and qualified personnel needs, paucity of funding, patient engagement, managing study teams, addressing methodological issues and facilitating dissemination and adoption on completion [28].

In an initial study, domains or outcomes of importance were first identified [29]. A broad range of globally dispersed stakeholders including 218 healthcare professionals, 307 patients or parents, 45 nonclinical researchers, 17 industry employees and 9 journal editors selected the 12 most important items to measure from an initial list of 24. Adverse events were advanced independently as a core outcome given its importance in risk-benefit analysis of interventions. After completion of three Delphi survey rounds, additional core domains identified were satisfaction with appearance, extent of dark marks and scars, long-term acne control, signs and symptoms, satisfaction with treatment and health-related quality of life [29]. These findings highlight the importance of patient-reported outcomes as three of these domains can only be determined by direct inquiry of patients (satisfaction with appearance, satisfaction with treatment and health-related quality of life), while another three could conceivably also involve patient input (extent of dark marks and scars, long-term acne control, signs and symptoms). This focus on patient-reported outcomes differs from the clinician-reported measures recommended by the FDA in determination of efficacy [17]. This likely represents the divergence in development where the domains included patient input. In COS development, there is still uncertainty about who is best positioned to evaluate signs and symptoms of acne – the clinician or the patient. This uncertainty is likely rooted in the dichotomy between the paradigm of disease (pathophysiology) and illness (circumstance and impact). HOME has taken the position that symptoms should be assessed by patients, while signs should be assessed by clinicians [27]. However, in acne, it can be posited that patients can assess both the way acne feels and how it looks. The latter may require training just as clinicians should be trained in lesion counting and global assessments [28].

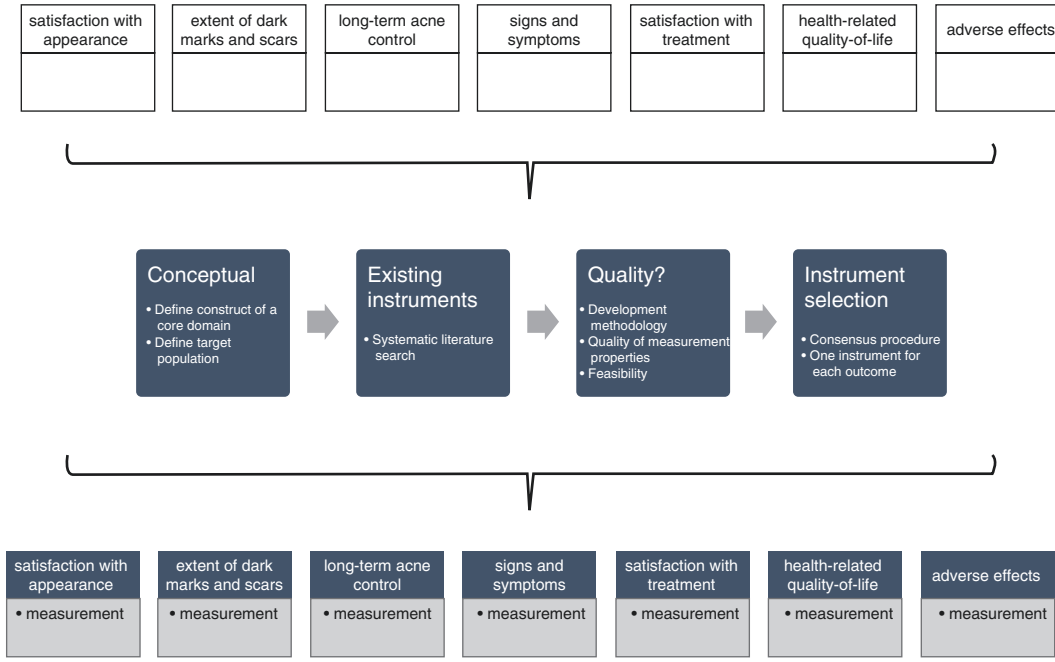

Fig. 3.4 From core domains to measurements. Based on evidence, quality assessment and consensus voting

The next steps in acne COS development will involve following the formalized methodology for selection of outcome instruments for potential inclusion in a core outcome set [25]. In this phase, critical aspects include a search for existing outcome instruments from systematic reviews, literature searches and other potential sources and quality assessment of these instruments for methodological quality and evaluation of measurement properties (reliability, validity), leading to recommendations on selection and a consensus procedure for final agreement on outcome measures, one per domain (Fig. 3.4). An alternative option is to conflate some domains, thereby necessitating fewer instruments (e.g. satisfaction with appearance, satisfaction with treatment received and long-term control could be assessed in a single patient-reported outcome measure). This determination will depend on whether there are pre-existing high-quality measures for these individual domains.

Summary

The multiplicity of outcome measures in acne research is costly and wasteful. It is an ongoing source of frustration to researchers involved in data synthesis, to clinicians trying to provide care based on best evidence and to patients seeking care. Addressing these issues requires a single-minded focus on what is needed, a COS. The first step is to ensure that clinical trials focus on the specific targeted condition and population at risk. The second is to ensure that what is evaluated is important to patients and to practitioners (core domains). Then, the best means to measure the latter (core measures) should be established to populate a COS for acne trials. Implementation is critical to ensure the acne COS is used in subsequent acne trials globally to avert yet more wasted effort. Ultimately, developing a COS for acne can improve patient care by helping future generations with acne and caring for acne patients to answer the following

questions: Does it work? How well does it work? What are the risks?

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Adult Acne Vulgaris

4

Hazel H. Oon, Shi Yu Derek Lim, and Chee Leok Goh

Epidemiology and Characteristics of Adult Acne

Acne vulgaris is a disorder of the pilosebaceous unit that primarily affects adolescents, although reports show that its prevalence remains significant beyond the teenage years. Adult acne is traditionally defined as acne in patients over 25 years of age and can be categorized as acne which is (a) persistent (continuing from adolescence into adulthood), (b) new-onset (acne appearing for the first time after 25 years old) or (c) recurrent (recurring acne episodes from adolescence into adulthood) [1].

Adult acne is more common in women than in men across all age bands. The prevalence of adult acne is highest in those aged 20–29 years (50.9% of women and 42.5% of men). The prevalence declines gradually with age but has been reported to occur in 15.3% of females and 7.3% of males older than 50 years [2]. A 10-year retrospective study analysing patients with acne in a tertiary dermatology referral center reported that the proportion of post-adolescent acne cases was approximately 30% of all the acne vulgaris cases seen, of which females predominate (64.1–69.6%) over the 10-year study period [3].

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Morphological features distinguishing adult from adolescent female acne include an increased ratio of lower- to upper-face lesions; increased presence of inflammatory nodules in the lower face with few or absent comedones, papules and pustules; and increased number of retentional lesions such as macrocomedones [4]. Adult acne tends to be persistent, with mild-moderate inflammatory activity, compared to adolescent acne and can present with severe flares [5].

Studies have demonstrated that the age of onset of acne may have bearings on its clinical features. Later-onset acne is reported to be associated with fewer total lesion counts, fewer comedones but an increased proportion of inflammatory lesions as well as a predominant "U-zone" distribution of lesions (i.e. affecting the cheeks, perioral and lower chin) [6].

Adult acne has a negative impact on the health-related quality of life, across self-perception, role-emotional and role-social domains. Adult acne is also associated with manifestation of mild to moderate symptoms of depression and/or anxiety and is reported to reduce productivity in work or school [7]. A study of 558 subjects aged 20 years and above found that when subjects with acne were compared with sex and age-matched controls, the mean difference in the dermatology life quality index (DLQI) was 2.4. There was no statistically

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significant difference in the magnitude of DLQI change when compared to those suffering from hidradenitis suppurativa, psoriasis, hand rash and atopic eczema [8].

Though there are many similarities between adolescent and adult acne, we will highlight the distinctive features and special considerations for adult acne in this chapter.

Pathogenesis of Adult Acne

Classically, the pathogenesis of acne has been linked to four key processes, viz. (a) increased sebum production, (b) alteration of follicular keratinization leading to comedone formation, (c) colonization of the follicle by *Cutibacterium acnes* (*C. acnes*) and (d) inflammation of the pilosebaceous unit [9].

Genetics

Current research provides greater insights into the molecular basis behind severe acne, as several genome-wide association studies have identified gene loci associated with severe acne in different populations – 1q24.2 and 11p11.2 in Han Chinese, 8q24 in European Americans as well as 1q41, 5q11.2 and 11q13.1 in the United Kingdom subjects [10–12]. A genome-wide meta-analysis conducted in 2018, involving a total sample size of 26722 subjects, identified a total of 20 risk association signals at 15 susceptibility loci [13]. The genes found in the Han Chinese population were not replicated in the meta-analysis, which may suggest a degree of ethnic variation in genetic contributors to acne. To date, there is no data differentiating gene loci between adolescents and young adults with acne vulgaris.

Dysbiosis

The role of skin dysbiosis in acne vulgaris, traditionally attributed to *C. acnes*, has been explored more deeply in recent years, to involve *Staphylococcus epidermidis* and *Malassezia* spp., among other microbes. There appears to be no difference in the quantity of *C. acnes* found in the skin of individuals with and without acne [14]. However, distinct subpopulations of *C. acnes* (classified by phylotype and ribotype) appear to predominate in acne skin. For example, phylotype IA1 has been found to predominate on the back of patients with acne, compared to a wide diversity in controls [15]. The loss of *C. acnes* phylotype diversity is thought to trigger the activation of the innate immune system, leading to cutaneous inflammation [16]. A novel way of classifying *C. acnes* by ribotype found that ribotypes 4 and 5 are strongly associated with acne, compared to ribotype 6 which is associated with healthy skin [14]. *S. epidermidis* has been found to inhibit *C. acnes* proliferation and *C. acnes*-mediated inflammation through the release of succinic acid [17]. The quantity of *Malassezia* spp. on the skin surface and within hair follicles has also shown a positive correlation with inflammatory acne [18]. Systemic antibiotics are also associated with changes in skin microbiota, some of which are transient and others persistent. In a longitudinal study involving four adult female patients suffering from persistent acne since adolescence, the relative abundance of *C. acnes* decreased, and *Pseudomonas* species increased after 4 weeks of minocycline. However, following 8 weeks of withdrawal from antibiotics, the levels of *C. acnes* and *Pseudomonas* species returned to baseline, while *Streptococcus* species remained increased and *Lactobacillus* species decreased from baseline [19].

Insulin-Like Growth Factor 1

IGF-1 (insulin-like growth factor 1) has been studied extensively for its role in acne, through suppressing FoxO1 and activating mTORC1 activity, initiating a cascade of events that potentiate inflammation and comedogenesis [20]. Raised IGF-1 is linked to diet and disorders of endocrine metabolism, which may be contributory factors to severe acne in adults.

Diagnostic Considerations and Patient Evaluation in Adult Acne

Acne Distribution and Severity Grading in Adult Acne

In female adult acne, the distribution of acne has been reported to be more common and prominent over the mandibular and neck area, with more inflammatory lesions overall [4] (Fig. 4.1). However, in a prospective observational study involving 374 subjects aged >25 years, these characteristics were present only in subgroups of their study cohort. Another report indicated that the distribution of acne was similar in 90% of cases of adult acne compared to adolescent acne [21].

In recognition of the differences in the clinical features in adults with acne compared to those without, AFAST (Adult Female Acne Scoring Tool), which assesses facial and mandibular acne separately, has been developed and validated for clinical use [22].

Severe Adult Acne and Associated Syndromes

Autoinflammatory Syndromes

Autoinflammatory syndromes have been described in association with acne eruptions (Table 4.1). While these syndromes are typically present in adolescence, some features may manifest in adulthood and are worthwhile diagnostic considerations. Other than the list described in Table 4.1, there exist other less-defined syndromes, some of which implicate similar genetic mutations [23–26].

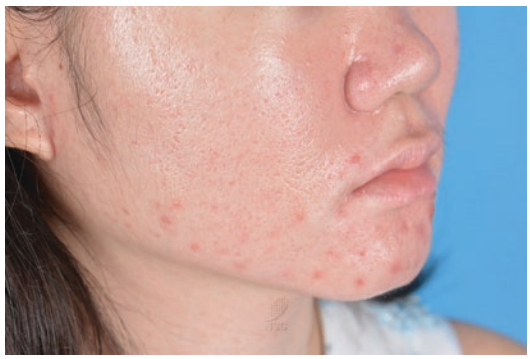

Fig. 4.1 Acne in this 26-year-old female is characterized by painful papules and macular erythema at the mandibular region and neck. The U-zone distribution and absence of comedones in adult female acne differentiates it from the T-zone distribution of comedonal acne in teenagers

Table 4.1 Autoinflammatory syndromes involving acne

Syndrome	Features	Genes implicated
PASH [23]	Pyoderma gangrenosum, acne, and hidradenitis suppurativa	*PSTPIP1*, *NCSTN*
PAPA [25]	Pyogenic arthritis, pyoderma gangrenosum, and acne	*PSTPIP1*
SAPHO [26]	Synovitis, acne, pustulosis, hyperostosis, and osteitis	Unconfirmed

Disorders of Endocrine Metabolism

Acne vulgaris in adults can be a manifestation of hyperandrogenism as androgens stimulate sebocyte activity [27] (Fig. 4.2). Careful evaluation for hyperandrogenism in adult women presenting with acne, coupled with appropriate hormonal evaluation, may uncover associated endocrinopathies such as polycystic ovary syndrome (PCOS).

Dietary Factors in Adult Acne

Diet is an important consideration in the management of adult acne. Recent studies have demonstrated the association of high glycemic load or index diet and the ingestion of milk/dairy products with acne severity [28–32]. This is believed to be mediated through the effects of IGF-1 [33]. The data on other aspects of diet remain mixed, and further evaluation is needed.

Approach to Evaluation of Adults with Acne

Table 4.2 summarizes an approach to the management of patients with adult acne.

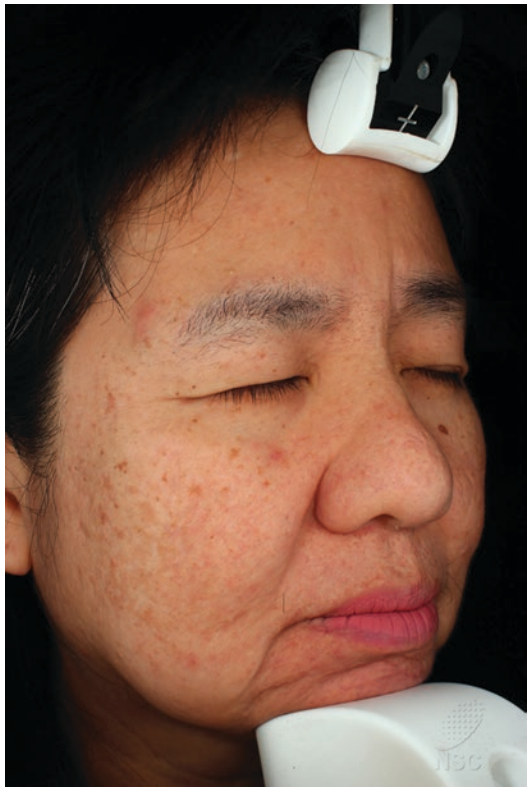

Fig. 4.2 Adult female acne in a 55-year-old showing inflammatory papules at the right temple and cheek, seborrhea and hirsutism with coarse hairs at the upper lip and chin. Free testosterone was mildly elevated at 11.72 pmol/L (normal range 0.45–9.02), but ultrasound of the ovaries was unremarkable. Although patients with adult female acne may not have PCOS or an overt endocrinopathy, they may still show some features of hyperandrogenism

Therapeutic Options for Adult Acne

The treatment options for adult acne encompass the conventional treatment of adolescent acne. However, there are additional treatment options for consideration if conventional treatment fails. The additional options will be discussed here.

Topical Dapsone

The use of topical dapsone gel has been found to be effective in the treatment of acne, with superior efficacy in females compared to males [34]. In addition, in subgroup analysis, adult females (ages 18–63) experienced a greater decrease in non-inflammatory and total lesions compared to adolescent females (ages 12–17), with a favourable tolerability and safety profile [35].

Oral Anti-androgens

Combined Oral Contraceptive Pills

Combined oral contraceptive pills (COCPs) containing estrogen suppress ovarian androgen production and increase sex hormone-binding globulin production, leading to decreased free testosterone [36]. A Cochrane review showed that COCPs were effective in treating acne [37]. The US Food and Drug Administration (FDA) has approved four types of combined oral contraceptives for treating adult acne (Table 4.3).

Caution should be exercised when starting female patients on oral contraceptive therapy. One should weigh the risks vs benefits with the therapy. Contraindications to oral contraceptive therapy include the following [42]:

- <21 days postpartum
- Age ≥35 and smoking ≥15 cigarettes per day
- Multiple risk factors for atherosclerotic cardiovascular disease
- Hypertension with systolic blood pressure ≥160 mmHg, diastolic blood pressure ≥100 mmHg or vascular disease
- Acute DVT (deep vein thrombosis)/PE (pulmonary embolism)
- Prior DVT/PE and with elevated risk of recurrent DVT/PE, regardless of whether patient is on anticoagulation
- Current or history of ischemic heart disease
- Stroke
- Known thrombogenic mutations
- Complicated valvular heart disease
- Peripartum cardiomyopathy of New York Heart Association severity class III or IV or class I or II within 6 months of diagnosis
- Systemic lupus erythematosus with positive or unknown antiphospholipid antibodies
- Migraine with aura
- Current breast cancer

Table 4.2 Approach to the management of adult acne

Points for evaluation	Possible diagnostic considerations	
History and examination Menstrual irregularity Infertility Virilization and hirsutism Weight gain Hypertension Additional laboratory evaluation Dehydroepiandrosterone Testosterone Luteinizing hormone: follicle-stimulating hormone ratio of 2 or above suggests PCOS Pelvic/abdominal ultrasound	Endocrinopathies	PCOS Congenital adrenal hyperplasia Androgen-secreting adrenal or ovarian tumour
History and examination Pyoderma gangrenosum Hidradenitis suppurativa Pyogenic sterile arthritis or synovitis Hyperostosis Osteitis or axial spondylarthritis Inflammatory bowel disease Psoriasis	Autoinflammatory syndromes	PASH syndrome PAPA syndrome SAPHO syndrome
History Dietary intake Family history	Dietary-aggravated acne Possible genetic association	
Differential diagnoses Rosacea Peri-oral dermatitis Folliculitis Acne cosmetica Acne mechanica Chloracne Drug-induced acneiform eruptions		

Table 4.3 US FDA-approved combined oral contraceptives for treatment of acne

Combined oral contraceptive	Estrogen (dosage in mg)	Progestin (dosage in mg)
Ortho Tri-Cyclen [38]	Ethinyl estradiol (0.035)	Norgestimate (0.180, 0.215, 0.250)
Estrostep [39]	Ethinyl estradiol (0.020, 0.030, 0.035)	Norethindrone (1)
Yaz, Beyaz [40, 41]	Ethinyl estradiol (0.02)	Drospirenone (3)

- Diabetes with severe neuropathy/retinopathy/neuropathy/vascular disease/ >20 years' duration
- Severe acute viral hepatitis or flare
- Decompensated cirrhosis
- Hepatocellular adenoma
- Complicated solid organ transplantation

Oral Spironolactone

Spironolactone, a diuretic, is an aldosterone receptor antagonist acting primarily through competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule. It also inhibits androgen synthesis. It is used off-label for female with adult acne. It is indicated when conventional antiacne therapy is ineffective and where androgenic effects are evident. Observational studies support the efficacy of oral spironolactone for the treatment of acne in women [43]. Menstrual irregularities, breast tenderness, dizziness, nausea, headache, polyuria and fatigue are common side effects [44]. Hyperkalaemia is a potential complication of spironolactone, though its incidence was not noted to be significantly elevated in young, healthy women receiving treatment for acne [45].

Oral Metformin

Metformin is a biguanide that has been used in the treatment of diabetes mellitus. Women with PCOS suffer from insulin resistance and thus hyperinsulinemia. Metformin is thus given to help prevent and treat diabetes mellitus in this setting. Through reducing ovarian hyperandrogenism in these patients, it also improves acne [46]. Furthermore, in patients with PCOS, metformin has also been reported to restore ovulation, reduce weight, decrease levels of circulating androgens as well as lower the risk of miscarriage and gestational diabetes [47].

There have been small-scale studies to show that it is an effective adjunct treatment for acne in adult males, though larger randomized controlled trials will be required to validate this [31, 48].

Laser and Light Therapies for Adult Acne

The efficacy of light therapy in the treatment of acne has been explored, of which blue light therapy and photodynamic therapy (PDT) have been most extensively studied [49, 50].

Blue light (in the 405–420 nm wavelength range) is believed to have an antimicrobial effect on *C. acnes* and to suppress sebocyte proliferation [51, 52]. Red light (680 nm) has been found to suppress sebum production [52]. In a split-face randomized trial, involving 90 patients with moderate to severe acne, receiving light-emitting diode blue light phototherapy twice weekly for 6 weeks, 51.7% of treated hemifaces achieved at least a two-grade reduction in the IGA scale, compared to 18% of the control hemifaces, and 81.6% of the treated hemifaces achieved a reduction of at least 40% of inflammatory acne lesions compared to 46% of controls 6 weeks after cessation of therapy [53]. A crossover extension of the trial, involving 49 of the original participants placed on a further 6 weeks of phototherapy on the contralateral hemiface, demonstrated that after further 12 weeks without treatment for the originally treated hemiface, the rate of return to baseline was 15.5% [54]. No serious adverse effects were observed in both phases [53, 54]. However, a systematic review and meta-analysis comparing blue light with nonlight interventions found that the benefits of blue light therapy were less clear, with an overall high risk of bias for most trials. The meta-analysis demonstrated that there was no significant mean difference in the number of inflammatory and non-inflammatory lesions in the blue light and comparator arms at weeks 4, 8 and 10–12 [50].

PDT with aminolevulinic acid (ALA), methyl aminolevulinate (MAL) and liposomal methylene blue (LMB) has been utilized for the treatment of adult acne [55]. ALA-PDT has been shown to suppress sebocyte growth and reduce lipogenesis [56, 57]. A meta-analysis demonstrated that ALA-PDT, MAL-PDT and LMB-PDT were effective for inflammatory acne, but adverse events such as pain, burning sensation, erythema, oedema and hyperpigmentation were more severe in the treatment than control groups [55].

Treatment of Adult Acne During Pregnancy and Lactation

Given the lack of safety data and the perception of acne as a low-impact disease, physicians often practise caution when prescribing treatment for acne in pregnant and lactating patients. Options for treatment in pregnancy include topical azelaic acid, erythromycin, clindamycin and benzoyl peroxide, as well as oral erythromycin (avoid the estolate salt) and azithromycin. In lactation, topical azelaic acid, erythromycin, clindamycin and tretinoin are thought to be safe, as well as oral erythromycin and azithromycin. It is recommended that systemic tetracyclines be avoided. The excretion of adapalene and benzoyl peroxide in breast milk is unknown, and thus caution should be exercised [58].

Comparison of Guidelines on Adult Acne

Most published guidelines on the treatment of acne vulgaris focus on its management in adolescents. Some differences regarding the management of adult acne arise between guidelines, primarily in the recommendations on the use of contraception and laser/light therapies.

The American Academy of Dermatology (AAD) recommends topical dapsone 5% gel for inflammatory acne, particularly for adult females. COCPs are found to be effective, with non-contraceptive benefits other than the treatment of acne. However, the AAD emphasizes that women on COCPs must also desire contraception as well and that the risks of COCPs must be compared to the risks of acne vulgaris in this setting. Spironolactone is useful in selected women, whereas the use of flutamide is discouraged in view of its side effects. The authors found that evidence recommending the use of physical modalities, such as pulsed dye laser and chemical peels, was limited, and more studies were needed for laser and light devices. Chemical peels may result in mild improvement in comedonal acne. In recent years, more favourable outcomes from PDT have emerged. It is likely that laser/light therapies may gain more use in the treatment of recalcitrant adult acne treatment [59].

The Global Alliance to Improve Outcomes in Acne guidelines place a special emphasis on the management of adult acne, recommending topical retinoids with or without benzoyl peroxide as important components in therapy, and skin care regimens such as moisturizers and pH-balanced cleansers to improve safety and tolerability of treatment. Strategies to minimize irritation are also emphasized, as dry and sensitive skin is more common in adult females. Oral therapies, including a limited duration of antibiotics, isotretinoin and hormonal treatments, can also be useful for adult female acne, though the authors recommend a risk/benefit analysis prior to initiating contraceptive medication for the treatment of acne. The use of topical azelaic acid, and topical dapsone or clindamycin/benzoyl peroxide in combination with topical retinoids, is also effective [9].

The S3 guidelines from Europe recommend that hormonal anti-androgens in combination with either a systemic antibiotic or a topical treatment (other than an antibiotic) can be considered for the treatment of severe papulopustular or moderate nodular acne. The authors commented that blue light monotherapy can be considered for mild to moderate papulopustular acne. They were not able to make a recommendation for or against light or laser therapies, otherwise noting that PDT is effective for severe papulopustular or moderate nodular acne but it lacked a standard treatment regimen to ensure a favourable safety and tolerability profile [60].

The Japanese Dermatological Association guidelines differed in some respects from the others, considering certain contextual factors unique to Japan. Oral contraceptives and spironolactone were not recommended in view of the lack of health insurance coverage, adverse effect profile and lack of comparison with other treatments. Laser treatment was also not recommended, citing equipment issues, lack of review in Japan and lack of health insurance coverage [61].

The Southeast Asia study alliance guidelines state that COCPs are effective; however the regional acceptability of COCPs is low, and adverse effects and cultural and religious factors need to be addressed during consultation. Energy-based devices and PDT may be considered as alternative treatment modalities in patients who are unable to tolerate or are nonresponsive to standard therapy [62].

The Dermatological Society of Singapore (DSS) has specific guidelines for adult acne in females, stratified according to disease severity, ranging from topical retinoids, benzoyl peroxide, topical and oral antibiotics and COCPs to oral isotretinoin, in conjunction with gentle cleansers, acne-specific moisturizers, sunscreens and lip balms to manage side effects. The guidelines state that adjunct therapies such as chemical peels and light/laser therapies like PDT with 5-aminolevulinic acid and intense pulsed light (IPL) or blue or red light in combination blue-red

light-emitting diode phototherapy and erbium-glass laser may be offered to patients [63].

The differences in treatment guidelines appear to arise from interracial variations in the skin, such as the propensity for post-inflammatory hyperpigmentation and irritation, as well as cultural acceptability of therapies, medical costs and insurance coverage.

Prognosis and Long-Term Outcomes

Adult acne in female typically persists in a mild-moderate disease state [5]. Thus, maintenance therapy is important. Topical maintenance therapies for the adult population reported to be effective include adapalene in combination with low-dose alpha- and beta-hydroxy acids and clindamycin in combination with benzoyl peroxide, azelaic acid and topical retinoid monotherapy [64–66].

Conclusion

Acne vulgaris is a common disorder that may persist beyond adolescence or indeed begin only in adulthood. Its burden in adult patients should not be underestimated. When evaluating an adult patient with acne, it is important to consider associated syndromes, endocrinopathies and the impact of lifestyle and diet on acne severity. In adult women, anti-androgen therapies are promising, though initiating treatment involves a careful discussion with the patient about the risks and benefits of therapy. Metformin, as well as light therapies, requires further studies for validation.

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Topical Retinoids and Acne

5

Mark C. Marchitto, Sewon Kang, and Anna L. Chien

Introduction

Acne vulgaris is an extremely common skin condition, affecting approximately 85% of adolescents with the potential to persist well into adulthood [1]. Acne vulgaris is a disease of the pilosebaceous unit characterized by sebum overproduction, abnormal follicular keratinization, the presence of *Cutibacterium acnes*, and inflammation [2–4]. Topical retinoids have been established as the first-line treatment for comedonal and inflammatory acne [5, 6]. Prior to the advent of retinoids, topical benzoyl peroxide (BPO) and sulfur-containing compounds were used for mild to moderate acne, with tetracycline antibiotics and oral steroids reserved for more severe and refractory cases [7–9].

The effects of vitamin A on the skin were first described in the literature in the early twentieth century [10–12]. However, it wasn't until the early 1960s when the first retinoid, tretinoin, was approved for medical use, pioneered by Albert Kligman and James Fulton of the University of Pennsylvania [13, 14]. Tretinoin remained the only topical retinoid approved for the treatment of acne until the development of the polyaromatic third-generation retinoids, adapalene and tazarotene, in the mid- to late 1990s [15–17]. Adapalene, a synthetic retinoid created by Galderma Laboratories in France, was found to be equally effective as tretinoin in the treatment of acne vulgaris with the added benefit of a lower skin irritation potential and thus greater tolerability [18, 19]. Tazarotene, also a third-generation topical retinoid, came onto the market in a similar time period and was FDA approved for the treatment of both psoriasis and acne [20, 21]. Tazarotene was shown to have similar efficacy to its counterparts, tretinoin and adapalene, in treating acne [22–25]. Over the years, several combination therapies of retinoids with topical antibiotics and BPO have also been developed and marketed with much success [26, 27].

In the past year, a new topical retinoid has emerged as a potent and well-tolerated option for the treatment of acne vulgaris. Trifarotene, a fourth-generation topical retinoid, has been shown to be effective in the treatment of both inflammatory and non-inflammatory acne on the face and trunk [28–30]. This retinoid appears to offer so far a better side effect profile and overall tolerability than its older counterparts.

Structure and Mechanism of Action

Topical retinoids can be classified as naturally occurring vs. synthetic. All-trans retinoic acid (tretinoin) and its precursor all-trans retinol are

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the only naturally occurring topical retinoids used in the treatment of acne. Adapalene, tazarotene, and trifarotene are synthetic retinoids and are not endogenously produced by the body. The structural differences between tretinoin and the synthetic retinoids are very evident, but similarity in retinoid effects is seen through their common ability to bind to and activate retinoid receptors (Fig. 5.1).

Retinoids exert their effects through the binding of retinoid receptors found within the nucleus of epidermal keratinocytes affecting gene transcription. There are two retinoid receptors in which the topical retinoids have varying affinity for, the retinoic acid receptors (RAR) and retinoid X receptors (RXR) [31]. RAR and RXR form dimers with their retinoid ligand and bind to retinoid acid response elements (RARE) in the promoter regions of retinoid-responsible genes [32–34]. Each receptor has three isotypes (α, β, and γ), with RXR-α being the most common retinoic acid receptor in the skin. The various topical retinoids have distinct binding properties to these receptors (Table 5.1), which may lead to the specific downstream effects seen for each retinoid.

One of these effects in acne involves the normalization of follicular keratinization and the cohesion of terminally differentiated keratinocytes comprising the stratum corneum (corneocytes). As a result, microcomedones, the earliest lesions of acne, are unseated and expulsed allowing sebum to reach the skin surface. This process reduces obstruction of the pilosebaceous unit and formation of new acne lesions [35–37]. Topical retinoids also have significant anti-inflammatory properties, as they have been shown to reduce the release of a number of inflammatory cytokines including IL-1β, IL-6, IL-12, TNF-α, and IFN-γ [38, 39]. Additionally, retinoids have also been found to decrease the expression of keratinocyte Toll-like receptor (TLR)-2, which upregulates the synthesis of inflammatory cytokines upon interaction with *Cutibacterium acnes* in acne lesions [40, 41]. Lastly, topical retinoid administration leads to atrophy of sebaceous glands and a decrease in sebum production inhibiting inflammation induced by sebum-dependent *C. acnes* [42–44].

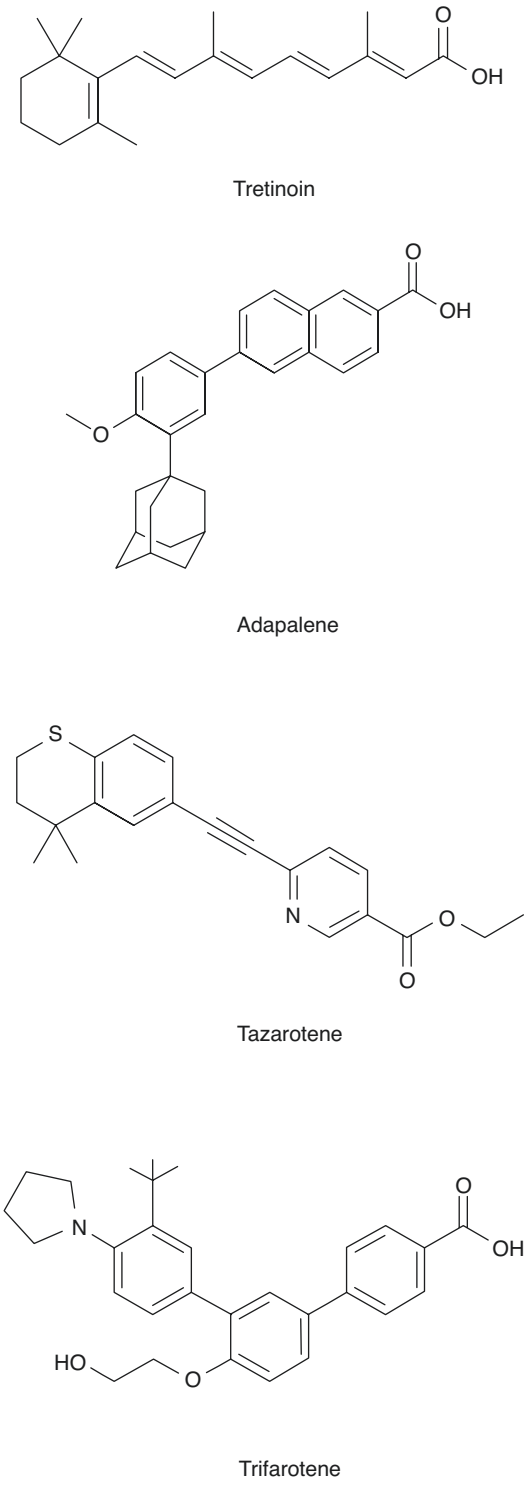

Fig. 5.1 Chemical structures of the topical retinoids

Table 5.1 Binding specificities of topical retinoids to nuclear receptors

Retinoid	RAR-α	RAR-β	RAR-γ	RXR-α	RXR-β	RXR-γ
All-*trans* retinoic acid (tretinoin)	++	++	++	(−)	(−)	(−)
Adapalene	*Weak*	++	++	(−)	(−)	(−)
Tazarotenic acid	+	+++	++	(−)	(−)	(−)
Trifarotene	(−)	(−)	+++	(−)	(−)	(−)

Adapted from Wolverton [94]
+ Minimal binding, ++ moderate binding, +++ relatively strong binding, (−) no binding

All-Trans Retinol and All-Trans Retinoic Acid

All-trans retinoic acid, tretinoin, is the prototypic topical retinoid used in the treatment of acne [45]. The mechanistic pathway of all-trans retinoic acid is shown in Fig. 5.2. Tretinoin is synthesized naturally within keratinocytes from all-trans retinol, which is the natural alcohol form of vitamin A. Retinol is stored in the liver and is transported to the skin from the blood bound to retinol-binding protein (RBP). Once in the dermal vasculature, all-trans retinol is taken up by basal keratinocytes where free all-trans retinol binds cellular retinol-binding protein (CRBP). Retinol can be stored in the epidermis as retinyl esters [46, 47]. Two distinct enzyme systems act to covert retinol to retinyl esters, acyl CoA:retinol acyltransferase (ARAT) and lecithin:retinol acyltransferase (LRAT). ARAT is more active in the upper epidermis and important for topically applied retinol, while LRAT acts to convert endogenous sources of all-trans retinol to retinyl esters in the lower portions of the epidermis [48].

When retinoic acid levels are low in the epidermis, retinyl esters are hydrolyzed to liberate retinol which is then oxidized to form all-trans retinoic acid. Newly synthesized all-trans retinoic acid binds to cytosolic retinoic acid-binding protein (CRABP), the predominant binding protein for all-trans retinoic acid in the human skin [49, 50]. Once bound to CRABP II, all-trans retinoic acid translocates to the nucleus of keratinocytes where it binds its retinoic acid receptors. While all-trans retinoic acid does not bind to RXRs, the 9-cis isomer of retinoic acid (9-cis retinoic acid) binds with high affinity to these receptors [51]. Together with their respective ligands, RAR and RXR form heterodimers binding to retinoid acid response elements (RARE) in the promoter regions of retinoid-responsible genes leading to the downstream effects mentioned above.

Topical tretinoin is available in numerous formulations (shown in Table 5.2), the most well-known being Retin-A cream (0.025%, 0.05%, and 0.1%). Other formulations include gel and solution. The highest concentration is 0.1% cream/gel. A complete list of the available topical retinoids and their preparations is shown in Table 5.2.

Adapalene

Adapalene is a third-generation synthetic topical retinoid that is photostable, rigid, and highly lipophilic. Compared to tretinoin, adapalene has a higher affinity for RAR-β and RAR-γ with weak affinity toward RAR-α. Given the fact that RAR-β is not expressed in keratinocytes, its primary target is RAR-γ, making it a more selective retinoid than tretinoin [15–19]. Consistent with this, adapalene has been shown to induce expression of CRABP-II despite not binding the cellular retinoic acid-binding proteins (CRABPs) [52, 53]. This occurs because adapalene activates RAR-γ/RXR heterodimer and CRABP-II is a RARE-containing gene. Adapalene does not interact with RXRs.

In addition to effects on inhibiting neutrophil chemotaxis and release of neutrophil-derived free-radical and reactive-oxygen species, adapalene has also been linked to numerous anti-inflammatory effects. Adapalene is associated with decreased inflammatory mediators such as

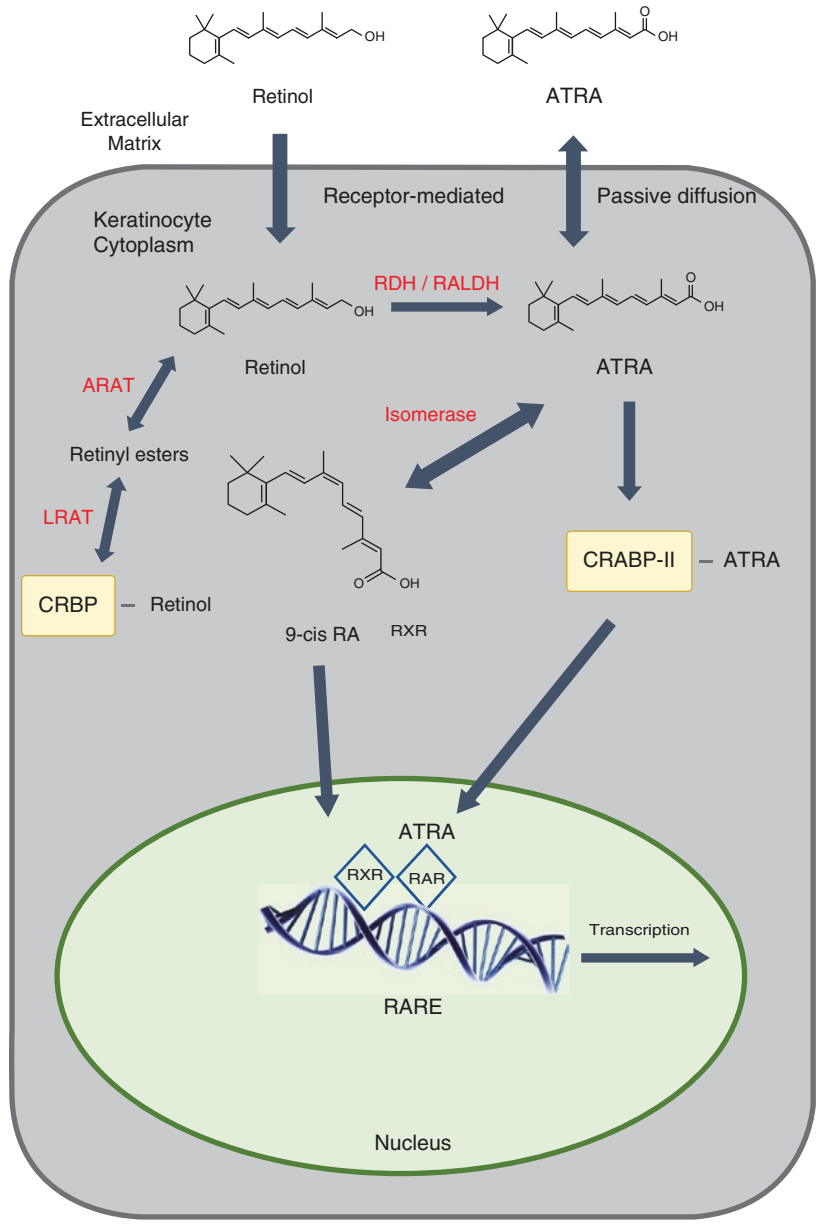

Fig. 5.2 Overview of retinoid activity. CRBP cellular retinol-binding protein, CRABP cellular retinoic acid-binding protein, ATRA all-trans retinoic acid, RA retinoid acid, RAR retinoic acid receptor, RXR retinoid X receptor, RARE retinoic acid response element, ARAT acyl CoA:retinol acyltransferase, LRAT lecithin:retinol acyltransferase, RDH retinol dehydrogenase, RALDH retinaldehyde dehydrogenase. (Adapted from Baert and De Spiegeleer [95])

Table 5.2 Preparations of the topical retinoids

Generic name	Trade name	Available formulations
All-*trans* retinoic acid (tretinoin)	Atralin®, Avita®, Retin-A®, Retin-A Micro®, Tretin-X®	Cream: 0.025%, 0.038%, 0.05%, 0.1%; gel: 0.01%, 0.025%, 0.04%, 0.05%, 0.1%
Adapalene	Differin®	Cream: 0.1%; gel: 0.1%[a], 0.3%; lotion: 0.1%
Tazarotene	Tazorac®	Cream: 0.05%, 0.1%; gel: 0.05%, 0.1%; foam: 0.1%
Trifarotene	AKLIEF®	Cream: 0.005%
Tretinoin/clindamycin	Ziana®, Veltin®	Clindamycin phosphate 1.2%/tretinoin 0.025% gel
Adapalene/benzoyl peroxide	Epiduo®	Benzoyl peroxide 2.5%/adapalene 0.1, 0.3% gel

[a]Adapalene 0.1% available over the counter

leukotrienes and prostaglandins by way of inhibition of the lipo-oxygenase pathway and arachidonic acid metabolism [54, 55]. In skin explant models, adapalene use was associated with increased keratinocyte CD1d expression, as well as decreased keratinocyte TLR-2 and IL-10 expression [41].

Unlike tretinoin, adapalene is photostable and is not prone to oxidation by BPO. Thus fixed combination formulations of adapalene with BPO have been developed and are approved for the treatment of both inflammatory and non-inflammatory acne vulgaris.

Given its highly lipophilic nature, adapalene is thought to penetrate follicles faster and more efficiently than its first-generation counterpart. The lipophilicity of adapalene also contributes to its negligible systemic absorption, as the drug dissolves within sebum after penetrating the follicle.

Adapalene is now available over the counter as a 0.1% gel. It is also available as prescription 0.1% cream, 0.1% solution, and 0.3% gel for the treatment of acne.

Tazarotene

Tazarotene is a third-generation synthetic retinoid. It is a prodrug in that tazarotene needs to be hydrolyzed in tissues to its active metabolite, tazarotenic acid. Similar to adapalene, tazarotenic acid selectively binds to the RAR-γ nuclear receptor and with lower affinity for the RAR-α and RAR-β [56]. Tazarotenic acid does not interact with the RXR nuclear receptors. Through binding of the RAR nuclear receptors, tazarotenic acid acts to normalize the follicular epithelium in acneiform skin by downregulating the abnormal expression of keratinocyte transglutaminase I (Tgase I), epidermal growth factor receptor, and hyperproliferative keratins K6 and K16 [57, 58].

As with adapalene, tazarotene is light-stable and not oxidized by BPO; thus it can be applied in the morning and in combination with BPO. Tazarotene is available in 0.05% and 0.1% cream, 0.05% and 0.1% gel, and 0.1% foam formulations. Tazarotene foam (FABIOR) is unique as it is the only FDA-approved topical retinoid in a foam vehicle for the treatment of acne. This formulation has been purported to increase compliance in some patient populations given its ease of use [59, 60].

Topical application of tazarotene gel has been shown to produce high cutaneous concentrations with very minimal systemic absorption, as it is rapidly metabolized to tazarotenic acid in the skin [61, 62].

Trifarotene

Trifarotene is a newly developed fourth-generation topical retinoid that has been shown to be highly efficacious in the treatment of acne vulgaris. Trifarotene is a selective RAR-γ agonist with virtually no effect on RAR-β and RAR-α receptors and no effect on RXR receptors [28, 29]. Although not proven, this receptor selectivity of trifarotene may be behind a better side effect profile and overall tolerability as compared to its early generation retinoid counterparts.

CD5789 (trifarotene) has been shown to be pharmacokinetically stable in cultured keratinocytes and rapidly metabolized in hepatic microsomes. Initial research in animal models established the potent anticomedogenic properties of trifarotene. In rhino mice, topical application of trifarotene eliminated almost all comedones with a dose ten times lower than that required for tazarotene and tretinoin [63]. Trifarotene was also found to have significant anti-inflammatory effects as well as rapid antipigmenting activity in vivo [63]. The strong antipigmentation effect of trifarotene may prove to be one of its greatest attributes as post-inflammatory hyperpigmentation (PIH) is a frequent sequelae of inflammatory acne with more significant PIH seen in darker skin types.

In addition to its comedolytic, anti-inflammatory, and antipigmenting effects, novel mechanistic pathways of trifarotene were identified in large-scale gene expression analyses including (1) downregulation of cell adhesion proteins, such as dystonin, leading to increased

comedolytic activity, (2) upregulation of aquaporin 3 (AQP3) channels and peptidyl arginine deiminase 1 (PADI1) activity resulting in improved skin hydration and barrier function, and (3) downregulation of membrane metalloendopeptidase (MM) resulting in decreased degradation of elastin fibers.

To date, three large-scale phase III clinical trials (the 12-week PERFECT1 and PERFECT2 trials and a separate multicenter open-label 52-week trial) have demonstrated substantial evidence for the efficacy and safety of trifarotene 50 μg/g cream in treating moderate facial and truncal acne [29, 30]. In these trials, trifarotene had a manageable tolerability profile. Expected local cutaneous irritation and pruritus were short-lived and improved with continuation of therapy. Trifarotene is now available as prescription 0.005% cream.

Combination Therapies

Topical retinoids can be used as the sole treatment for mild to moderate acne, but synergistic effects can be achieved when they are combined with an additional topical anti-acne agent. Combination of a topical retinoid with topical clindamycin, BPO, and/or salicylic acid has been shown to be superior to topical retinoid monotherapy [26, 27]. This therapeutic advantage is consistent with acne's multifactorial disease pathogenesis [64–68]. By targeting multiple pathways concurrently with combination agents, clearance of lesions occurs at a faster rate compared to monotherapy [69, 70]. Available combination therapies of topical retinoids are listed in Table 5.2.

Adverse Effects

Patient-reported cutaneous adverse effects (AEs) to topical retinoids are common. In a number of studies, up to 70% of patients receiving topical retinoid therapy reported cutaneous AEs [71–73]. By far, the most common AE of topical retinoids is skin irritation characterized by erythema and skin peeling or desquamation. All topical retinoids are known to produce this reaction, termed "retinoid dermatitis." and the severity depends on the strength of the retinoid. It has been shown that temporary reduction in the frequency, amount, and/or duration of retinoid application improves the erythema and desquamation. Other localized cutaneous AEs include pruritus, burning, stinging, dryness, and irritation. Application of topical retinoids also leads to a decreased tolerance to solar radiation. Therefore applying broad-spectrum sunscreens should be strongly recommended while patients are being treated with topical retinoid-containing products.

Patients should be counseled regarding these side effects and that they are often temporary and improve with continued use. Temporary worsening of acne may occur within the first weeks of therapy. Additionally, patients should be advised to avoid the use of irritating topical products, abrasive soaps, and certain cosmetics (i.e., cosmetics containing microbeads). Retinoids are also applied in the evening to minimize photosensitivity and to avoid the inactivation of retinoids by ultraviolet rays. Without proper counseling, the side effects of topical retinoid use may lead to patient non-adherence.

It is important to note that systemic absorption of retinoids from topical application is negligible and the levels of endogenous retinoic acid in the blood are not increased by twice-daily application of 0.025% tretinoin to more than 40% of body area over a period of 1 month [74, 75]. Furthermore, controlled topical administration of tretinoin at doses used for acne therapy (2 g of 0.025% gel applied daily to the face, neck, and upper part of the chest for 14 days) has less influence on plasma levels of endogenous retinoids than diurnal and nutritional factors [75]. Indeed, a large, population-based study demonstrated no excess risk of birth defects in offspring born to mothers who were exposed to topical tretinoin during pregnancy [76]. Therefore, no evidence exists for teratogenicity of topical tretinoin when appropriately used in humans. However, given the well-known teratogenicity of systemic retinoids and that acne is not a life-threatening condition to the mother or fetus, generally it is recommended to hold off on topical retinoid ther-

apy during pregnancy. Tretinoin and adapalene are pregnancy category C, while tazarotene is pregnancy category X. Trifarotene does not yet have a pregnancy categorization.

Topical Retinoids in the Treatment of Acne Sequelae

Two widely observed sequelae of acne include atrophic scarring and post-inflammatory pigmentary skin changes. Post-acne scarring affects up to 95% of individuals with inflammatory acne [77]. Moreover, there is evidence to suggest that atrophic scarring can result from initially non-inflammatory comedonal acne lesions [78]. It is well established that topical retinoids aid in collagen restoration in photodamaged skin by stimulating fibroblasts to increase dermal procollagen, thus protecting against UV-induced loss of procollagen [79–81]. In recent years, topical retinoids have been explored for the treatment of post-acne scarring. Tretinoin-based chemical peels and iontophoresis with tretinoin have been shown to be effective in improving superficial scarring related to acne [82–84]. More recently, adapalene gel (0.1% and 0.3%) was shown to improve atrophic scarring including skin smoothness and overall scar number [85–87]. Tazarotene 0.1% gel was also found to be effective in treating atrophic post-acne scarring and was noted to be similarly efficacious as microneedling [88].

Post-inflammatory hyperpigmentation (PIH) occurs commonly in patients with acne. PIH occurs more frequently in darker skin types and can be a distressing cosmetic concern [89]. Acne-related PIH occurs more commonly in darker skin types and is considered to be a default pathophysiologic response of melanocytes to irritation or inflammation [90]. All three currently available topical retinoids (tretinoin, adapalene, and tazarotene) have been shown to prevent and reduce acne-associated hyperpigmentation [91–93]. While not fully understood, retinoids are thought to reduce epidermal melanin via (1) the direct inhibition of tyrosinase and tyrosinase-related protein I (TRP-1) activity, (2) reducing the transfer of melanosomes from melanocytes to keratinocytes, and (3) increased turnover of melanin-laden keratinocytes [94].

In conclusion, topical retinoids are the mainstay therapy in comedonal and inflammatory acne vulgaris. They have been shown to be safe and highly efficacious. Topical retinoids have broad anti-acne activity and are suitable for long-term use. Tretinoin, adapalene, and tazarotene are currently widely used as both monotherapy and in conjunction with other anti-acne agents. Trifarotene, an emerging fourth-generation topical retinoid with selectively for the RAR-γ receptor, may provide a better side effect profile and overall tolerability for patients with acne.

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New Drug Developments in Acne

6

Harald P. M. Gollnick, Clio Dessinioti, and Christos C. Zouboulis

Introduction

Acne vulgaris is a chronic inflammatory disease of the sebaceous gland and follicle (pilosebaceous unit). Currently, it is estimated that more than 650–700 million people are affected worldwide [1, 2]. However the database sources often do not discriminate between clinical and physiological acne and between data mining originating from over-the-counter (OTC) and from ethical drug statistics. Furthermore, the varying reimbursement policy for anti-acne drugs in different countries influences the choice of therapeutic regimens and consequently the development of new ones. Despite an emerging need, drug development for acne treatment seemed not to be a priority of pharmaceutical development in the past, possibly because some new compounds failed to meet the endpoints set in clinical trials or due to industry-related financial reasons. Current investigational drugs in phase 1–3 clinical studies for acne treatment and recent abstracts and publications present exciting new agents in the pipeline.

The pathogenesis of acne is multifactorial. The most important factor in initiating the different steps in its pathogenesis is a change in sebaceous cell proliferation and differentiation almost always induced by insulin-like growth factor (IGF)-1 and androgens at the early beginning. Furthermore, corneocytes of the follicular channel are in parallel stimulated to proliferate. Via the insulin-like growth factor (IGF)-1, toll-like receptors (TLR)-2 and 4 are upregulated on the basal sebocytes later followed by *Cutibacterium acnes* (*C. acnes*)-induced signals on the follicular keratinocytes with upregulation of the same TLR. Inflammatory cells of the CD4 and CD17 subtypes as well as CD209+ macrophages act in the follicular surrounding or invade the infundibulum. Further factors such as cannabinoids, melanocyte-stimulating hormone (MSH), ectopeptidases, neuropeptides, corticotropin-releasing hormone, the androgen-induced c-myc-p53 ratio on sebocytes and others contribute in different amounts to changes of gland function at the start of puberty and during the adolescent time. An alteration of the sebum composition is consecutively appearing which contributes to the inflammation. In addition, the microcomedo leads to intensification of perifollicular inflammation [3–5]. The keratinocytes of

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the infrainfundibulum and less prominent of the acroinfundibulum hyperproliferate, a disturbed cornification and reduced desquamation of follicular corneocytes lead to increased amount of corneocyte layers. The change of the follicular milieu promotes a dysbiosis by overgrowth of different *C. acnes* strains, which now find an ideal nutritional support and better living conditions (pH, low oxygen) [6–11]. A vicious cycle has developed and finally promotes the chronicity of acne.

The treatment phases of acne are intervention (phase A), maintenance (phase B), and medical adjunctives (phase C) including lasers and cosmeceuticals. The currently available topical agents for phase A (intervention) by the start of therapy and phase B (maintenance) for treating relapses are based on different recommendation levels from evidence-based trials in S3 guidelines and from algorithms of expert panels. Established topical agents are azelaic acid, different types of retinoids, benzoyl peroxide, antibiotics, and combinations either in a fixed combination or sequentially applied. Systemic drugs include oral tetracyclines in particular doxycycline, lymecycline, and minocycline; hormonal anticonceptives for women including antiandrogens with cyproterone acetate, drospirenone, chlormadinone acetate, or dienogest; and finally isotretinoin. There are a couple of reports on the off-label use of spironolactone and metformin [12–16]. Furthermore, photodynamic therapy (PDT) with topical application of aminolevulinic acid or methyl aminolaevulinate (MAL) has been used off-label for the treatment of inflammatory acne.

Limitations of Acne Treatment

Various limitations of current pharmacological treatments highlight the need for the development of new acne treatments. For optimal effectiveness, all therapies have to target at least two out of the four major pathogenetic factors. Oral isotretinoin targets all key factors [4, 17]. All established acne treatment regimens have never become the final solution with regard to the efficacy/cost/risk ratio. Clinical trials on the topical route have shown that the 50% breakthrough in reducing inflammatory and non-inflammatory lesions takes at least 12–16 weeks. The cutaneous adverse drug profile mostly appears during the first 4–14 days. A limitation of established anti-acne therapies includes their local adverse event profile, which is quite varying, including burning, redness, desquamation, itching, stinging, discoloration, or even producing irritative contact dermatitis. Regarding topical PDT, the current European guidelines 2016 state that although PDT is effective in the treatment of severe papulopustular/moderate nodular acne, a recommendation for or against could not be made due to a lack of standard treatment regimens that ensure a favorable profile of acute adverse reaction [18]. Oral isotretinoin requires mandatory pregnancy prevention measures for all female patients of childbearing potential [27]. Depending on the individual adherence of patients, the success rate under daily clinical conditions may vary significantly. Some acne subpopulations show contraindications for certain drugs because of gender, age, adherence/compliance, climate, and cultural behavior (antiandrogens, isotretinoin, humidity, dryness, sun exposure, pregnancy). Furthermore, the increasing emergence of microbial resistance associated with oral and topical antibiotics followed by the development of cross-resistance to erythromycin or clindamycin with implications to community-associated infections poses the pressing need for change of therapy regimen [13, 19, 20].

The prevalence of antibiotic-resistant *C. acnes* is increasing worldwide, from 20% in 1979 to 64% in 2000, with rates varying in different parts of the world [20]. Increasing numbers of *C. acnes* come on the follicular scene when the microcomedo is already present [6, 10]. However numbers are not correlating with severity but with different strains [20]. Implications of the use of antibiotics and of microbial resistance in acne patients include the decreased efficacy of antibiotics and the possible emergence of other resistant bacterial species through selection by antibiotic use [21–23]. Among 118,496 acne patients, the probability of developing an upper respiratory tract infection within the first year of observation was

2.15 ($p < 0.001$) times greater in acne patients receiving antibiotic treatment compared to those not receiving antibiotic treatment [24]. Furthermore, there is a negative influence of antibiotic anti-acne treatment on intestinal and vaginal microbiota [19]. However, a recent publication presenting short- and long-term effects after oral or topical antibiotic acne treatment fueled the discussion on *Staphylococcus aureus* resistance [21].

For patients with moderate to severe inflammatory or nodular acne, treatments via the systemic route are almost antibiotics or isotretinoin as state of the art [16, 25, 26]. Whereas teratogenicity is the main complication of all systemic retinoid therapies, which has led to a variety of prescription regulations (i.e., iPLEDGE program) and restrictions for safety reasons, teratogenic events by topical application of the currently available retinoids are uncertain [27]. A large controlled prospective study in females becoming pregnant under exposure or no exposure to a topical retinoid showed no higher prevalence of embryotoxic outcomes in the exposed cohort. Current regulations advise the discontinuation of topical application but no interruption of pregnancy [12, 15, 16]. According to newer drug regulations, contraceptive measurements with 0.3% adapalene are not recommended anymore. Combined oral contraceptives with antiandrogenic properties or spironolactone (off-label) or metformin (off-label) are frequently indicated in females particularly with irregular menstrual cycle, changes in the hormonal profile, and the context of polycystic ovary syndrome [14, 25]. Antiandrogens may not be indicated in some female patients because of contraindications [14, 26] or because of cultural or religious reasons [25]. Phase 3 and 4 contraceptives are claimed to increase the risk of thrombosis and, therefore, should be prescribed under strict surveillance.

Therefore, the adverse drug profile of future new medications under clinical investigation has to be thoroughly considered. Furthermore, the varying reimbursement policy for anti-acne drugs in different countries influences the choice of therapeutic regimens and consequently the development of new ones.

Methodology

New Drug Developments in Acne

This review chapter presents systemic and topical drug developments in acne. The publication by Zouboulis, Dessinioti, Tsatsou, and Gollnick (2017) *Expert Opinion on Investigational Drugs* 26(7) 813–823 was used. In this publication, we reviewed drug developments in acne reported up to January 2017 [28].

Furthermore, we conducted a new search in the English literature in PubMed and in the US National Institutes of Health database of clinical trials and the European Medicines Agency database with the keywords "acne" and "treatment," with date of last search in September 2019. Medical devices or photodynamic treatment and trials on acne scarring are out of the scope of this chapter.

Topical Drugs

Mechanism of actions of topical agents presented here includes the inhibition of sebum production, antikeratinizing, antimicrobial and anti-inflammatory actions (Table 6.1).

Effects on Sebum Production

Currently no sebosupressive agent with evidence-based controlled results is available as a registered substance. Systemic antiandrogenic substances are reserved for females [29]. Already in the past galenic preparations with topical antiandrogens or anti-α-reductase type I failed in clinical or pilot trials to convince. In animal experiments a new formulation of spironolactone in microemulsion was quite promising concerning penetration to the sebaceous gland [30].

Dimethylcurcumin is a nonsteroidal antiandrogen and a synthetic curcuminoid which is under development as a topical medication for the treatment of acne. ASC-J9 topical cream, which promotes downregulation/degradation of the androgen receptor, was tested in a phase 2, multicenter, randomized, double-blind, vehicle-controlled clinical study to evaluate the safety

Table 6.1 Topical drugs under development

Study identifier	Topical drugs under development	Phase	Compound	Sponsor	Proposed completion date
Innovative compounds					
NCT02774590	Timolol for the treatment of acne and rosacea	1	Timolol	Johns Hopkins University	Ongoing
Eudract-2014-001491-62	Clinical efficacy and safety of NAI-acne gel 3% applied twice a day to patients with facial acne vulgaris	2	Semisynthetic thiopeptide highly selective against *P. acnes*	Naicons	Ongoing
NCT02796066	Safety and efficacy of TSN2898 in the treatment of acne vulgaris	2	TSN2898	Thesan	2017
NCT02720627	An evaluation of the adrenal suppression potential and PK of CB-03-01 cream in pediatric patients with acne vulgaris	2	Cortexolone 17α-propionate	Cassiopea	2017
NCT02656043	A safety, tolerability, efficacy, and exposure study of XEN801 topical gel	2	XPF-005 (active compound XEN801)	Xenon	2017
NCT02832063	Clinical trial in subjects with mild to moderate acne vulgaris	2/3	B244	AOBiome	2017
2016–000540-33	A double-blind, randomized, placebo-controlled clinical study to evaluate the efficacy and safety of N-acetyl GED-0507-34-LEVO gel, 1 and 2%, applied once daily for 12 weeks in patients with mild to moderate facial acne vulgaris	2	N-Acetyi-GED-0507-34-LEVO	PPM	2017
NCT02571998	A study to evaluate the safety and efficacy of omiganan (CLS001) topical gel versus vehicle in female subjects with moderate to severe acne vulgaris	2	Omiganan pentahydrochloride	Cutanea	2016
NCT02935036	Efficacy study in patients with acne vulgaris	2	Sodium 3-(ethyl(3-methoxyphenyl)amino) propane-1-sulfonate product	Taro	2016
NCT02431052	A dose-ranging study of DRM01 in subjects with acne vulgaris	2b	Olumacostat glasaretil	Dermira	2016
NCT02575950	Explorative trial evaluating the efficacy and tolerability of LE043204 in moderate to severe acne	2	Ingenol disoxate	LEO	2016
NCT02395549	A study to determine the efficacy of topically applied MTC896 gel in subjects with acne vulgaris	2	MTC896	Mimetica	2016
EudraCT 2013-001716-30	Exploratory, controlled, randomized, observer-blind intraindividual clinical trial to evaluate the efficacy and the tolerability of topically applied 0.1% tyrothricin (Tyrosur® gel) in patients with mild to severe facial papulopustular acne	2	Tyrothricin	Charitè-Clinical Research Center for Hair and Skin Science	2016
NCT02404285	A study to evaluate the clinical effect of daily Next Science™ Acne Gel (NAG) on mild to moderate facial acne	1–2	Next Science Acne Gel	Next Science	2015

NCT02242760	P2 multicenter study of 58,204 gels in the treatment of acne vulgaris	2b	SB204	Novan	2015
NCT01938482	Study to evaluate the safety, tolerability, and pharmacokinetic of single and 14-day repeat topical application of GSK1940029	1	GSK1940029	GSK	2015
NCT02205892	Clinical study for topical Lupeol in acne	NR	Lupeol	Seoul National University Hospital	2014
NCT01694433	Clinical trial to determine the efficacy of vitamin 0 for acne therapy	2/3	Calcipotriene	University of California Los Angeles	2014
NCT01616654	Dose range study of CD5789 in acne vulgaris	2	CD5789	Galderma	2013
NCT02189629	CD5789 (trifarotene) long-term safety study on acne vulgaris	3	CD5789	Galderma	2019
EudraCT 2011-004998-83	A double-blind, randomized, dose selection vehicle-controlled multicenter clinical study for evaluation of the safety, tolerability, efficacy, and pharmacokinetics of topical neramexane in subjects with moderate to severe acne	2	Neramexane	Merz	2013
NCT01326780	A study of a new drug treatment for acne	2	JNJ 10229570-AAA	Valeant	2012
NCT01289574	Topical ASC-J9 cream for acne	2	ASC-J9	AndroScience	2012
NCT01293552	Clinical trial to evaluate ANT-1207 in subjects with acne	2	ANT-1207	Anterios	2012
NCT04045119	Effect of a facial cream containing cannabidiol and hemp oil on skin hydration and acne-prone skin (dahlia)	na	Dahlia	Avicanna Inc.	2019
EudraCT 2009-018024-15	A phase 2, randomized, open-label pilot study to evaluate the efficacy and safety of two dosage regimens of subcutaneous bioresorbable afamelanotide implants in patients with mild to moderate acne…	2	Afamelanotide	Clinuvel Pharmaceuticals Limited	Ongoing
NCT03573518	A randomized, double-blind, vehicle-controlled study to evaluate the safety and efficacy of BTX 1503 in patients with moderate to severe acne vulgaris	2	BTX 1503	Botanix Pharmaceuticals	2019
NCT04080869	Retinyl palmitate-loaded ethosomes in acne vulgaris	2	Retinyl palmitate ethisome	Assiut University/Egypt	2020
NCT02815332	BPX-01 minocycline 1% or 2% topical gel in the treatment of inflammatory non-nodular acne vulgaris	2	BPX 01	BioPharmX, Inc.	2017
NCT04104685	A study to compare FCD105 foam to minocycline 3%/ adapalene 0.3	2	FCD105	FoamMix	2020
NCT03900676	Efficacy and safety study of VB-1953 topical gel for inflammatory facial acne vulgaris	2	VB-1953 – 2%	Vyome Therapeutics Inc.	2020
NCT04106778	DMT310-003 topical in the treatment of acne vulgaris	2	DMT-310	Dermata Therapeutics	2020
NCT02832063	Efficacy of B244 in participants with mild to moderate acne vulgaris from baseline to week 12	2/3	Biological: B244	AO Biome LLC	2017

(continued)

Table 6.1 (continued)

Study identifier	Topical drugs under development	Phase	Compound	Sponsor	Proposed completion date
NCT02998671	Study of efficacy and safety of CJM112 in patients with moderate to severe inflammatory acne	2	CJM112	Novartis	2018
Generic studies					
EudraCT 2013-001753-26	Clinical and biophysics evaluation of the cutaneous modifications following the local use of a lotion containing 0.1% of tretinoin	1	Tretinoin	Pierre-Fabre	Ongoing
EudraCT 2015-002699-26	Pilot study of tolerability and effectivity following application of two combination topical acne products clindamycin 1 and 0.025% tretinoin gel (Acnatac® gel), adapalene 0.1% and benzoyl peroxide 2.5% gel (Epiduo® gel)	2	Clindamycin/tretinoin/ adapalene/benzoyl peroxide	GWT-TUD	Ongoing
NCT02661958	Efficacy, safety, and tolerability of S6GST-1 and 56G5T-3 for the treatment of acne vulgaris	2	Benzoyl peroxide/tretinoin	Sol-gel	2017
NCT02932306	Efficacy and safety of IDP-121 and IOP-121 vehicle lotion in the treatment of acne vulgaris	1	Tretinoin	Valeant	2017
NCT02815332	BPX-01 minocycline topical gel in the treatment of acne vulgaris	2	Minocycline	BioPharmX	2017
EudraCT 2015-004765-90	A randomized, double-blind, vehicle-controlled study of the safety and efficacy of DFD-03 lotion in the treatment of acne vulgaris for 12 weeks	2/3	Tazarotene	Dr. Reddy's	2017
EudraCT 2016-000063-16	Efficacy and safety of CD5024 1% in acne vulgaris	2	Ivermectin	Galderma	2017
NG03003247	Efficacy and safety of IOP-120 gel in the treatment of acne vulgaris	2	Combination of tretinoin with an undisclosed compound	Valeant	2016
NG02938494	Safety and efficacy of IDP-123 lotion to Tazorac® cream, in the treatment of acne vulgaris	2	Combination of tazarotene with an undisclosed compound	Valeant	2016
NG02593383	Compound adapalene and clindamycin hydrochloride gel in treatment of patients with acne	1/2	Adapalene + clindamycin hydrochloride	Lee's	2016
NG02849860	Absorption and systematic pharmacokinetics of IDP-121 lotion in subjects with acne vulgaris	1	Tretinoin	Valeant	2016
NG02929719	Study comparing test to aczone 5% and both to a placebo control in the treatment of acne vulgaris	1	Dapsone	Taro	2016
NG02709902	Study comparing adapalene/BP gel to Epiduo® Forte and both to a placebo control in treatment of acne vulgaris	1	Adapalene/benzoyl peroxide	Taro	2016
NG02595034	A study CLBG and benzoyl peroxide gel 1%/5% to BenzaClin® gel in the treatment of acne vulgaris	1	Clindamycin/benzoyl peroxide	Taro	2015

NCT02411942	Study comparing adapalene gel 0.3% to Differin® and both to a placebo control in treatment of acne vulgaris	1	Adapalene	Taro	2015
NG02411955	A study comparing tazarotene cream 0.1% to Tazorac® and both to a placebo control in the treatment of acne vulgaris	1	Tazarotene	Taro	2015
NG02578043	A study comparing clindamycin and benzoyl peroxide gel 1.2%/3.75% to Onexton™ gel in the treatment of acne vulgaris	1	Clindamycin/benzoyl peroxide	Taro	2015
NG02218034	Safety, tolerability, and pharmacokinetics of AGN-190168 in subjects with acne vulgaris	1	Tazarotene	Allergan	2015
NG02250859	A pharmacokinetic study of minocycline in male and female volunteers	1	Minocycline	Foamix	2015
NG02073461	Efficacy and safety study of two different concentrations of CD1579 gels versus vehicle in the treatment of acne vulgaris	2	Benzoyl peroxide	Galderma	2014
NG01494285	Clinical study to evaluate tolerability and safety of ARK-E021 foam and to monitor clinical effect in acne vulgaris patients	1/2	Minocycline	M. Arkin 1999	2013
NG01527123	A study to evaluate the pharmacokinetics of benzoic acid and hippuric acid after topical administration of GSK2585823 in Japanese subjects with acne vulgaris	1	Clindamycin 1%-benzoyl peroxide 3%	GSK	2012
NG01461655	Efficacy and the tolerability of the sequential application of two marketed products in patients with acne vulgaris	2	Marketed retinoid/topical	LEO	2012
NG01682200	An open-label pilot clinical trial on the efficacy and safety of ProOxy facial spray (topical 15% oxygen solution) in the treatment of moderate facial acne vulgaris among Filipino patients	1	Oxygen solution	Medivet	2011
NG01241331	BLI1100 for the treatment of moderate to severe acne vulgaris	2	BLI1100	Braintree	2011
NG01301586	A novel combination oral agent to treat acne vulgaris	1/2	Doxycycline and S-equol	NexGen	2011
NG01194375	A dose-ranging study evaluating the safety and efficacy of IDP-107 in patients with acne vulgaris	2	IDP-107 (antibiotic)	Dow	2011
NG01180543	Acne treatment with active Oplon's patches	2	Oplon active patch (azelaic acid, citric acid, salicylic acid, and 2% ascorbic acid)	Oplon-Pure	2010

and efficacy of 0.1% and 0.025% ASC-J9 creams applied topically twice daily for 12 weeks for the treatment of moderate facial acne (NCT01289574). In 2011 results reported that both concentrations of ASC-J9 showed better outcome on total lesion count than vehicle [30].

Olumacostat glasaretil is a prodrug hydrolyzed in vivo to ultimately form 5-tetradecyloxy-2-furoyl-CoA, a fatty acid mimetic that competes with acetyl-CoA and inhibits the formation of malonyl CoA and fatty acid production in the sebaceous glands [31]. An olumacostat glasaretil 7.5% gel (DRM01) was evaluated in two phase 2a and 2b, multicenter, randomized, vehicle-controlled studies in 108 patients with moderate to severe facial acne vulgaris (NCT02431052, Table 6.1). However, no efficacy on the primary objective of hyperseborrhea could be detected. Olumacostat glasaretil was well tolerated, and common adverse events included application-site dryness, erythema, and pain. In an additional investigational treatment, olumacostat glasaretil (formerly DRM01) did not meet the co-primary endpoints in its two phase 3 pivotal trials (CLAREOS-1 and CLAREOS-2) in patients aged 9 years and older with moderate to severe acne vulgaris. Development was discontinued due to failure to meet endpoints in trials in 2018.

Clascoterone, or cortexolone 17α-propionate or 11-deoxycortisol 17α-propionate, is a synthetic steroidal antiandrogen – specifically, an androgen receptor antagonist (CB-03-01). In comparison to established antiandrogenic substances, it was threefold less effective than flutamide (CAS 13311-84-7), twofold stronger than finasteride (CAS 98319-26-7), and equivalent to cyproterone acetate (CAS 427-51-0). A phase 2 study has evaluated the adrenal suppression potential of CB-03-01 1% cream applied every 12 hours for 2 weeks in children 9–12 years old with acne (NCT02720627, Table 6.1) [30]. The drug was also evaluated in a randomized trial compared to placebo or topical tretinoin 0.05% cream in 77 adult men with acne. Cortexolone 17α-propionate once daily at bedtime for 8 weeks was significantly more effective than placebo in total lesion count improvement and led to greater reduction in inflammatory lesion count compared to placebo or tretinoin. The cortexolone 17α-propionate cream was well tolerated, and no patient discontinued the treatment. A phase 3 trial was successfully finished in 2019. It seems that the topical clascoterone does not work as a fast intervention drug, but more for long term or maintenance use. The drug is now approved on the market in U.S. since October 2020.

Stearoyl-CoA desaturase 1 (SCD1 inhibitor) is a Δ19-desaturase endoplasmatic reticulum enzyme that catalyzes the biosynthesis of monounsaturated fatty acids from saturated acyl-CoAs [31]. The compound GSK1940029 and others such as TSN 2898 or Xen103 inhibit lipid metabolism in the sebaceous gland effectively. XEN801 gel and GSK 1940029 were also evaluated in clinical phase 2 trials (Table 6.1) [32].

The rationale for investigation on melanocortin peptide α-MSH and the melanocortin (MC) receptors includes the anti-inflammatory effects and expressing receptors on the sebocytes [33–35]. MC1R and MC5R antagonist (JNJ-10,229,570) inhibited the production of sebaceous lipids in vitro in human sebocyte culture and in vivo in human skin xenograft models [35, 36].

α-MSH suppressed IL-1β-mediated IL-6 and IL-8 expression and signaling in human sebocytes in vitro, with no melanotropic activity [37]. JNJ-10229570 dose dependently inhibited the production of sebaceous lipids in cultured primary human sebocytes [36].

The α-MSH analog afamelanotide (Nle4-D-Phe7-a-MSH) has been studied for acne (NCT01326780, EudraCT Number: 2009-018024), but results are not available [33]. Afamelanotide 16 mg in a subcutaneous resorbable implant formulation was investigated in a phase 2 trial in three patients with mild to moderate facial acne vulgaris. After 2 months, there was an improvement in inflammatory and non-inflammatory acne lesions. There was skin tanning observed in all three patients and pre-existing naevi darkened.

The results of a phase 2 study with the peroxisome proliferator-activated receptor (PPAR)γ modulator N-acetyl-GED-0507-34-LEVO in a gel 1% and 2% preparation are expected soon (2016-000540-33). PPARy has been shown to control sebaceous lipogenesis and inflammatory

signaling on SZ95 sebocytes [38]. A phase 2 clinical trial in acne vulgaris in Hungary (EudraCT 2016-000540-33) is not published yet. Results shown at the World Congress on acne in Shanghai 2016 demonstrated first results with efficacy in inflammatory lesions and on sebum excretion rate and, recently published, also on decrease of IL-1 alpha levels [39–41]. A randomized phase 2/3 clinical trial with the 2% gel formulation has been initiated (EudraCT 2018-003307-19).

Cannabinoids have effects on sebocyte activity. Cannabidiol (CBD) exerts complex anti-acne effects in vitro, and in vivo efficiency of topically administered CBD in moderate to severe acne is currently being assessed in a phase 2 clinical trial (NCT03573518). The effects are anti-inflammatory and sebosupressive [40].

A facial cream containing 0.5% cannabidiol and 0.1% hemp oil is currently tested on skin hydration and acne-prone skin (NCT04045119).

Botulinum neurotoxin type A ANT-1207 (NCT01293552) with possible sebosupressive effects was first studied in 2011 with no further results published so far.

Silybum marianum fruit extract is under investigation on the production and regulation of sebum components. *Silybum marianum* fruit extract decreased sebum content by 25% in in vitro models, thus the same level compared to the reference molecule isotretinoin. In the ShiPS model, the compound significantly decreased lipid accumulation by 90%. *Silybum marianum* fruit extract can become a good candidate for the modulation of hyperseborrhea in acne and androgenetic alopecia [42].

Effects on Follicular Hyperkeratosis

A formulation of retinyl palmitate-loaded topical ethosome will be investigated in a phase 2 trial in a split-face design (NCT04080869). Encapsulation of retinoids into vesicular carriers as liposomes and ethosomes and nanoparticulate carriers can significantly improve their effects for the treatment of acne having probably less adverse local effects.

Trifarotene (CD5789) is a selective retinoic acid receptor (RAR)-γ agonist. When topically applied it can influence and modulate several genes involved in epidermal proliferation and differentiation such as keratinization in the follicular wall, desquamation, and cell adhesion. It has also some effects on pigmentation. A 0.005% cream formulation was assessed in two identical 12-week, randomized, multicenter, parallel-group, double-blind, vehicle-controlled clinical trials of 2420 patients showed that trifarotene cream significantly reduced inflammatory lesions as early as 2 weeks on the face and 4 weeks on the back, shoulders, and chest compared to vehicle ($p < 0.05$).[1] The concentration of 0.005% was well tolerated when used on the face, back, shoulders, and chest (NCT02189629). The most common adverse reactions (incidence>1%) included application site irritation, application site pruritus (itching), and sunburn. Trifarotene achieved FDA approval in October 2019 for acne patients 9 years and older [43] and in Europe in 2020.

Effects on the Microbiota

The substance omiganan pentahydrochloride is a synthetic, cationic, antimicrobial peptide (AMP) being developed for the prevention of catheter-related infections and for the treatment of acne and rosacea. Omiganan gel 0.1–2% is antibacterial (gram-positive and gram-negative) and antifungal [44]. A phase 2, randomized, double-blind, vehicle-controlled, parallel-group multicenter study evaluated the safety and efficacy of omiganan gel (CLS001) versus vehicle applied once daily for 12 weeks to female subjects with moderate to severe acne vulgaris. There are currently no results available (NCT02571998). It would be interesting to investigate the compatibility of this new antimicrobial compound in a fixed combination with retinoids or new sebosuppressive agents in order to avoid the benzoyl peroxide tolerability-related adverse events.

Minocycline 1%, 3%, and 4% in foam galenic preparations were evaluated in two phase 2 and 3, prospective, multicenter randomized, double-blind, vehicle- or adapalene 0.3% gel-controlled, dose-finding studies for moderate to severe acne vulgaris of the face (NCT02815332/NCT0410468) [45]. Minocycline 4% foam (FMX101) once daily for 12 weeks resulted in a greater mean percentage reduction from baseline in inflammatory and non-inflammatory lesion

counts and in significant higher rates of Investigator's Global Assessment (IGA) score of "clear" or "almost clear" compared to vehicle. The phase 3 trial in 1488 patients FMX101 showed in the intent-to-treat population significantly greater reductions in the number of inflammatory lesions from baseline ($p < 0.0001$) and a greater rate of IGA treatment success ($p < 0.0001$) versus foam vehicle group at week 12 [46]. The results comparing minocycline foam and adapalene are not published yet. The 4% formulation got FDA approval in October 2019.

VB-1953 is a first-in-class topical bactericidal antibiotic clinical drug candidate targeted for moderate to severe inflammatory acne, with a novel mechanism of action that includes inflammation-reducing capabilities as well as the demonstrated ability to treat antibiotic resistant *C. acnes* strains. In the first, proof-of-concept, double-blind, vehicle-controlled randomized study, topical VB-1953 2% gel was tested over a 12-week period in adult subjects with moderate to severe facial acne vulgaris (NCT03900676). The study demonstrated that 12 weeks of treatment with twice daily VB-1953 2% resulted in a significant reduction of 71.46% inflammatory lesions ($p < 0.05$ versus vehicle), in a post hoc analysis with 40 and 21 evaluable patients in treatment and vehicle arms, respectively. In as early as 8 weeks, an approximately 60% reduction in inflammatory lesions was observed after VB-1953 treatment ($p < 0.01$ versus vehicle). Safety signals were similar between vehicle and treated arms. In the second, open-label, single-arm, investigator-initiated clinical study, VB-1953 2% gel was tested for efficacy in moderate to severe acne patients who did not respond to clindamycin and who were also colonized with clindamycin-resistant *P. acnes*. Treatment with twice-daily VB-1953 resulted in a reduction in absolute inflammatory lesion count from baseline 34.4 ± 6.4 (mean ± SD) to 16.7 ± 9.0 ($p < 0.001$) at week 12. The proportion of subjects achieving a IGA success score was 26.3% at 12 weeks of treatment. Resistant bacteria reduced by 94.3% ± 1.0% ($p < 0.05$) within 4 weeks of treatment with VB-1953.

DMT310-003 is a complex natural product. It is a sponge powder which contains precisely sized and shaped silica spicules that upon application may help exfoliate the skin, open closed comedones, and facilitate penetration of the sponge's naturally occurring chemical compounds. Currently DMT310 powder is mixed with hydrogen peroxide and is under trial investigation (NCT04106778).

Ammonia-oxidizing bacteria-based compound (B244/AOB/NCT02832063) is a first-in-class, topical formulation of a single strain of beneficial AOB, *Nitrosomonas eutropha*. A phase 2b study achieved the primary endpoint at week 12 of a statistically significant 2-point reduction in the IGA score compared to vehicle control ($p = 0.03$). The compound was well tolerated.

To avoid bacterial resistance, the efficacy and safety between silver nanoparticle gel and 1% clindamycin gel both combined with 2.5% benzoyl peroxide for the treatment of moderate severity of acne vulgaris were compared [47]. This was an experimental, double-blinded, randomized-controlled study. At the study endpoint (8-week visit), average mean percent change from the baseline of inflammatory acne count showed slightly better reduction in silver nanoparticle group (79.7%) than clindamycin group (72.6%) with no significant difference ($p = 0.18$). The average mean percent change from the baseline of non-inflammatory acne count reduction was also not different between the silver nanoparticle and clindamycin groups (61.1% and 66.8%, respectively, $p = 0.22$).

Further antibiotic compounds for topical application in clinical studies are the semisynthetic thiopeptide highly selective against *C. acnes* NAI (2014-001491-62) and the biofilm matrix degradation Next Science Acne Gel (NCT02404285, Table 6.1) [48].

In patients with moderate to severe inflammatory acne, the NCT02998671 trial was started in December 2016 and recently finished in October 2019. Results are not available yet. Preliminary efficacy, safety, and an adequate clinical profile for further clinical development will be determined. In addition, sustainability of response and dose relationship will be explored. Neramexane (2011-004998-83), Kanuka honey 90%/glycerin10% [49], and tyrothricin (2013-

001716-30) [50] were found inefficient in clinical trials.

First findings from phase 1 and 2a trials on microbiota transplantation with different *C. acnes* strains applied in different amounts on normal skin in acne prone areas did show acceptance of newly introduced strains and after stop of application reoccurrence of the former microbiota profile. When applied to acne patients to influence the microbiota of the lesional skin with concurrent *C. acnes* strains, at first to emphasize, it did not deteriorate the clinical course of acne but improved the lesion count already after 5 weeks. This is a new approach for topical acne treatment using *C. acnes* strains with specific enzyme characteristics which are not related to those promoting the inflammatory course. Those strains are accepted by the host and lead to reduce the pathological ones in number [51].

Further promising agents involved in active clinical trials with topical preparations include the anti-inflammatory agents sodium 3-(ethyl(3-methoxyphenyl)amino)propane-1-sulfonate (ADPS, NCT02935036), the ammonia-oxidizing bacteria-based compound (B244, NCT02832063), the polymer-based nitric oxide-releasing compound S8204 (NCT02242760), and the alcoholic, pentacyclic triterpenoid lupeol, a modulator of NF-κB, and PI3K/Akt pathways inducing Fas-mediated apoptosis via inhibition of Ras signaling (NCT02205892, Table 6.1). The protein kinase C activator ingenol disoxate exhibited comparable safety and efficacy with ingenol mebutate in a phase 2a study [52]. A phase 2 trial is evaluating the efficacy and tolerability of ingenol disoxate in moderate to severe acne (NCT02575950).

Systemic Acne Drugs Under Investigation in Phase 1 and 2 Trials

The systemic drugs under investigation for acne treatment can be classified in three groups based on their primary mode of action, namely, agents targeting sebosuppression, including finasteride, antimicrobial compounds (levamisole, sarecycline HCI), biologics (CJMl 12, gevokizumab, RA-18(3)), and primary anti-inflammatory agents, such as anti-inflammatory low-dose doxycycline, apremilast, and inhibitors of leukotriene (LTB4) synthesis (acebilustat, zileuton).

Among the 11 retrieved trials in systemic drugs (Table 6.2), most trials do not report any results, and only few PubMed-included publications could be detected.

Effects on Sebum Production

In the skin, the enzyme 5α-reductase catalyzes the conversion of the potent androgen testosterone to the most potent tissue androgen 5α-dihydrotestosterone [53, 54]. There are three isoenzymes of 5α-reductase in the skin; the activity of 5α-reductase types 1 and 2 is concentrated in the sebaceous glands, while 5α-reductase type 3 has been localized within the companion layer of the follicle and the sebaceous gland [55, 56]. Finasteride is a specific competitive inhibitor of 5α-reductase. It has preferential selectivity for 5α-reductase type 2 and a weak effect for type 1. A retrospective study of finasteride 5 mg in six normoandrogenic adult women with acne resulted in a self-reported improvement in the symptoms of acne [48]. A double-blind, randomized, placebo-controlled, dose-ranging study has been conducted to evaluate the efficacy and safety of once weekly, high-dose oral finasteride (23.5 and 33.5 mg) compared to placebo for the treatment of severe nodulocystic acne in male subjects (NCT02502669). The trial was completed in 2017, and there are still no reported results. However, there is no rationale for acne treatment with finasteride in female patients. Furthermore, considerable finasteride and post-finasteride adverse effects have been reported [57, 58].

Effects on the Microbiota

Levamisole (CD25) is an antihelminthic agent with known immunomodulatory effects [59]. In a double-blind, randomized, placebo-controlled trial in 60 patients with severe nodulocystic acne, the efficacy and safety of a combination of oral levamisole 2.5 mg/kg/week (up to 150 mg/week) plus doxycycline 100 mg daily were compared to those of 100 mg oral doxycycline

Table 6.2 Systemic investigational drugs in phase 1 or 2 trials for acne (www.dinicaltrials.gov and www.ema.europa.eu/ema/)

Study identifier	Title	Phase	Compound	Sponsor	Completion date
NCT02998671	Study of efficacy and safety of CJM112 in patients with moderate to severe inflammatory acne	2	CJM112	Novartis	2018
NCT02S02669	Finasteride treatment of severe nodulocystic acne	2	Finasteride	Elorac	2016
NCT02385760	CTX-4430 for the treatment of moderate to severe facial acne vulgaris	2	Acebilustat	Celtaxsys	2016
NCT01628549	Double-blind, placebo-controlled study to evaluate three doses of P005672 in treatment of facial acne vulgaris	2	Sarecycline HCl	Warner Chilcott	2013
NCT01498874	Efficacy and safety study of gevokizumab to treat moderate to severe acne vulgaris	2	Gevokizumab	XOMA	2013
NCT01320033	Placebo-controlled efficacy and safety study of CD2475/101 40 mg tablets versus placebo and doxycycline 100 mg capsules once daily in the treatment of inflammatory lesions of acne vulgaris	2	Doxycycline 30 mg immediate release+10 mg delayed release (Oracea™)	Galderma	2012
NCT01474798	Phase 2 trial of RA-18C3 in subjects with moderate to severe acne vulgaris	2	RA-18C3 (Xilonix™)	XBiotech	2012
NCT01348321	Comparison of efficacy of azithromycin and levamisole versus azithromycin in the treatment of acne	2/3	Levamisole	Ahvaz Jundishapur (University of Medical Sciences	2009
NCT00612573	Treatment of moderate to severe facial acne vulgaris	2	Doxycycline (0.6 mg/kg/day)	Warner Chilcott	2008
NCT00725439	An open-label trial to assess the safety and efficacy of oral R115866 in the treatment of facial acne	2	Talarozole	Stiefel/GSK	2007
NCT00098358	Study of oral zileuton in the treatment of moderate to severe facial acne vulgaris	2	Zileuton (Zyflo™ currently Zyflo CR)	Critical Therapeutics (currently Chiesi)	2005

daily and placebo. Results indicated that adding oral levamisole to doxycycline was an effective treatment for severe nonresponsiveness to conventional treatments of acne vulgaris [60]. However, this study was criticized that it presented statistical significance of treatment effects that were clinically insignificant. In addition, the combination of levamisole and doxycycline may exhibit additive liver toxicity. An investigator-blinded randomized prospective 2-month study in 169 patients with inflammatory acne vulgaris showed superior efficacy of levamisole and azithromycin versus azithromycin alone (NCT01348321). The combination was more effective than azithromycin alone in decreasing inflammatory acne lesions, especially in nodulocystic acne. In addition to the reported side effects of levamisole, a long-term administration of a potent antibiotic systemic agent, such as azithromycin [60–64], which should be reserved for the treatment of infections, cannot be recommended.

Sarecycline, a tetracycline derivative, was tested in two double-blind studies 1.5 mg/kg compared to placebo. In both studies SC1401 (sarecycline n = 483, placebo n = 485) and SC1402 (sarecycline n = 519, placebo n = 515), at week 12, IGA success (≥2-grade improvement and score 0 [clear] or 1 [almost clear]) rates were 21.9% and 22.6% (sarecycline), respectively, versus 10.5% and 15.3% (placebo, $p < 0.0001$ and $p = 0.0038$). Gastrointestinal and vulvovaginal adverse events were lower than with other cyclins. The rates of nasopharyngitis were 2.5–2.9%. The drug was recently approved by the FDA. The dosage is antimicrobial. If a low-dose, the so-called submicrobial dosage, is going to be tested is not known yet. Any new systemic antibiotic has the unwanted chance of developing systemic resistance for local and systemic microbiota and is not a decisive step forward in acne treatment [62].

In an open two-arm study with 25 patients with papulopustular and nodulocystic acne in each arm, therapy with oral serratia peptidase (5 mg 3x/d for 1 month), a biofilm inhibitor, topical isotretinoin 0.05%, benzoyl peroxide 5%, and oral doxycycline over 3 months was compared with a group, which did not receive serratia peptidase. There was a significantly faster onset of improvement and a slightly better outcome in the serratia peptidase with 80% excellent improvement (>85% global assessment) compared to 64% in the nonserratia group. Studies on *S. aureus* infections have shown that the adjuvant use of serratia peptidase in combination with a systemic antibiotic may lead to a faster improvement [65].

The potential for vaccination against *P. acnes* has been investigated, but relevant studies stopped in 2011. *P. acnes* CAMP factor-targeted acne vaccine showed anti-inflammatory activity in acne ex vivo explants. It has not clearly been shown that vaccines against *P. acnes* antigenic structures are effective in humans with acne. The potential role of vaccination has to be questioned in particular to patient selection, the role of *P. acnes* in acne, and efficacy of vaccination in diseases of no viral background [66–69].

Biologics with Different Actions in Acne

During the last 5 years, pharmaceutical companies intended to test biologics already in use in other indications – in particular in psoriasis – also in acne. Since the inflammasome is activated in acne [70], anti-interleukin-1 (IL-1) monoclonal antibodies have been considered proper candidates for acne treatment. A randomized, double-blind, placebo-controlled phase 2 study was conducted in order to evaluate the efficacy and safety of gevokizumab, an IL-1β monoclonal antibody, in patients with moderate to severe acne vulgaris (NCT01498874). Low-dose (30 mg) and high-dose (60 mg) gevokizumab were administered subcutaneously on days 0, 28, and 56. However, the detected efficacy was similar to placebo and in the range of results, which can be achieved with vehicle alone. The study results have not yet been fully disclosed.

For similar reasons, a phase 2, open-label study of the safety, pharmacokinetics, and efficacy of RA-18C3 (Bermekimab), a human anti-IL-1α monoclonal antibody was conducted in patients with moderate to severe acne vulgaris. Ten patients received RA-18C3 via three subcutaneous injections at days 0, 21, and 42. Patients weighing 27–53 kg received 100 mg (1 ml) RA-18C3, and patients weighing >53 kg received 200 mg (2 ml) RA-18C3, every 3 weeks (NCT01474798). The study results have neither been disclosed yet.

A clinical trial (NCT02998671) with high dose, low dose, and placebo arms, to assess preliminary efficacy and safety of human anti-IL-17α monoclonal antibody, CJM112 in patients with moderate to severe inflammatory acne (NCT02998671) was started in December 2016. The study was terminated early due to futility in October 2019.

Apremilast, a specific inhibitor of PDE-4, was investigated for moderate to severe acne in 2010, but the study was terminated due to lack of funding (NCT01074502). A phase 2 trial will investigate apremilast in 16 patients with acne conglobata (NCT04161456).

Further Agents with Anti-inflammatory Effects

Cutaneous inflammation is one of the major components in the pathogenesis of acne [3, 71]. Bacteria, esp. *P. acnes*, interact with proteins of the innate immunity signal pathway, such as TLR, AMP, protease-activated receptors, and the matrix metalloproteinases (MMP), and upregulate the secretion of pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, IL-8, IL-12, IL-17, TNF-α, or granulocyte macrophage colony-stimulating factor) by human keratinocytes, sebocytes, or peripheral blood mononuclear cells [3, 6]. Epidermal and follicular keratinocytes as well as sebocytes also response to bacteria through AMP secretion, such as cathelicidin (LL-37) [72].

In addition to its antibacterial activity, doxycycline prevents cathelicidin activation in vitro and inhibits MMP activity in human skin and cultured keratinocytes [73]. Among oral antibiotics, doxycycline and lymecycline may be indicated for severe papulopustular or moderate nodular acne for a limited period of 3 months, due to the risk of the development of bacterial resistance [15] as well as the missing evidence of further improvement. However, an absence of bacterial selection pressure of doxycycline in sub-antimicrobial doses was shown in microbiologic studies of 6–18 months with specimens obtained for the mouth, gastrointestinal tract, vagina, and skin [74]. The efficacy and safety of a sub-antimicrobial dose of doxycycline (40 mg) with 10 mg in a delayed releasing vehicle was compared to doxycycline 100 mg for the treatment of inflammatory lesions in moderate to severe acne in a randomized, double-blind, placebo-controlled study [75]. Routine use of doxycycline 100–200 mg/day for the treatment of moderate to severe acne may be associated with the development of bacterial resistance and gastrointestinal adverse events and change of the microbiota, thus potentially impacting patient adherence. Sub-antimicrobial dose anti-inflammatory doxycycline, which is approved for the treatment of rosacea, has demonstrated comparable efficacy and superior safety to doxycycline 100 mg in the treatment of moderate to severe inflammatory acne.

A randomized, multicenter, double-blind, placebo-controlled 12-week study assessed the safety and efficacy of three doses of an oral formulation of doxycycline in patients with moderate to severe facial acne vulgaris (NCT00612573). Doxycycline was dosed at 0.6 mg/kg/day (40 mg/day to subjects of appropriate weight), 1.2 mg/kg/day (80 mg/day to subjects of appropriate weight), and 2.4 mg/kg/day (160 mg/day to subjects of appropriate weight) and compared to placebo. Results of this 2008 study have not been published until now. A retarded release of low-dose minocycline (40 mg) form has been registered in the US market. The administration of sub-antimicrobial doses of antibiotics with anti-inflammatory properties represents unattractive therapeutic option that may be used for regimens longer than 3 months, provided that its effectiveness in acne will be proven.

Certain leukotrienes (LT) are potent PPAR ligands, such as LTB4 and 15- as well as 12-hydroxyeicosatetraenoic acids. LTB4 synthesis is controlled by the enzymes 5-lipoxygenase and leukotriene A4 hydrolase [76, 77]. It binds on the G protein 8-LT2 receptor, further activates 5-lipoxygenase in sebocytes and professional inflammatory cells, and stimulates sebocyte and follicular keratinocyte differentiation, increasing sebum production and comedogenesis as well as the migration of neutrophils to the sebaceous follicles. Zileuton is a selective oral 5-lipoxygenase inhibitor, registered in the USA for the treatment of asthma that has been investigated in experimental and clinical studies in order to clarify its mode of action, its efficacy, and its safety in the treatment of acne vulgaris [78]. The compound directly inhibits sebum synthesis in a transient manner with a potency similar to low-dose isotretinoin [68]. An open-label study investigated zileuton 600 mg 4x/day for 12 weeks in ten patients with moderate inflammatory acne. The patients showed a significant mean decrease in inflammatory lesions compared to the baseline [79]. Total sebum lipids were significantly suppressed, and free fatty acids and hydroperoxides in sebum were markedly but not significantly decreased at week 12. Interestingly, there was a correlation of the

reduction in total lipids and free fatty acids in sebum with that of inflammatory acne lesions. A phase 2, randomized, double-blind, placebo-controlled, parallel-group multicenter clinical proof-of-concept study of zileuton in 101 patients with mild to moderate facial acne vulgaris (NCT00098358) showed a significant efficacy in the subset of patients with moderate acne (n = 26, baseline inflammatory lesions), with a mean decrease in inflammatory lesions of 41.6% compared to 26.2% in the placebo group ($p = 0.025$). Acebilustat (CTX-4430), a leukotriene A4 hydrolase inhibitor, is also under clinical investigation (NCT02385760) in patients with moderate to severe acne [80, 81].

Acebilustat is the only selective LTA4H inhibitor currently in clinical development for acne. A phase 2 trial tested the effect of once-daily oral acebilustat treatment on lesion counts in 124 patients with moderately severe facial acne vulgaris [82]. In this study, acne patients were treated for 12 weeks 100 mg acebilustat or placebo in a 2:1 randomization. This trial has been completed but is not yet reported.

Other Systemic Compounds Under Investigation

Talarozole (Rl15866) has received in August 2012 FDA orphan drug status to treat autosomal recessive congenital ichthyosis, keratinopathic ichthyosis, and recessive X-linked ichthyosis. It inhibits the metabolism of retinoic acid by blocking the cytochrome P450 enzyme isoform CYP26. Because of this mechanism, it is called a retinoic acid metabolism blocking agent. Phase 2 clinical trials of an oral formulation of talarozole in patients with psoriasis and acne and a phase 1 clinical trial of a topical formulation have been completed without announced results. The efficacy, safety, and tolerability of systemic talarozole 1 mg once daily for 12 weeks were assessed in an exploratory, nonrandomized open-label pilot trial in 17 male patients with moderate to severe facial acne vulgaris (NCT00725439). The drug was efficacious and well tolerated. However, earlier clinical studies have not been convincing, and the development of talarozole for acne was suspended [83–85].

Summary

Despite the enormous progress of knowledge in the pathophysiology of acne, the progress in the development of new drugs is rather disappointing. The most urgent need for new developments on topical treatment is the effective follicular targeting by new substances affecting sebocyte function via new anti-antiandrogenic substances, agents which influence on PPARs, ectopeptidases, leukotrienes, the corticotropin-releasing hormone signaling pathway, cannabinoid metabolism, TLR, and other modifiers of skin lipid composition. Those compounds may also affect the follicular keratinocytes and in addition the release of cytokines and MMPs. Microbiota transplantation of concurrent strains to fight against those of C. acnes promoting the dysbiosis seems quite promising and will probably become concurrent to antibiotics. On the systemic route, similar compounds may be effectively acting; however, systemic side effects have to be considered and to be as much as possible avoided [86–92].

Further consideration deserves acne in age groups of special interest, such as neonates, infants, young children 8–12 years, or adults [93]. Treating acne in children may pose several challenges leading to the development of new drugs and formulations. Recently only two drugs adapalene and BPO in a fixed combination and trifarotene are allowed to be prescribed from 9 years on. Oral isotretinoin is still the only systemic highly effective retinoid in acne but with strong side effects and specific contraceptive measurements necessary because of its teratogenic potential, been characteristic for retinoids. Whether a new systemic retinoid-like substance will be developed is not to be seen at the horizon. Special considerations have to be taken for treatment of adult female acne. A high number of cases do not react properly to standard treatments. Adult female skin is more sensitive to possibly irritant topical compounds, shows often delayed response, and requires drugs indicated

for use during the years of reproduction and desire for pregnancy [94–97].

The current research in the pathophysiology of acne, the various functions of the sebaceous gland demonstrating it as an endocrine skin organ, and the reactions of the innate and adapted immune system initiating and maintaining the inflammation have discovered critical steps in the cascade from the initial acne lesion to the fully developed lesion and its chronic evolution. These advances in our understanding of acne pathogenesis may stimulate research for the development of new acne treatments.

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7 Scientific Connection Between Acne and Diet

Ji Hoon Yang and Dae Hun Suh

Acne is the most prevalent sebaceous gland–related skin disease characterized by excessive sebum production, inflammation, altered keratinization, and overgrowth of *Cutibacterium acnes* [1, 2]. In the past, it was commonly believed that acne had no relationship with diet [3, 4]. It was generally believed that there was no relationship between acne severity and total calorie intake, carbohydrates, lipids, proteins, and so on. Chocolate was also presumed to be innocent [5]. But, the controversy about the correlation between acne and food continued [6, 7]. In one study, 32% of acne patients suggested diet as the third main cause of acne after hormones and genetic factors, and 44% of them considered foods as an aggravating factor for acne [8]. In another study, 11% of English teenagers responded that greasy food is the main cause of acne [9]. In addition, in a survey of final-year medical students in the University of Melbourne, 41% answered that diet is an important factor of acne exacerbation even though they learned from school that acne has no relationship with diet [10].

A pioneering observational study by Cordain et al. became a turning point in this long controversy and resulted in the change of paradigm. In this article, authors suggested that acne is a disease of western civilization. They performed cross-sectional studies for two tribal people: 1200 Kitavan islanders in Papua New Guinea and 115 Aché hunter-gatherers in Paraguay. They could not find any acne patients among these people with the age of 15–25 [11]. However, other tribal people living in more westernized civilization whose ethnic backgrounds are similar to these two tribes were reported to have much higher acne prevalence [12, 13]. Therefore, although genetic factors cannot be ruled out, the authors began to suspect the role of diet in acne development. The Kitavan islanders and Aché hunter-gatherers consumed dairy products, coffee, tea, oil, margarine, cereal, sugar in negligible amounts and their fat intake was considerably low. Instead, they ingested carbohydrate in the form of low glycemic load diet like tubers, fruits, and vegetables [11].

Glycemic load, defined as a function of glycemic index and carbohydrate intake, is a measure of total glycemic response to a food or meal. Glycemic load is calculated as glycemic index multiplied by grams of carbohydrate in 100 g of food [14]. Glycemic index measures how much of a rise in circulating blood sugar level a carbohydrate can trigger compared to glucose which is set equal to 100 [15]. If the glycemic load of a food is more than 20, it is considered high and if it is less than 10, it is considered low. Western

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refined foods such as crisped rice cereal, jelly beans, rice cake, and table sugar have high glycemic loads which are more than 50. On the contrary, unrefined food like parsnips, baked potatoes, fruits, and vegetables have low glycemic loads which are less than 10 [16, 17].

Hormonal cascade triggered by high glycemic load diet-induced hyperinsulinemia was suggested to explain the mechanism of acne development [17]. High glycemic load diet causes acute or chronic hyperinsulinemia which subsequently increases insulin-like growth factor-1 (IGF-1), a potent mitogen for all kinds of tissues [18, 19]. IGF-1 can promote keratinocyte proliferation, hyperkeratinization of hair follicles, and sebocyte growth, which play important roles in acne pathogenesis. Hyperinsulinemia also decreases IGFBP-3 directly or indirectly, which further increases the bioavailability of free IGF-1 in blood [15, 20]. In addition, insulin and IGF-1 can increase sebum production directly or indirectly by decreasing sex hormone binding globulin (SHBG) synthesis in the liver [21] and increasing synthesis of androgen in ovary and testicular tissues [22, 23].

There are several clinical evidences that support the role of endocrine factors in acne provocation and aggravation. Women with post-adolescent acne maintain elevated serum concentrations of IGF-1, androgen, and insulin and they are mildly insulin-resistant [24]. Also, polycystic ovary syndrome (PCOS) patients show acne as a characteristic clinical feature. PCOS patients are hyperinsulinemic, insulin-resistant, and hyperandrogenic. In these patients, IGF-1 serum level is elevated and SHBG level is decreased, which are consistent with hormonal cascade in acne development [25, 26]. Metformin, an anti-hyperglycemic agent, is used for the treatment of PCOS and also demonstrated to improve acne [27].

In native environments, non-westernized people were neither overweight nor hypertensive. They maintained low serum concentration of insulin, plasminogen activator inhibitor 1, and leptin. However, after they were adapted to westernized diet, they frequently became hyperinsulinemic and developed higher rates of type 2 diabetes [28]. More importantly, in dermatological aspect, acne began to occur. Significantly, lower prevalence of acne was observed in tribes such as Inuit, rural villages of Kenya, Zambia and Bantu, Okinawa, Arequipa in Peru, and Purus valley in Brazil [29–31]. In fact, even in white races such as young Irish women, who were not adopting western diet, showed no or at least far less prevalence of acne [32]. They started to develop acne after they moved to the urban area [33].

Although chocolate was presumed to have no association with acne, debates are still ongoing over that issue. There are several studies which investigated the association between chocolate and acne. In one study, a crossover single-blinded study was conducted to confirm the effect of chocolate on acne. Patients were assigned to eat either chocolate bar or control bar daily for 4 weeks and were assessed for the change of acne severity. The authors found out that acne severity did not change during the study periods and concluded chocolate is innocent [34]. However, the control bar used in this study was inappropriate because it contained similar total sugar and fat content as the chocolate bar [35]. In another study which investigated university students with mild to moderate acne, the authors also concluded that chocolates are innocent in acne development [36]. However, the sample size was only eight, and study participants consumed chocolate only on two successive days. In addition, although four subjects developed up to five new papules or pustules, the result was described as not significant change without statistical evaluation and controlled follow-up. In 1971, university students with acne who identified dietary triggers were investigated. It was concluded that chocolate consumption and acne severity had no correlation [37]. However, there were also several limitations in this study: Sample size was not specified, no statistical evaluation, no control group, and follow-up of patients was not clear. These limitations made these articles unconvincing. New evidences for the positive relationship between chocolate and acne have been published recently [38].

In a Korean study of investigating dietary patterns in acne patients, 783 acne patients and 502 controls were enrolled. Study participants answered the questionnaire about the association

of acne and food which was verified for accuracy, reproducibility, and validity by specialists in nutrition and statistics [39]. According to their result, food intake was the major aggravating factor in male acne patients, and it was second to menstruation in female acne patients. Vegetables and green peas were eaten significantly higher in the control group than in acne patients, and glycemic loads of those foods were less than 10. On the other hand, compared to control group, significantly higher percentage of acne patients consumed junk foods such as donuts, waffles, carbonated drinks and instant noodles, which have glycemic load higher than 20. The intake of processed cheese, pork, chicken was also higher in acne patients. Especially, roasted pork and fried chicken consumption was more significantly associated with the aggravation of acne. Although these kinds of foods have no or very low carbohydrate, they have higher fat content so that increased consumption of such food can lead to acne aggravation. There was also an article about the reduction in fat intake resulting in the decrease of androgen level [40]. After low fat diet, decrease in serum and urine androgen levels was observed. In biochemical parameters, IGF-1 was significantly higher in acne patients aggravated by foods than in acne patients not aggravated by foods while IGFBP-3 was lower in acne patients aggravated by foods. Conclusively, high glycemic load diet, dairy food intake, high fat diet, irregular dietary patterns were found to aggravate acne.

As for the possible association between the dietary dairy intake and acne, there was an interesting study that investigated more than 47,000 women [41]. The authors found significant association between acne and milk, sherbet, cheese, trans-unsaturated fat, and vitamin D supplement. They divided milk into 4 kinds: whole milk, low fat milk, skim milk, and powdered milk. Especially skim milk had strong association with acne which made fat content of milk unlikely to cause acne. Instead, they suspected hormonal content of milk as a cause of acne [41]. In addition to estrogen and progesterone, milk contains androgen and its precursors which are involved in the process of comedogenesis [42]. It contains glucocorticoid and IGF-1 that can also act on sebaceous gland [43]. While processing milk to cheese, androstenedione is converted to testosterone, a more potent form of androgen. Skim milk processing may increase the bioavailability of bioactive molecules or change their interaction with binding proteins while whole milk contains more estrogen, which tends to reduce acne, than skim milk [44]. α-Lactalbumin, a primary transport protein in milk, has biologic effects similar to those of androgen and is added to low-fat and skim milk in processing [45]. Clinical relationship between acne and dairy products was confirmed again in a large case-control study [46].

Accumulated scientific evidences suggest signal transduction caused by IGF-1, insulin, and glucose in high glycemic load diet, high milk and dairy food intake. IGF-1 and insulin activates IRS-1/PI3K/Akt pathway, and this pathway plays an important role in acne pathogenesis [47]. Yoon et al. reported that epigallocatechin-3-gallate (EGCG), a constituent of green tea, improves acne by modulating intracellular molecular targets and inhibiting *C. acnes*. In this study, EGCG inhibited IGF-1R, IRS-1, PI3K, Akt in AMPK-dependent manner in sebocytes (Fig. 7.1) [48]. Activation of this pathway inhibits TSC1/TSC2 which controls Rheb, a GTP-binding protein ubiquitously expressed in humans and other mammals. Consequently, IGF-1, insulin, and glucose upregulate Rheb which subsequently activates mTORC1 signaling pathway, and it leads to high protein, lipid synthesis, and increased sebocyte and keratinocyte growth and proliferation [49].

mTORC1 is a nutrient-sensitive kinase and integrates signals of cellular energy, growth factors like insulin, IGF-1, and protein-derived signals, predominantly leucine [50, 51]. It stimulates ribosome biogenesis, protein synthesis, cell growth, and proliferation while suppressing autophagy. Importantly, it is the central activator of lipogenesis. When mTORC1 is inactivated, lipin 1 in the nucleus prevents SREBP from being attached to promoter site of target gene. But when mTORC1 is activated, lipin1 is phosphorylated and stays in the cytoplasm, being unable to prevent SREBP binding to promoter site, which leads to lipogenesis [52].

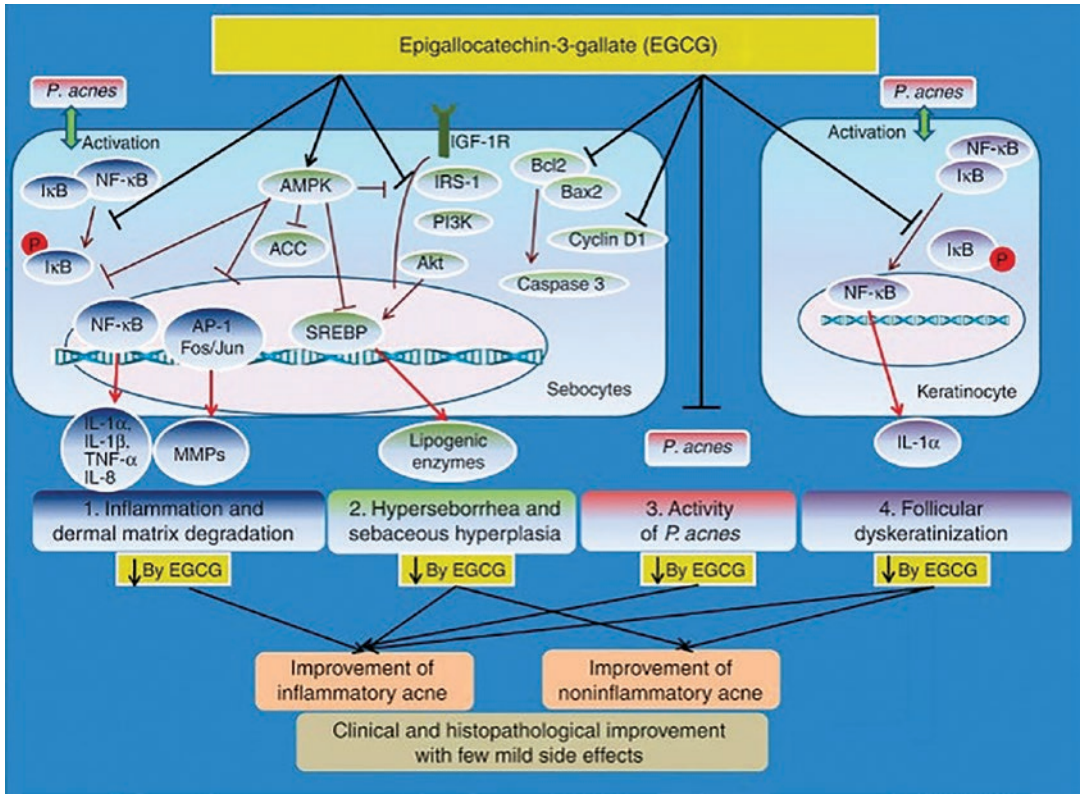

Fig. 7.1 Possible therapeutic mechanisms of epigallocatechin-3-gallate (EGCG) in the improvement of acne (cited from Journal of Investigative Dermatology 2013;133:437)

Leucine, enriched in beef, cheese, and milk, is also an important factor in signaling pathway. In cooperation with Ras GTPase, leucine translocates inactive form of mTORC1 into lysosomal department which contains Rheb, turning mTORC1 into active form. Leucine also acts as a structural lipid precursor for de novo sebaceous lipid synthesis in the presence of insulin [49].

IGF-1 and insulin also controls FoxO1 by Akt signaling. FoxO1 is in the nucleus to prevent androgen receptor from being activated. When IGF-1R/IRS-1/PI3K/Akt pathway is activated, FoxO1 is phosphorylated and it moves into cytoplasm resulting in androgen receptor activation [53]. Other than that, FoxO1 has various functions. When FoxO1 expression is increased, it acts against the development of acne by inhibiting lipogenesis, cell proliferation, and androgen receptor activation. Isotretinoin, one of the most widely used treatment option for acne patients, decreases cell proliferation and promotes apoptosis of sebocytes. Its mechanism is suggested to involve the increased function of FoxO1 which subsequently activates TSC1/TSC2 by way of AMPK [54, 55]. Activation of TSC1/TSC2 results in the downregulation of mTORC1 signaling. From these findings, we can hypothesize that reduced glycemic load diet, less dairy products and less fat intake will be able to improve acne.

Kwon et al. investigated clinical and histological effect of high glycemic load diet in the treatment of acne patients. In their results, non-inflammatory and inflammatory acne lesions were significantly decreased at week 10 and 5, respectively, compared with the control group. Changes in glycemic load and acne lesion counts showed positive correlation in linear regression analysis. In skin biopsy specimen, the size of sebaceous gland was significantly decreased after low glycemic load diet. They also confirmed

reduced expression of SREBP1 and IL-8, which altogether suggested the mechanism of improvement of acne in this 10 week clinical trial of dietary intervention [56].

There are some suggestions for best diet for acne. According to Jung et al., the higher frequency of vegetables and fish intake seems to be associated with low prevalence of acne [39]. Also, there was an interesting article that dietary supplementation with omega-3 fatty acid and gamma-linolenic acid decreased inflammatory and non-inflammatory acne lesions significantly. In their results, patient subjective assessment of improvement showed similar results with objective assessment. In the skin biopsy of this clinical trial, reductions in inflammation and IL-8 were observed after supplementation. Although the exact mechanism is yet to be studied more, omega-3-fatty acid was known to have anti-inflammatory effect, reduce sebum production, and decrease IGF-1 while increasing IGFBP-3. Gamma-linoleic acid may ameliorate acne by producing prostaglandin E1 (PGE1) and 15-hydroxydihomo-γ-linolenic acid (15-OH-DGLA). These molecules showed the decrease of pro-inflammatory cytokines and eicosanoids, and the anti-proliferative effect on keratinocytes [57].

The mechanism involved in the scientific connection between acne and diet continues to expand. In addition to high glycemic load diet and dairy products, saturated fat such as palmitate can activate mTORC1. FoxO1 and mTORC1 are affected by many molecules through various signaling pathways, and they can also activate many other target molecules. Ultimately, they can activate inflammasome with IL-1β release and Th17 cell differentiation which are important in acne pathogenesis [58].

In conclusion, the relationship between acne and diet cannot be overemphasized in view of accumulating scientific evidences. High glycemic load diet should be avoided. The ingestion of high amount of fat, leucine, milk, and dairy products may aggravate acne. Because we cannot test all foods, it would be appropriate to advise patients to avoid foods that they believe would worsen acne.

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8 Photodynamic Therapy for Acne Vulgaris: Mechanism and Clinical Practice

Ying Ma and Leihong Flora Xiang

Acne vulgaris, a chronic inflammatory disease that affects the pilosebaceous unit, has become the eighth most common disease worldwide [1]. The occurrence and development of acne are found to be related to massive secretion of sebum under the action of androgen, the change in sebum composition, the abnormal keratosis of hair follicles and sebaceous glands, the colonization of microbial, inflammatory reaction and immunity [2]. Microorganism colonization, especially *Cutibacterium acnes* (*C. acnes*), a commensal Gram-positive bacterium, has been considered as an additional pathogenetic factor [3]. Oral or external antibiotics, retinoids, and hormone therapy are widely used as conventional treatment. However, those methods are limited due to the side effects or intolerance. Photodynamic therapy (PDT) has emerged as a new option for dermatologist in the treatment of moderate and severe acne [4]. PDT employs a photosensitizer (PS) and visible light in the presence of oxygen, causing the damage of cellular organelles and leading to cell death. In dermatology, PDT has usually taken the form of topical photosensitizer irradiated by specific light wavelength, causing cell membrane disruption and cell apoptosis, leading to tumor destruction or immunomodulatory effects improving inflammatory condition [5].

Mechanism of PDT in Acne

There are three essential requirements for PDT: photosensitizer, light, and oxygen. 5-aminolevulinic acid (ALA), the first committed precursor of heme synthesis, is metabolized to protoporphyrin IX (PpIX) taken up by the pilosebaceous units, possessing the potential to cause reversible damage to sebaceous glands. ALA itself is not a photosensitizer, porphyrins are the active photosensitizers in ALA-PDT. Porphyrin molecule absorbs a photon, provides the chemical activation energy for PDT, which promotes an electron within the porphyrin to a higher triplet state. The excited triplet porphyrin molecules are prone to transfer energy to molecular oxygen, producing excited singlet oxygen ($^1O_2$) or other reactive oxygen species (ROS). ROS will directly destroy target cells or will indirectly promote oxidative stress by transcription and translation of several cytokine genes. The mechanisms for ALA-PDT of acne are dose-related. Low-dose [6–9] PDT by low drug concentration, low light irradiation dose, short incubation time between drug application and light exposure, use of blue light with minimal penetration depth, various pulsed source exposures caused transient antimicrobial or immunomodulatory mechanisms.

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High-dose [10, 11] PDT by prolonged application of high ALA concentration followed by high fluence red light led to the reduction of sebaceous gland function.

PDT on Sebaceous Glands

In 1990, Divaris injected ALA intraperitoneally into albino mice, and showed that red fluorescence characteristic of PpIX was present in the sebaceous glands, weak in the epidermis and hair follicles. From then on, ALA began to be used as a photosensitizer for the treatment of sebaceous gland-related disorders [12]. The mechanism of PDT action, firstly described in detail by Hongcharu, described the efficacy of topical ALA followed by red light for acne vulgaris with the application of 20% of ALA under 3 hours occlusion and compared with red light alone. After ALA application, intense fluorescence produced by porphyrin accumulation was noted grossly in acne areas especially in sebaceous glands and hair follicles. Histological findings were described as vacuolization of sebocytes and keratinocytes after irradiation, followed by sustained atrophic glands, granulomatous reaction, obliterated follicles, and perifollicular fibrosis up to 3 weeks after a PDT session. Sebum output fell dramatically in treated skin compared with control. In addition, sustained reduction of sebum output was observed for at least 20 weeks of patient follow-up, evidence of a longstanding effect [13].

Antimicrobial Effects

The antimicrobial photodynamic therapy (aPDT) is a therapeutic modality based on photosensitizing molecules that end up generating ROS that induce the destruction of the target cells when irradiated with light of a suitable wavelength and at a proper dose. The cells targeted by aPDT are all types of microorganisms (bacteria, fungi, and parasites) including viruses and aPDT has been proven effective against representative members of all of them [14, 15]. Therefore, aPDT is presented as a possible treatment option against acne. PDT was believed to work by reducing *C. acnes* colonization and sebum secretion. However, Yung observed only transient reduction in mean density of *Propionibacterium spp* [14–16]. What is more, bacterial reduction was not observed by evaluating the quantity of *C. acnes* after PDT [17]. The formation of bacterial biofilm leads to antibiotic resistance, which eventually has been proved to be part of the reasons for the failure of clinical treatment. ALA-PDT has the potential to eliminate the biofilm of *Staphylococcus*, especially antibiotic-resistant strains, effectively [18].

Anti-inflammation Effects

Fabbrocini found the PDT effect on the noninflammatory acne lesions. The noninvasive study using cyanoacrylate follicle puncture showed that PDT had a positive effect on microcomedones and macrocomedones [19]. Therefore, reduction of follicular obstruction and hyperkeratosis may be affected by PDT. It may enhance epidermal turnover, reducing hyperkeratosis and unplugging the follicles, thereby reducing the trigger mechanism involved in acne formation [20]. Ma also demonstrated that ALA-PDT could attenuate the expression of IL-1α, TNF-α, and IL-8 in keratinocytes cocultured with *P. acnes.* The effect of ALA-PDT on TLR2 and TLR4 expressions can be influenced by different light sources. In vivo immunohistochemical assay showed that the overexpression of TLR2 and TLR4 in the epidermis in acne lesion could be attenuated by ALA-PDT [21]. ALA-PDT can down-regulate the inflammatory reaction in keratinocytes through TLRs pathway. Jeong demonstrated that apoptosis of the sebaceous glands was associated with the improvement of acne by PDT. PDT had shown to downregulate TLR-2 and TLR-4 expressions in the sebaceous glands of acne [22]. These findings suggested that PDT has a potential immunologic contribution to clinical efficacy for acne.

Clinical Practice of PDT in Acne

Photodynamic therapy (PDT) has been widely used for acne in the last 20 years; however, the efficacy and safety need to be determined. We reviewed randomized controlled trials (RCTs) on the treatment of acne with PDT by searching PubMed, CNKI, and the Cochrane Library. A total of 23 RCTs were included to evaluate the multiple influences such as photosensitizer, light source, incubation time, and skin preparation.

Photosensitizer

In the USA, Food and Drug Administration (FDA) approved 20% ALA as photosensitizer, indicated for the treatment of actinic keratoses, basal cell carcinoma, and Bowen's disease and used off-label for acne. The most commonly used photosensitizers are ALA and methyl aminolevulinate hydrochloride (MAL). ALA has the largest body of currently existing evidence, having been investigated in most of the clinical trials. But the concentration of ALA were not the same. The clinical effects were thought to be related to the drug concentration directly. Yin reported that 180 patients with moderate to severe facial acne were recruited with different concentrations (5%, 10%, 15%, and 20%) of ALA-PDT to the facial lesions every 10 days for four sessions. After 24 weeks, each side treated by ALA-PDT showed clinical improvement compared with the control. Statistically significantly more patients treated with 20% ALA than with 15% or 10% ALA achieved complete clearance. Regarding side effects, a trend towards more serious erythema and pigmentation were observed with increasing ALA concentration [23].

Methyl aminolevulinate hydrochloride (MAL) is the methyl ester of ALA in a cream formulation. ALA is a water-soluble amino acid, MAL is a more lipid-soluble derivative. In theory, MAL may partition more easily into the lipid-rich milieu of sebum. Wiegell compared the ALA-PDT and MAL-PDT for acne vulgaris. Twelve weeks after treatment, a 59% decrease in inflammatory lesions was observed from baseline. PDT appeared to be an effective treatment for inflammatory acne vulgaris with no significant differences in the response rate between ALA-PDT and MAL-PDT. ALA-PDT resulted in more prolonged and severe adverse effects compared with MAL-PDT. This may be related to the tissue selection specificity of the photosensitizer, as MAL is enriched in acne tissue and causes less damage to normal tissue [24].

Less commonly used photosensitizers are chlorophyll, indole-3-acetic acid (IAA), indocyanine green (ICG), and gold-coated silica. Song performed a 4-week randomized split-face trial that compared chlorophyll-a under blue and red light in 24 patients for eight sessions. The chlorophyll-treated side showed a significant reduction in both inflammatory and noninflammatory lesions and the procedure was well-tolerated [25]. To evaluate the clinical efficacy of IAA PDT, 14 acne patients were treated with the following IAA PDT regimen: three times each with a 15 minutes incubation and a 2-week interval. IAA produced free radicals with green light irradiation. Inflammatory lesions and sebum secretion were significantly reduced. Importantly, IAA lost its photosensitizing ability after exposure to certain amount of light. This implied IAA PDT would not require post-procedure photo protection. Interestingly, there was no significant difference between a 4 hours and a 30 minutes incubation, which means that longer absorption time is not necessary for IAA PDT [26]. ICG is a photosensitizing dye that was used as the photosensitizer for PDT and showed improvement in acne, especially after multiple treatment [27]. Gold-coated silica microparticles combined with an 800 nm diode were shown to be effective in reducing inflammatory acne in 99 patients [28]. To enhance skin penetration and reduce systemic absorption, photosensitizers have been encapsulated in liposomes like liposomal methylene blue (LMB), a photosensitizing dye derived from phenothiazine with maximum absorption at 668 and 609 nm. Moftah investigated the effect of PDT in truncal acne vulgaris using LMB versus IPL alone. Thirty-five patients with varying degrees of acne were treated with topical 0.1% LMB hydrogel applied on the back, with three sessions

and 1-week interval. On LMB-PDT side, inflammatory acne lesion counts were significantly decreased by 56.40% compared with 34.06% on IPL alone [29].

Light Source

The key of photodynamic technology is that photosensitizers should be activated by specific light sources, corresponding to their maximum absorption spectrum which controls the depth of penetration of light into the skin. A variety of light and energy-based devices are used to activate photosensitizers. Red light, due to its longer wavelength, can penetrate deeper into the dermis to target the sebaceous glands, which play a key role in the pathogenesis of acne. Red LED therapy is the most common light source in the studies, although blue light has occasionally been reported because it corresponds to the maximum absorption peak of PpIX (410 nm). IPL is a high-intensity flash that has a wide range of wavelengths (560–1200 nm) and can target various absorption peaks of PpIX. Other lasers such as PDL (595 nm) and diode lasers (800–810 nm) are also used as lighting sources for PDT. In addition to the different wavelengths, the total energy dose and power of light sources also vary and affect the photodynamic effect. Several light sources used alone have shown some efficacy in acne, but PDT in combination with light sources has proven to be more effective in most of the trials.

Red light was the most widely used light source of illumination in half of our incorporated studies, using ALA or MAL as the photosensitizer. A wide array of energy dose with 2–4 treatment sessions were used in the clinical trials, from 15 to 126 J/cm^2, achieved approximately 59–92% reduction in lesions. Bissonnette et al. reported that 44 patients with facial acne vulgaris received 4 MAL applications (80 mg/g) at 2-week intervals by either 25 or 37 J/cm^2 of red light. At 18 weeks, the percentage of inflammatory lesions was reduced by a median of 59.4% and 55.8%. The results did not show much difference between the two groups with different light doses [30]. Nicklas compared the ALA-PDT and antibiotic administration. Forty-six patients with moderate inflammatory facial acne received two sessions of PDT separated by 2 weeks (ALA 20% incubated 1.5 hours before red light irradiation with 37 J/cm^2) and doxycycline 100 mg/day plus adapalene gel 0.1%. At 12 weeks, there was a greater reduction of inflammatory lesions in PDT group with 84% versus 74% for group who received doxycycline plus adapalene as well as in reducing total lesions with 79% versus 67% respectively [31]. Blue light was utilized as a light source in only a few small studies that investigated its use with MAL or ALA, showing a 66–71% reduction in acne lesions [32] (Table 8.1).

Intense pulsed light (IPL) alone and IPL combined with PDT using topical photosensitizer were observed [33–35]. Yeung investigated 30 subjects with moderate acne enrolled for a randomized, half-facial treatment study with IPL alone and IPL with 16% MAL. The subjects were treated four times at 3-week intervals. There were no statistically significant differences between the intervention group and the control group in the mean reduction of inflammatory lesions. 25% of the subjects in the PDT group withdrew because of intolerance to procedure-related discomfort [36].

PDL and long pulse dye lasers (LPDL) have been studied as photodynamic excitation of light in a few clinical trials. Haedersdal reported 15 patients received a series of three full-face LPDL treatments and half-face prelaser MAL treatments. Inflammatory lesions were reduced more on MAL-LPDL-treated than on LPDL-treated sides (week 4: 70% vs 50%; week 12: 80% vs 67%). Fluorescence measurements detected photobleaching with MAL-LPDL (35.3%) and LPDL (7.3%) treatments [37]. Forty-four patients received three pulsed dye laser (PDL) treatments with ALA application, while the contralateral side remained untreated. Although there were no statistically significant differences between treated and untreated sides of the face in terms of counts of any subtype of acne lesions, 30% of patients were deemed responders to this treatment with

Table 8.1 Characteristics of included studies

Study	Age (years)	Skin type	Severity	Sites of lesions	Photosensitizer	Light source and irridiation doses	Preparation
Hongcharu (2000) [13]	18–44	I–IV	Mild to moderate acne (Burke and Cunliffe)	Back	ALA 20%, 3 h	Broadband light (550–700 nm), 15 J/cm^2	70% isopropyl alcohol
Pollock (2004) [6]	16–40	I–IV	Mild to moderate	Back	ALA 20%, 3 h	Red light (635 nm), 15 J/cm^2	NA
Santos (2005) [33]	20–50	Unclear	Mild to severe (acne grading scale)	Face	ALA 20%, 180 min	IPL (560 nm cutoff filter starting at a fluence of 26 J/cm^2)	NA
Horfelt (2006) [7]	15–28	I–III	Moderate (Leeds score)	Face	MAL 160 mg/g, 180 min	Red light (635 nm, 37 J/cm^2)	Covered with an adhesive occlusive dressing, nodular or cystic prepared using a cannula (1–2 mm)
Wiegell (2006) [24]	>18	Unclear	Moderate to severe	Face	MAL unclear ALA 20%, 3 h	Red light (Aktilite, PhotoCure ASA) 37 J/cm^2	NA
Yeung (2007) [36]	18–41	IV–V	Moderate	Face	MAL 16%, 30 min	IPL (530–750 nm) 7.0–9.0 J/cm^2	With soap and alcohol scrub
Taub (2007) [34]	26.5 ± 9.1	II–IV	Moderate to severe	Face	ALA unclear, 30 min	IPL (600–850 nm), 8–12 J/cm^2; IPL + RF (580-980 nm, 16–36 J/cm^2 + 5-25 J/cm^2); blue light (417 nm, 6-10 min)	NA
Haedersdal (2008) [37]	18–31	I–III	At least a total of 12 inflammatory acne lesions	Face	2 g of MAL cream, 90 min	LPDL (V-beam Perfecta, 595 nm, 7.5 J/cm^2)	NA
Orringer (2009) [38]	15–50	I–IV	Unclear	Face	5-ALA 20%, 60–90 min	PDL (V-beam, Candela, 6.5–7.5 J/cm^2)	Acetone scrubs
Oh (2009) [40]	18–30	III–IV	Moderate to severe (Evaluator Global Severity Score)	Face	ALA 20%, short incubation group 30 min vs. long incubation group 3 h	IPL (590 nm, BBL, fluence of 12–15 J/cm^2)	With a mild soap and 70% alcohol
Bissonnette (2010) [30]	>18 years	I–IV	Moderate to severe	Face	MAL 80 mg/g, with or without occlusion 90 min	Red light 25 J/cm^2 and 37 J/cm^2	NA
Yin (2010) [23]	18–38	III–IV	Moderate to severe inflammatory acne	Face	Different ALA concentration, 1.5 h	Red light (633 ± 3 nm, 126 J/cm^2)	With 70% isopropyl alcohol

(continued)

Table 8.1 (continued)

Study	Age (years)	Skin type	Severity	Sites of lesions	Photosensitizer	Light source and irridiation doses	Preparation
Barolet (2010) [42]	26.2	I–III	Mild to moderate (combined acne severity classification)	Face and back	ALA 20%, 60 min	LED at 630 nm (50 mW/cm^2, 70 J/cm^2)	IR pretreatment (15-minute exposure to radiant IR-LED at 970 nm, 80 mW/cm^2, 72 J/cm^2)
Na (2011) [26]	Unclear	Unclear	Inflammatory acne	Face	IAA (0.015%)	Green light (15 minutes, 520 nm, 9 J/cm^2)	NA
Yang (2013) [8]	22.32 ± 1.05 years		Acne conglobata	Face	ALA5%, 3 h	Red light (633 ± 10 nm, 100 mW/cm^2, 50 J/cm^2)	Cleaning
Mei (2013) [35]	>18	II–IV	Moderate to severe (global rating scale)	Face	10% ALA, 60 min	IPL (420–950 nm,10–13 J/cm^2)	Cleaning
Liu (2014) [10]	16–36	Unclear	Moderate to severe (Burton classification)	Face	5% topical ALA, 60 min	Red light (633 ± 6 nm, 105 mW/cm^2, total energy dose: 126 J/cm^2)	With water
Chen (2015) [43]	18–33	Unclear	Low to severe grade	Face	20% ALA, 90 min	Red light (LED-IB, 633 ± 10 nm, energy density, 10 mW/cm^2, standard of energy, 120 J/cm^2)	With 70% isopropyl alcohol
Pariser (2016) [9]	12–35	I–VI	Severe (IGA scale)	Face	80 mg/g MAL, 90 min	LED (635-nm red light, total dose 37 J cm^2)	Saline wipe
Moftah (2016) [29]	>13	II–IV	Variable (Burton's acne severity scale)	Trunk	Liposomal methylene blue hydrogel, 60 min	IPL (fluence of 13–16 J/cm^2)	Degreased with isopropyl alcohol
Xu (2017) [11]	15–35	Unclear	Grade of 3 or 4 (IGA scale)	Face	5% topical ALA, 90 min	Red light (633 nm, 20 min, 100 mW/cm^2, 120 J/cm^2)	70% isopropyl alcohol
Kim (2017) [41]	19–45	III–IV	Grade 3 or 4 (IGA scale)	Face	1 g of MAL cream 160 mg/g, 30 min	Daylight outdoors for 90 min	Pretreated with non-ablative 1550 nm fractional erbium glass laser (50 spots/cm^2 and fluence of 20 J/cm^2)
Nicklas (2019) [31]	18–30	I–IV	III–IV (Leeds revised acne grading system)	Face	20% ALA 90 mins + adapalene and doxycycline	Red light (37 J/cm^2)	Mild soap and 70% isopropyl alcohol

Study	Number of patients	Duration	Efficacy	Adverse events	Continent
Hongcharu (2000) [13]	22	4 treatments	Clinical and statistically significant clearance of inflammatory acne by ALA-PDT for at least 20 weeks after multiple treatments and 10 weeks after single treatment	Transient pigmentation, superficial exfoliation, crusting	USA
Pollock (2004) [6]	10	3 treatments	Statistically significant reduction in inflammatory acne lesion counts after the second treatment at the ALA-PDT treated site, sustained after the final treatment	Marked discomfort during exposure to the light, mild tingling or burning, urticated erythema reaction, mild perifollicular eruption, postinflammatory pigmentation	Europe
Santos (2005) [33]	13	2 treatments	By the fourth week, improvement of facial acne was more significant on the ALA-treated side, persisted until the eighth week posttreatment	ALA-treated side showed edematous erythema, crusting with exfoliation and slight darkening, IPL-treated side showed very minimal erythema	Asia
Horfelt (2006) [7]	30	2 treatments	Greater median percent reduction in total inflammatory lesion counts at both week 6 reduction 63% vs. 28% and week 12 reduction 54% vs. 20%	Pain, erythema, and skin swelling related to the PDT treatment	Europe
Wiegell (2006) [24]	15	3 treatments	Median percentage decrease of inflammatory lesions of 59% in both treatments, no significant differences in absolute or percentage reduction of inflammatory and noninflammatory lesions between the two treatments	Moderate to severe pain, edema, severe inflammation, pustular eruption and epithelial exfoliation, yellow crusting	Europe
Yeung (2007) [36]	30	4 treatments	Mean reduction of lesion counts in the PDT group vs. the IPL group (53% vs. 22%, W4; 65% vs. 23%, W12)	Stinging, burning, erythema, edema, temporary crusting and hyperpigmentation, transient acneiform flares	Asia
Taub (2007) [34]	22	3 treatments	Improvements were highest with IPL activation and lowest with blue light activation	Moderate redness and peeling, blister, acne flare, and bruise required treatment with steroid	USA
Haedersdal (2008) [37]	15	3 treatments	Inflammatory lesions were reduced more on MAL-LPDL-treated than on LPDL-treated sides (week 4: 70% vs 50%; week 12: 80% vs 67%)	Moderate to severe pain, erythema, edema, pustular eruption, epithelial exfoliation, yellow crusting	Europe
Orringer (2009) [38]	44	3 treatments	Inflammatory papule decreased statistically significantly in treated skin (−4.63) compared with untreated skin (−0.13) at W10	Pain, edematous erythema, pustular eruption, yellow crusting and epithelial exfoliation	USA

(continued)

Table 8.1 (continued)

Study	Number of patients	Duration	Efficacy	Adverse events	Continent
Oh (2009) [40]	20	3 treatments	Mean reduction of lesions in the long incubation time group, short incubation time group, and IPL alone (84.4% vs. 72.6% vs. 65.9%); inflammatory acne lesions (89.5% vs. 83.0% vs. 74.0%)	Transient erythema and edema, posttreatment hyperpigmentation, acneiform eruption	Asia
Bissonnette (2010) [30]	44	4 treatments	No significant difference between W18 and W0 for all groups	Pain during red light exposure, erythema after PDT	Canada
Yin (2010) [23]	180	4 treatments	Great reduction in all groups comparing to baseline; greater improvement in higher concentration groups than lower concentration groups	Erythema, edema, hyperpigmentation, mononorphic acneiform eruption, scaling and dryness with exfoliation	Asia
Barolet (2010) [42]	10	2 treatments	Inflammatory acne revealed a statistically significant reduction in lesion count on the IR-treated side in comparison to the control side (73% vs. 38%)	Slight erythema, mild crusting, acneiform folliculitis	Canada
Jung-Im Na (2011) [26]	14	2 treatments	Inflammatory lesions and sebum secretion were significantly reduced, the growth of *P. acnes* and *S. aureus* were significantly suppressed with IAA PDT	Procedure was painless, no adverse effect was observed	Asia
Yang (2013) [8]	75	3 treatments	Treatment group had statistically higher cure rate than control (87.5 vs. 62.86%) and response rate (100 vs. 91.43%)	Mild to moderate erythema and edema	Asia
Mei (2013) [35]	41	4 treatments	Mean reductions of inflammatory and noninflammatory lesion counts in ALA-PDT group were 83.6% and 57.5%	ALA-PDT group had transparent erythema and monomorphic acneiform eruptions, IPL group had burning pricking pain and skin hot flush	Asia
Liu (2014) [10]	150	4 treatments	Clearance or moderate improvements were seen significantly in the PDT group than in the other groups: 46 (92%) in the PDT group, compared with 29 (58%) in the IPL group and 22 (44%) in the LED group	Mild to moderate pain, erythema, edema, and hyperpigmentation were reported in PDT treatment, minimal erythema and slight stinging sensations in the IPL and LED groups	Asia
Chen (2015) [43]	50	3 treatments	Total effective rate was 83.3% at 6 weeks, statistically significant over control	PDT group complained of burning, pain, erythema, transient hyperpigmentation, and acute acneiform lesions	Asia
Pariser (2016) [9]	153	4 treatments	MAL group had significantly larger decrease in inflammatory lesion counts than controls (−15.6 vs. −7.8); no significant difference in noninflammatory lesions	Pain and erythema similar between groups	USA

Moftah (2016) [29]	35 (split backed control	3 treatments	PDT group had statistically significant improvement in inflammatory lesion count vs. control (56.4% vs. 34.1% reduction)	More pain in PDT group than in controls (mean reported severity 7.8 vs. 4.64); photosensitizer caused staining, pruritus, desquamation	Africa
Xu (2017) [11]	95	4 treatments	Minocycline plus PDT treatment led to a greater mean percentage reduction versus minocycline alone for both inflammatory (74.4% vs 53.3%) and noninflammatory lesions (61.7% vs 42.4%)	Minocycline group patients complained of dizziness, mild headache; minocycline plus PDT group complained of pain, mild to moderate erythema and hyperpigmentation	Asia
Kim (2017) [41]	28	2 treatments	Inflammatory lesion counts significantly decreased by 36.0% in the PDT group and 51.8% in the PDT + fractional laser group	In the first session, the pain score in the PDT + fractional laser group was significantly higher than the PDT group; minimal erythema, slight transient skin tanning, and hyperpigmentation were similar in both groups	Asia
Nicklas (2019) [31]	46	2 treatments	PDT group had greater reduction of inflammatory lesions vs. control: 84% vs. 74% as well as in reducing total lesions: 79% vs. 67%	PDT group reported well-tolerated pain, erythema, mild sterile pustular eruption vs. control group reported abdominal pain, nausea, vomiting, and photosensitivity	USA

respect to improvement in inflammatory lesion counts, while only 7% of patients responded in terms of noninflammatory lesion counts [38]. It is recognized that laser-mediated PDT may be an interesting alternative treatment to conventional PDT. This is attributed to the less adverse effect profiles. The intense skin reactions may be explained by a higher degree of photobleaching with conventional PDT than LPDL-PDT.

Daylight photodynamic therapy (DL-PDT) is a simpler and more tolerable treatment procedure for both clinicians and patients; it has been gradually applied for acne treatment. 46 patients with facial acne were applied with the novel variant of 1.5% 3-butenyl ALA-bu gel, using daylight only as the potential visible light source every other day for 12 weeks. At the final 12 week, both inflammatory and noninflammatory acne lesions had decreased significantly by 58.0% and 34.1% in the ALA-bu group, respectively. Only a few patients expressed mild adverse effects. Daylight PDT was effective, very well tolerated, and convenient for treating inflammatory acne lesions. This novel regimen would provide a viable option for acne therapy [39].

Incubation Time

Throughout the studies, the incubation time varied significantly from a minimum of 30 minutes to a maximum of 3 hours. The photodynamic efficacy of different incubation times was compared by Oh et al. Three sessions with short incubation (30 minutes) or long incubation (3 hours) with ALA plus IPL were performed in 20 Korean subjects at 1-month intervals. The degree of improvement in inflammatory acne lesions was greater in the long incubation time group than the short incubation time group, although the mean reduction of inflammatory acne lesions was statistically different only between the long incubation group and the IPL-only group. PDT with a long ALA incubation time might be more adequate for a pronounced outcome with inflammatory acne [40].

Skin Preparation

Skin preparation affects the uptake of topical photosensitizers. Various skin preparations for degreasing skin might help drug penetration and have been used in different clinical studies of photodynamic therapy for acne. 70% isopropyl alcohol, mild soap, 70% alcohol scrub, and saline have been described before the application of ALA. Several strategies to enhance the penetration of the photosensitizer have been reported, such as curettage, microdermabrasion, fractional lasers, and microneedling. However, stratum corneum ablation is accompanied by pain, increased severity of immediate skin reactions, and long-term adverse effects. Kim et al. evaluated the efficacy and safety of DL-PDT in moderate to severe acne and compared outcomes with those of non-ablative fractional laser-assisted DL-PDT. The mean inflammatory lesion counts significantly decreased by 51.8% in the treated group and 36.0% in the control group at 8 weeks, and the beneficial effects lasted 16 weeks. The combination of non-ablative fractional laser and DL-PDT achieved higher uptake of MAL, with shortened incubation periods and minimal disruption of the skin barrier [41]. Barolet and Boucher reported therapeutic effects may be due to enhanced induction of alterations in transcutaneous diffusion kinetics of the photosensitizer at higher skin temperature and conversion of ALA to PpIX. Ten patients exhibiting inflammatory acne were assigned to be pretreated for 15 minutes with radiant IR light emitting diode (IR-LED, 970 nm), followed by ALA-PDT. The trial revealed a significant difference in median reduction of inflammatory lesions on the IR pretreated (73%) versus the control side (38%) [42]. Pre-PDT radiant IR-LED exposure appears to be a promising method to enhance PDT efficacy for the treatment of acne lesions.

Adverse Effects

Moderate to severe pain, erythema, edema, transient hyperpigmentation, superficial exfoliation, and crusting are the most common side effects of

PDT in acne. The intensity of side effects is related to the incubation time, light source, light dosimetry, and photosensitizer species. A majority of the studies noted that the adverse events were minimal and the procedure was well tolerated by the patients. In general, the risk of permanent side effects, such as ulceration and scarring caused by PDT and allergy to ALA or ALA derivatives, is very rare. Pain is most obvious at the beginning of light irradiation and can be reduced by using cooling fans and water spritzing. Pigmentation after PDT is caused by melanogenesis, which is a photodynamic reaction to the accumulation of PpIX in the epidermis. Patients should be advised to avoid bright light exposure after treatment because of persistent phototoxicity up to 48 hours. The decrease in sebum production often leads to dry skin and superficial exfoliation, released with the level of sebum secretion recovery about 1 month after the PDT treatment. Sterile pustular eruption also known as acute acneiform lesions was observed, starting on the second or third day posttreatment, lasting typically 3 days, after high fluence PDT [43].

Conclusion

PDT as a new technology is widely used in severe inflammatory and moderate to severe cystic nodular acne in various skin types, and for either facial or truncal lesions. With the development of photosensitizers, light sources, irradiation time, treatment sessions, and pretreatment, PDT could be progressively improved to aid clinical applications in acne.

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Insulin Resistance Associated Acne

9

Raj Kubba

The important role of insulin, insulin-like growth factor-1 (IGF-1), and insulin resistance (IR) in the pathogenesis of acne emerged following a seminal article by Cordain and colleagues in 2002, titled "Acne vulgaris: a disease of western civilization" [1], and has steadily grown in the ensuing years to bring us to yet another thought-provoking article by Bodo Melnik titled "Acne vulgaris: the metabolic syndrome of the pilosebaceous follicle" [2]. Time has come, perhaps, to look at the accumulated body of research on the subject through the prism of clinical practice, and to connect the relevant "scientific dots". Time has come, perhaps, to incorporate insights so gleaned in the assessment and management of IR-associated acnes.

Acne is acknowledged in the literature pertaining to IR [3], especially in the context of PCOS [4]; however, such acnes are credited to hyperandrogenemia rather than insulin or IR [3, 4]. The concept of a distinctive insulin resistance associated acne (IRAA) has been mooted, and its distinctive features have been described [5–7]. Presented below is an account that makes a case for IRAA, an acne that is a distinct metabolic entity, and a harbinger of metabolic syndrome (MetS).

Molecular Aspects of IRAA

To comprehend IRAA, it is necessary to understand insulin and insulin resistance (IR). Insulin is a peptide hormone produced by the beta cells of the pancreatic islets in direct response to circulating levels of blood glucose [Wikipedia]. Insulin regulates carbohydrate metabolism and contributes to the metabolism of lipids and proteins [8]. Insulin is also a mitogen, that is, it promotes cell growth, cell division, and migration, and inhibits apoptosis [8]. A part of the mitogenic effect of insulin is direct, and a larger part is through its collaboration with IGF-1 [8]. Insulin is a potent mitogen when it binds to insulin receptor A (IR-A) or IGF-1 receptor (IGF-1R); for its metabolic actions and in glucose metabolism, it binds to insulin receptor B (IR-B) [9]. Insulin also potentiates other growth factors, namely, PDGF (platelet derived growth factor), VEGF (vascular endothelial growth factor), and EGF (epidermal growth factor) [8]. Insulin activates Ras-Raf-Map kinase signalling pathway for its mitogenic effect [8]. This promotes phosphorylation and activation of farnesyltransferase, an enzyme that farnesylates Ras

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protein [8]. Increased availability of farnesylated Ras at the plasma membrane enhances mitogenic responsiveness of concerned cells to various growth factors [8].

IR describes defective insulin stimulation of glucose uptake by skeletal muscle, adipose tissue, liver and endothelial cells resulting in compensatory hyperinsulinemia which is the fundamental metabolic effect of IR [1]. Hyperinsulinemia is the key driver of MetS [10] which evolves asynchronously along multiple axes, over a lifetime, to reveal in random order hypertension, type 2 diabetes mellitus, dyslipidemia, coronary artery disease, hyperuricemia, fatty liver, obesity, abnormalities of fibrinolysis (major components) along with acanthosis nigricans (AN), acrochordons, acne, PCOS, male pattern hair loss, early menarche, tall stature, myopia, and increased risk of epithelial cancers (minor components) (Table 9.1) [10]. Hyperinsulinemia is acute and intermittent in the early years in individuals with IR and corresponds to insulinotropic stimuli such as excess ingestion of westernized foods and milk consumption [11]. With time, hyperinsulinemia becomes persistent and chronic [10].

Hyperinsulinemia results in increased insulin/IGF-1 signalling with many metabolic consequences of which acne is one [2]. There are many pathways through which such enhanced signalling operates of which activation of mTORC1 (mechanistic target of rapamycin complex 1; a nutrient-sensitive kinase) is the most notable. Activated mTORC1 induces sebaceous lipogenesis via activation of SREBP1 (sterol response element binding protein1) [12] which in turn is a master regulator of sebaceous activity and sebaceous lipogenesis, a major pathogenetic factor in acne (Fig. 9.1). Increased mTOR gene expression has been observed in lesional as well as non-lesional skin of acne patients as compared with normal healthy controls [13]. Immunohistochemical studies have shown more intense cytoplasmic expression and nuclear expression of mTORC1 in inflammatory sebaceous glands in the backs of acne patients compared with controls [14]. Another pathway is S6K1 (ribosomal protein S6 kinase beta-1) which via IRS-1 (insulin receptor substrate–1) phosphorylation induces IR [2]. Increased insulin/IGF-1 signalling directly inhibits nuclear FoxO1 activity in human sebocytes [15]. Hyperinsulinemia upregulates gonadal androgen production [16] with downstream effects such as acne, hirsutism, and PCOS. Androgenemia fuels acne through several mechanisms one of which is to augment mTORC1 expression through AR (androgen receptor) repression of DEPTOR (DEP domain-containing mTOR-interacting protein) [17].

Increased insulin/IGF-1 signalling is responsible for physiologic IR that accompanies puberty. However, high caloric westernized diet that is commonly consumed at this age compounds the physiologic IR and hyperinsulinemia. Insulin/IGF-1 signalling occupies an important position in the upstream mechanisms of acne pathogenesis and in this way it impacts on all four major pathogenetic factors of acne, namely, abnormal keratinization, sebaceous lipogenesis, disturbances in follicular microbiome, especially *Cutibacterium acnes*, and follicular and perifollicular inflammation [1] (Fig. 9.1).

Table 9.1 Major and minor components of metabolic syndrome

Major components	Minor components
Type 2 diabetes mellitus	Acanthosis nigricans
Hypertension	Acrochordons
Dyslipidemia (↑TG, ↓HDL)	Acne
Coronary artery disease	Alopecia
Obesity	Early menarche
Hyperuricemia	↑ Physical growth
Abnormalities of fibrinolysis	PCOS
	Myopia
	Epithelial cancers (breast, prostate, colon)

Data from: Cordain et al. [10]

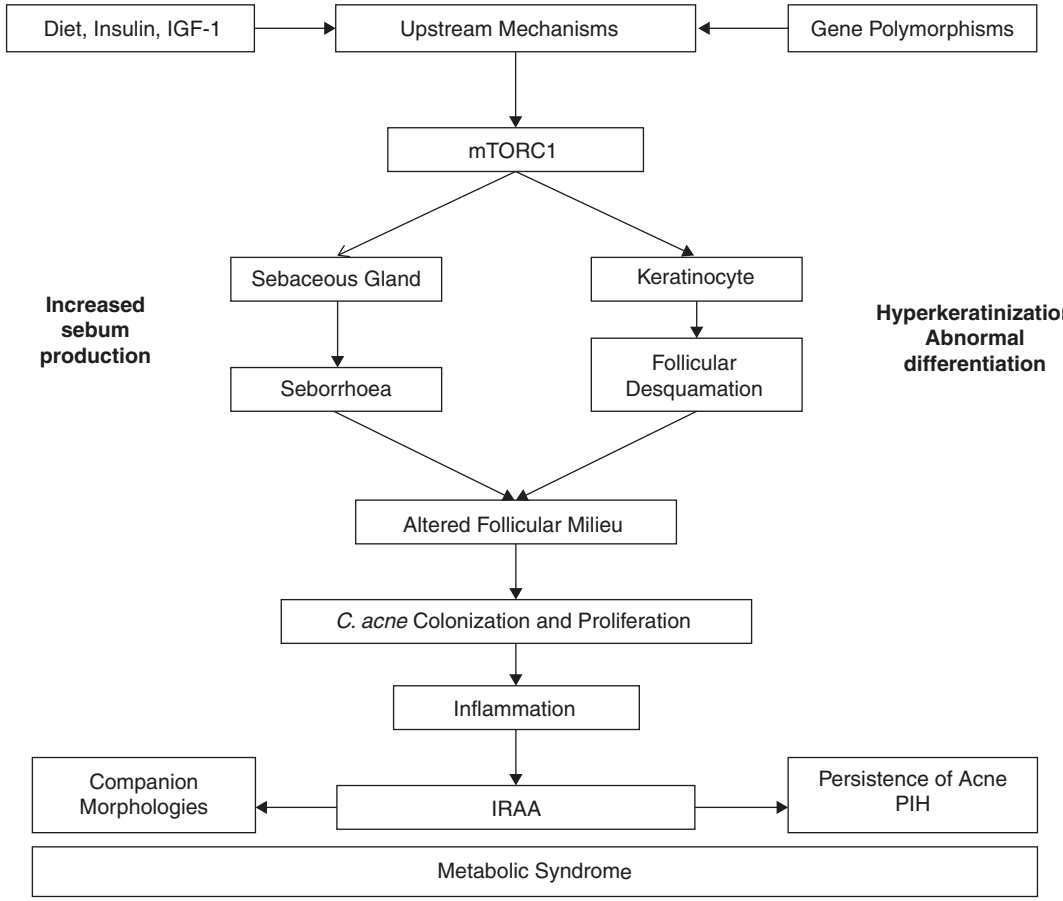

Fig. 9.1 Schematic overview of IRAA pathogenesis

Racial, Ethnic, Regional, Geographic Aspects of IRAA

IRAA exemplifies racial/ethnic and regional/geographic differences reported in acne populations globally. Most literature implicating insulin in acne vulgaris pathogenesis has emanated from South & East Asia, Latin America, Turkey, and Italy [18–22]. There are racial predilections for IR [23]. Indians, Hispanics, and Africans are stated to be more prone to IR [23]. The role of changing dietary habits with transition to westernized diet in developing societies offers compelling explanation for rising prevalence of IR and acne in such societies [10]. It certainly applies well to India where observations over the past 30 years corroborate this hypothesis. IR impacts on microbiome, vulnerability to environmental stressors (air pollution, infectious agents, exposure to chemicals, and UVR), immune and endocrine health, all of which are subject to regional and geographic factors. The aggravating impact of air pollution on acne is a good example [24]. Air pollution with particulate matter 2.5 (PM 2.5) has been noted to aggravate pre-existing IR [25]. In summary, genetic predisposition, changing diets, and air pollution, are accentuating regional differences in acne expression of which IRAA is a good example.

Clinical Profile of IRAA

IRAA and Age IRAA runs a protracted course (Fig. 9.2). When it commences early in life (vide infra), it can be predicted to persist and evolve into

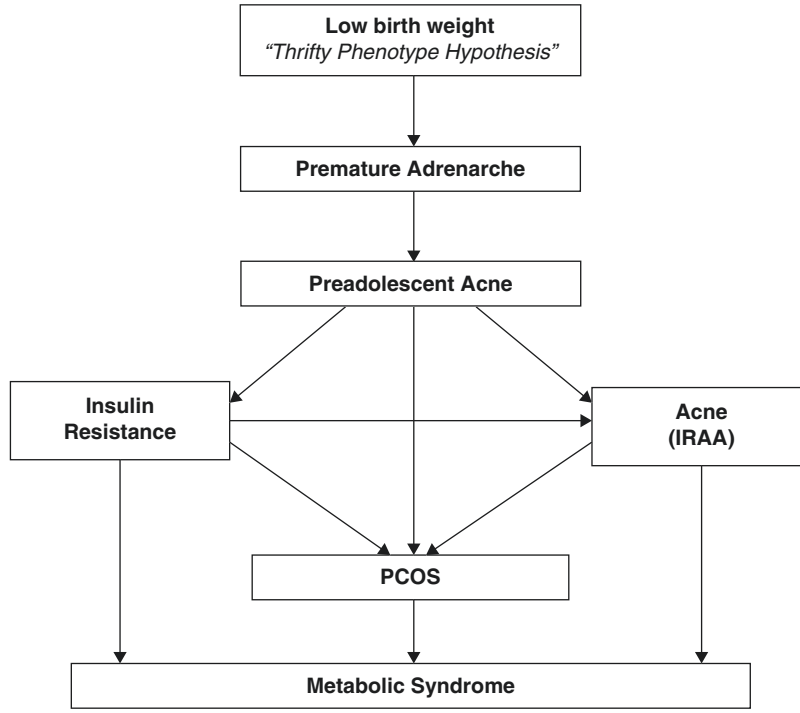

Fig. 9.2 Proposed schematic to show IR, acne, and age. (Data from: Idkowiak et al. [26])

adult acne [6]. With passage of time, IR worsens and hyperinsulinemia becomes constant (chronic hyperinsulinemia). This reflects clinically with appearance and subsequent evolution of companion morphologies, with increasing comorbidities, and with systemic signs of MetS. Clinical severity of facial acne diminishes especially after the age of 22 years and acne sequelae begin to draw greater attention [6]. Adolescent IRAA is viewed as a predictor of MetS whereas adult IRAA is a sign of evolving or already developed MetS [6].

Preadolescent IRAA Onset of acne in preadolescence may be explained on the basis of premature adrenarche (PA), which in turn is validated by increased levels of DHEA and DHEAS before the age of 8 years in girls and 9 years in boys, and the concurrent presence of signs of androgen excess including adult-type body odor, oily skin and hair, and pubic hair growth [26]. Acne may be triggered by IR, and when so it is likely to be associated with presence of acanthosis nigricans (AN) [27] and, in some instances, with polycystic ovaries, accelerated skeletal growth, and physical maturity [27] (Fig. 9.3). Preadolescent acne may also occur in children with NCAH (Nonclassic Congenital Adrenal Hyperplasia), and NCAH and IR may co-occur [6]. Preadolescent IRAA portends more severe acne to follow and serves as the earliest clinical clue to MetS in the distant future [6].

Adolescent IRAA Presence of facial acanthosis nigricans (FAN) in adolescent acne is the most prevalent clue to IR/MetS [28] and is clinically evident as dark (eye) circles, shaded forehead, and shaded chin (Fig. 9.4). Other clinical clues in adolescent IRAA are: diffuse hypertrichosis (including hypertrichosis on forehead and zygomatic areas) (Fig. 9.5), seborrhoea, signs of Malassezia overcolonization (dandruff, malar seborrheic dermatitis), and occasional benign hyperplasia, such as dermatosis papulosa nigra (DPN) and acrochordons [6]. Commonly, adolescent IRAA is mild (grade 1) and shows a transition from T-zone distribution to pan-facial distribution [6]. However, severe acne in the context of IR has been reported [29].

Postadolescent IRAA This represents persistence and continuation of adolescent acne. FAN and benign hyperplasias are more pro-

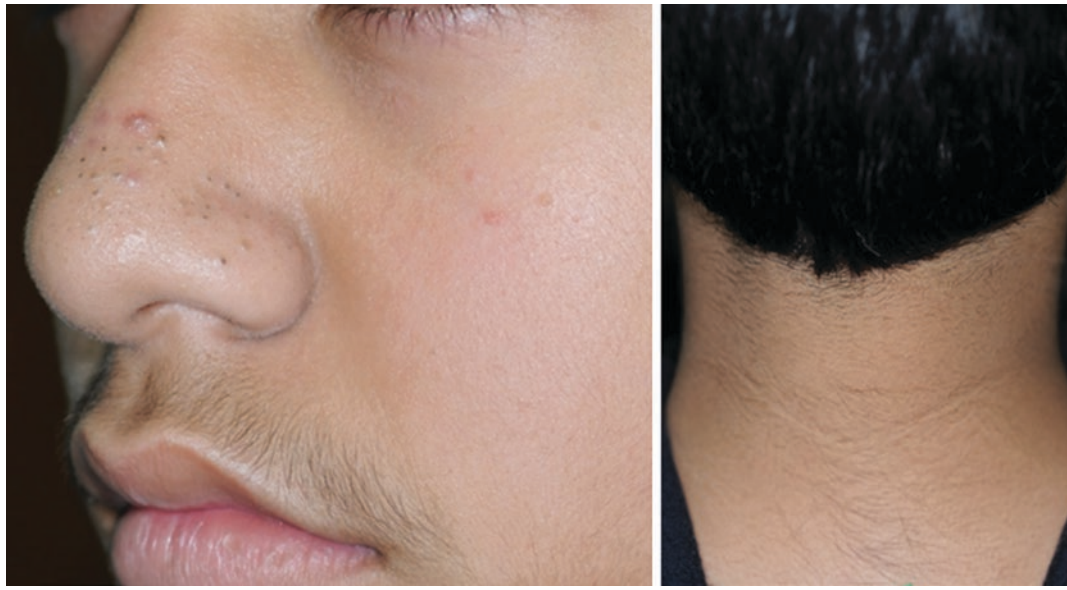

Fig. 9.3 Early IRAA at age 13. Comedonal acne on nose with stray papules on cheeks, acanthosis nigricans, and pubarche. Onset of acne before age 12 (preadolescent)

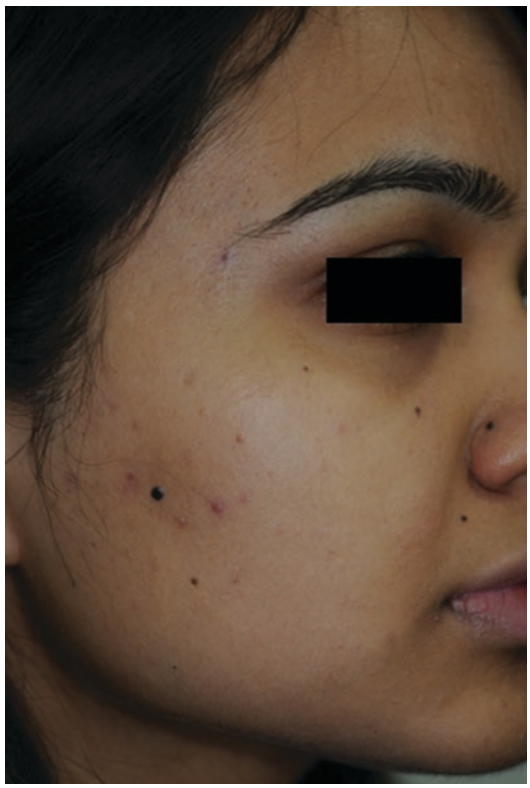

Fig. 9.4 Mild acne with companion morphologies as shaded chin and eyelids (FAN), melanocytic nevi, and occasional DPN (IRAA)

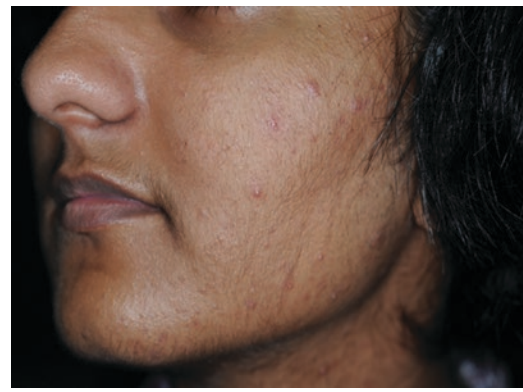

Fig. 9.5 Adolescent IRAA with PCOS showing hypertrichosis and worsening of skin colour (onset in preadolescence)

nounced. Acne severity appears to wane and settles in the "V-zone" distribution. An occasional patient in this group may exhibit grade II or even grade III (nodular) acne (Fig. 9.6 a, b). Acne sequelae become evident, especially post-inflammatory hyperpigmentation (PIH). Some patients experience worsening of skin colour (WOSC) which they describe as "persistent tan" [6]. Androgen excess is more common and PCOS comes to the fore.

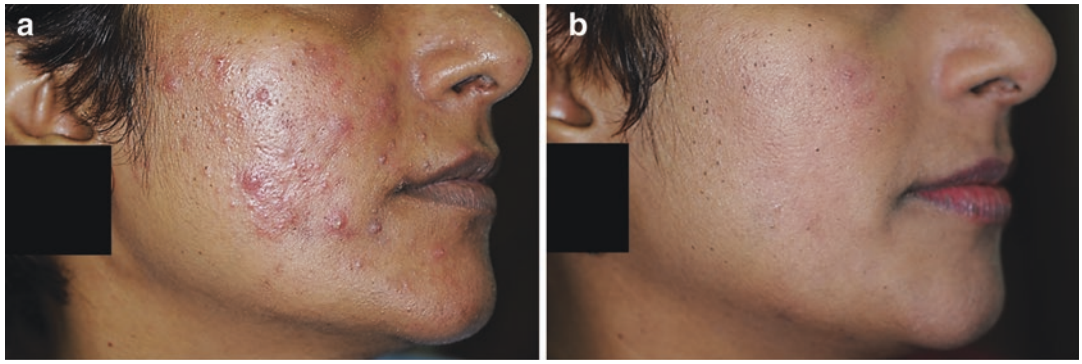

Fig. 9.6 (**a**) Nodular adult IRAA with DPNs. (**b**) DPNs more visible when acne remitted after 3 months

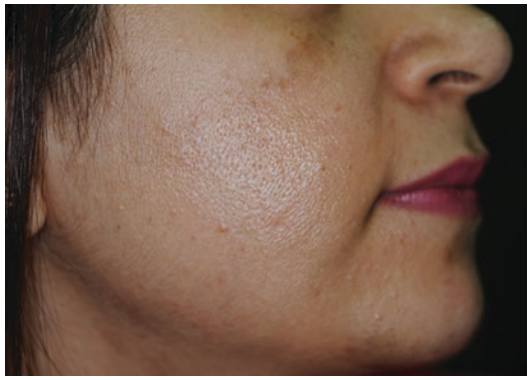

Fig. 9.7 Adult IRAA showing V-zone acne, malar melasma, seborrhoea, and hypertrichosis

Adult IRAA Acne continuing beyond 25 years of age represents persistence, less commonly late relapse and, rarely, de novo late-onset occurrence [6]. At this stage, companion morphologies such as pigmentary disturbances/ melasma-like hyperpigmentation (Fig. 9.7), hirsutism, and hair loss (especially hormonal) assume dominance and are often the primary presenting complaint of the patient [6]. Benign hyperplasias such as DPNs, syringomas, acrochordons, ephelides/lentigines, and melanocytic nevi are more florid [6]. In mature adults (beyond age 35 years), sebaceous hyperplasia, seborrheic keratosis, angiomas, and xanthelasma are encountered [6]. IRAA patients are at higher risk for developing other benign growths such as lipomata and fibroids. Photoaging makes an appearance at this stage and is insidiously progressive [6]. More importantly, adult IRAA patients begin to show stigmata of evolving MetS [7]. IRAA tends to linger on as sporadic acne in middle-aged men, and as chin acne in perimenopausal women [6].

IRAA Subtypes Over time hyperinsulinemia results in hormonal imbalance, immune dysfunction, and chronic inflammation, all of which contribute to and modulate the expression of attendant acne. We have observed the following subtypes of IRAA: Malassezia IRAA, Dystrophic IRAA, Autoimmune IRAA, and Hormonal IRAA based on predominant clinical features and attendant laboratory abnormalities (unpublished). In *Malassezia IRAA*, malassezia overcolonization as substantial and stubborn dandruff, and malar seborrheic dermatitis are strikingly evident along with acne which presents as superficial papules/pustules, sandpaper comedones, and mini-scars, with a predilection for skin along the frontal and temporal hairline (Fig. 9.8) and/or in an O-zone pattern, that is, paranasal and perioral distribution. *Dystrophic IRAA* features dermal dystrophy in addition, which is typically observed on the temples and zygomatic areas, and displays bilateral asymmetry (Fig. 9.9). *Autoimmune IRAA* is observed mostly in women who clinically present with recalcitrant inflammatory acne; it features immune dysfunction as elevated total IgE and elevated organ-specific autoantibodies, such as thyroglobulin antibodies and thyroid peroxidase antibodies and, paradoxically, in some such patients relatively reduced levels of sex hormones (AMH, DHEAS, 5αDHT, LH, FSH, prolactin). In *Hormonal IRAA*, androgen excess/ SAHA syndrome predominate acne and evi-

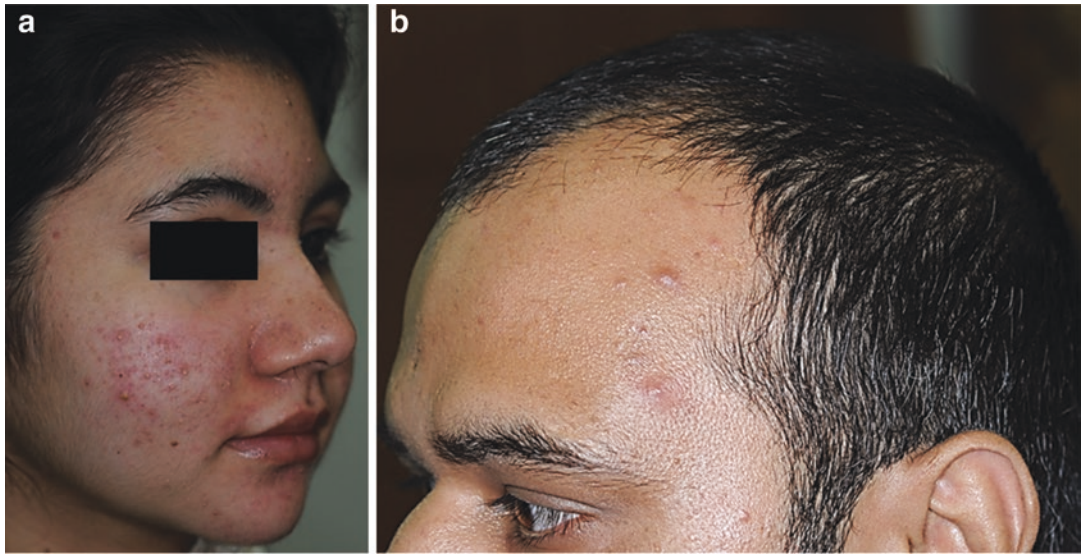

Fig. 9.8 (**a**) Malassezia IRAA – centrofacial and along the hairline, showing superficial pustules and seborrheic dermatitis. (**b**) Adult Malassezia IRAA, showing predilection for upper face. Documented case of MPHL with male equivalent of PCOS

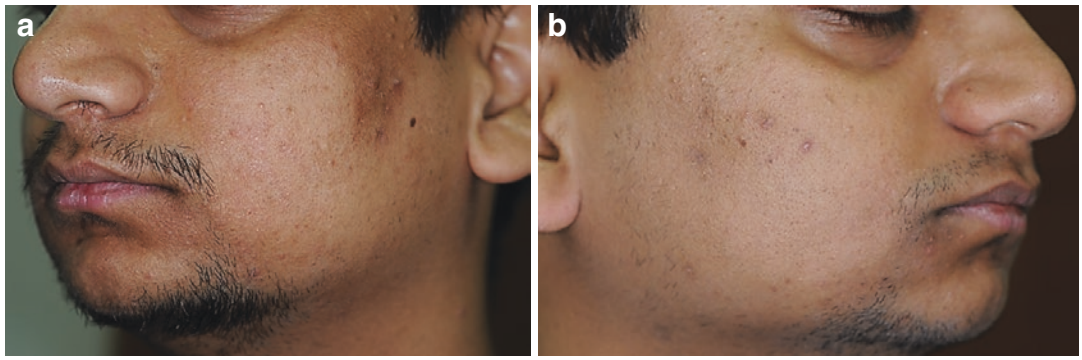

Fig. 9.9 (**a**, **b**) Example of dystrophic IRAA. Note bilateral asymmetry

dence for PCOS, prolactinemia, or NCAH is discernible. There is considerable overlap between the aforementioned IRAA subtypes (unpublished).

IRAA Syndromes APAAN syndrome is an acronym for Acne, Patterned Alopecia, Acanthosis Nigricans, and is viewed as a counterpart of SAHA in men (Fig. 9.10) [5]. Male equivalent of PCOS is a recently described entity [30] presenting as male pattern hair loss (Ludwig Type), recalcitrant Malassezia overcolonization, with elevated serum insulin, prolactin, and LH hormonally; such patients have acne as well and male equivalent of PCOS appears to overlap with IRAA (unpublished). HAIR-AN syndrome is an acronym for HyperAndrogenism, Insulin Resistance and Acanthosis Nigricans; a hereditary genetic defect consisting of mutations in the tyrosine kinase domain of the insulin receptor gene [31, 32] and clinically expressing as hirsutism, acne, AN, obesity, and PCOS (Fig. 9.11) [33].

Fig. 9.10 (**a**, **b**) APAAN syndrome. Note dystrophic acne. Ludwig type MPHL

Companion Morphologies in IRAA

IRAA does not occur alone! Benign hyperplasias as enumerated above serve as a clinical clue (Table 9.2). AN and FAN are recognized markers of IR [28, 34]. AN is a significant indicator of insulin sensitivity independent of body mass index [34]. However, it has been noted that skin phototypes (SPT) IV express more AN than SPT II-III and, furthermore, it has been opined that AN in SPT II-III is more specific and more predictive of IR than in SPT IV [35]; an opinion that warrants more scrutiny? Coexisting patterned hypertrichosis especially when observed on forehead, zygomatic areas, and nuchal areas favours IRAA [6]. This is more evident in adolescent IRAA. Diffuse hair loss and thinning (DHLT), sometimes accompanied by laxity of the scalp, is noted in some cases, both males and females, [6] and is a striking finding when encountered in a male adolescent IRAA. In time, the loss of hair volume escalates in to Ludwig type of alopecia (Fig. 9.10). Concurrent scalp folliculitis, relapsing and remitting, is a disabling and frustrating companion morphology, often mistakenly referred to as "scalp acne" which, in our opinion, is a part of IRAA in the appropriate context [6]. Acne keloidalis nuchae has been reported as a cutaneous symptom of MetS [36]. IRAA patients also experience other forms of folliculitides (Table 9.2).

IRAA Comorbidities

IRAA has many systemic comorbidities [37] that can only be elucidated by diligent and holistic assessment of every acne patient through appropriate laboratory evaluation for each of the known comorbidities that include vitamin D3 deficiency, vitamin B12 deficiency, atopy, immune dysfunc-

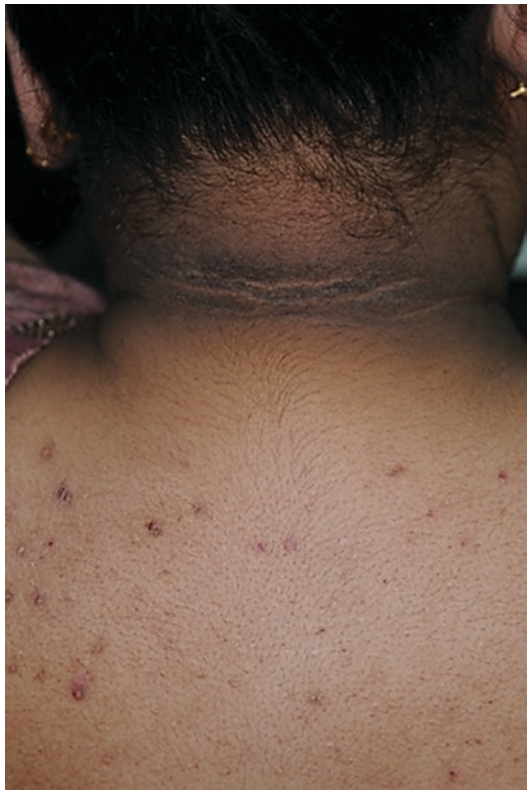

Fig. 9.11 HAIR-AN syndrome, showing florid acanthosis nigricans, truncal acne, hypertrichosis, and obesity

Table 9.2 List of companion morphologies in IRAA

Acanthosis nigricans
Acrochordons
Benign cutaneous hyperplasias
DPNs, syringomata, cherry angiomas, xanthelasma, seborrhoeic keratosis
Pigmentary lesions
Ephelides, lentigines, eruptive melanocytic nevi
Facial acanthosis nigricans (FAN)
Worsening of skin colour/persistent tan
Melasma
Disturbances in hair growth
Hypertrichosis, hirsutism
Diffuse hair loss and thinning (DHLT)
Patterned alopecia
Follicular issues
Keratosis pilaris
Folliculitis nuchae
Recurrent scalp folliculitis
Malassezia folliculitis
Deep folliculitis – pubic area, buttocks, thighs
Folliculitis following waxing
Miscellaneous
Seborrhoeic dermatitis
Stubborn dandruff

tion, PCOS, prolactinemia, adrenal hyperplasia, NCAH (nonclassic congenital adrenal hyperplasia), thyroid dysfunction, gastrointestinal dysfunction, dyslipidemia, and chronic inflammation [38–44]. Systemic comorbidities lend credence to systemic/metabolic nature of IRAA and require to be addressed with suitable therapeutic initiatives.

Pathogenesis of IRAA

IRAA is a component of MetS which in itself represents multiple aberrations in the extremely complex body system with numerous interlocking and interplaying subsystems. IRAA results from qualitative deviations, quantitative deviations, and deviations in interrelationship of all four major pathogenetic factors.

The molecular mechanisms of IRAA are complex and involve multiple pathways and multiple bioactive molecules of which insulin/IGF-1 induced PI3K/Akt/FoxO1/mTORC1 signalling is proposed as the most important [45]. IGF-1 signalling through MAPK additionally activates mTORC1 [45]. A nutrient-sensitive kinase, mTORC1 regulates growth and anabolism in general and is also incriminated in the causation of obesity, T2DM, and MetS [2]. BCAAs (branched chain amino acids) and palmitic acid (from dietary fats and milk) also activate mTORC1 [2]. Increased mTORC1/ SREBP1 signalling enhances the expression of key enzymes of fatty acid synthesis such as acetyl-CoA carboxylase (ACC) and desaturases such as Δ6-desaturase and stearyl CoA desaturase (SCD1) [quoted from2]. Other biological effects of activated mTORC1 include oxidative stress, inflammation, and migration of peripheral blood mononuclear cells [2].

Increased insulin/IGF-1 signalling inhibits FoxO1 activity in sebocytes and sebaceous glands of acne patients [46]. FoxO1 (Forkhead Box O1) is metabolic transcription factor which from its nuclear location represses SREBP1 and AR signalling and in this way, and in some other ways, plays a protective role against acne Fig. 9.12) [46]. IGF-1 induces proliferation in sebocyte, and both insulin and IGF-1 induce sebocyte differentiation [46]. The expression of

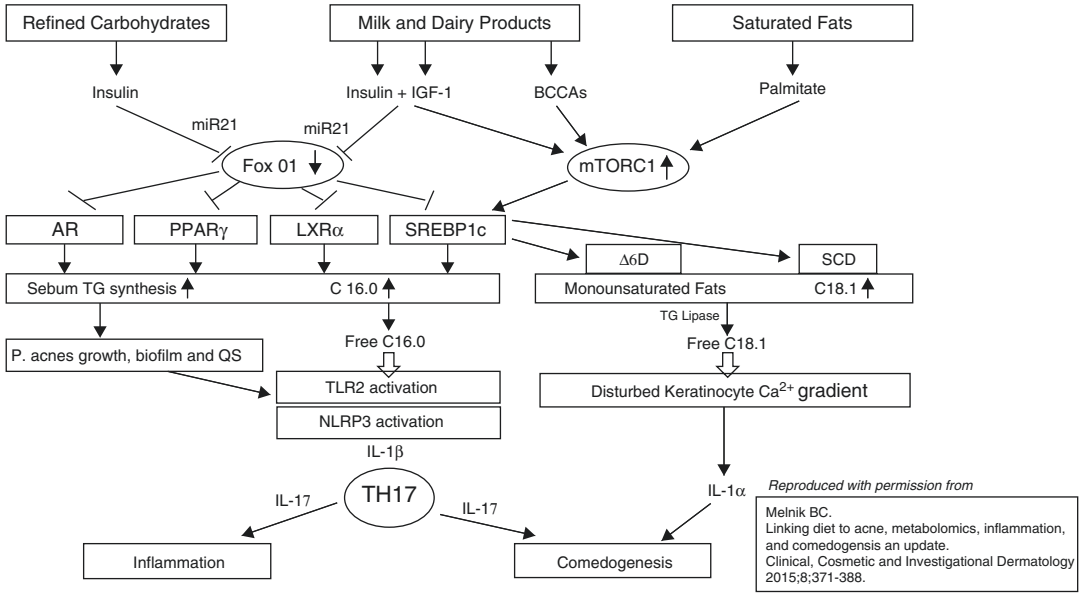

Fig. 9.12 Molecular pathways showing yin and yang relationship between FoxO1 and mTORC1 (Image courtesy of Bodo C. Melnik)

IGF-1 is strongest in the sebaceous gland and the pattern of expression suggests a role for IGF-1 as a sebaceous mitogen and morphogen [47]. *C. acnes* extracts (membrane fraction) increase IGF-1/IGF-1R expression in the epidermis of explants [48]. IR is reported to increase inflammatory responses within and adjacent to the comedo [49].

Insulin/IGF-1 signalling contributes to comedogenesis and inflammation via activation of mTORC1/SREBP1, causing increased production of palmitic acid, sapienic acid, and oleic acid by the sebaceous gland, which in turn promotes *C. acnes* growth and biofilm formation, and enhanced triacylglycerol lipase expression [50].

Insulin/IGF-1 signalling may also be influenced by gene polymorphisms and gene mutations. Higher levels of IGF-1 have been reported in acne patients who are homozygote for 192/192 allele base pairs of IGF-1 gene [51]. It is suggested that individuals who are homozygotes for IGF-1 gene are not only likely to experience more acne but also more severe acne [51]. Unusual or severe forms of IRAA may also arise from mutations in the INSR gene that encodes for insulin receptor [52].

Increased insulin/IGF-1 signalling causes worsening of skin colour as a combined effect of AN and dermal vasculature changes (endothelial dysfunction, accelerated atherosclerosis, and deposition of glycation end products) [53]. Additionally, it increases melanogenesis [53] and increases expression of α-MSH [54] and POMC [55]. Insulin is also mitogenic for melanocytes in vitro [56].

Laboratory Validation of IRAA

First and foremost in this initiative is the validation of IR in a given acne subject. The gold standard of IR validation is the hyperinsulinemic-euglycemic clamp technique [57] which requires IV infusions and is, therefore, not practical. The next best option is HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) [58], a computer-derived formula in which value of fasting blood glucose is multiplied with that of fasting insulin and the product is divided by 405 (in the metric system the denominator is 22.5); derived value above 4.50 is accepted as confirmatory of IR across all dis-

ciplines of healthcare. In acne population, this figure has been revised downward to 2.50 [17] and 2.70 [29]. HOMA2-IR is a computerized updated model which is regarded as more accurate and reliable and has a cutoff of 1.80 for IR [59, 60].

Insulin testing is subject to technical variables such as the brand of the testing toolkit and technique used [61], the care in handling of specimen, and the precision with which the test is carried out. Another variable is blood rheology which is reported to impact on fasting serum insulin levels and IR [62]. Inter-laboratory differences in test results are commonly encountered in our practice. Furthermore, there is confusion as to what are normal serum levels of fasting and PP insulin? The standard reference range quoted by textbooks is <25 μIU/ml for fasting insulin and 16–166 μIU/ml for 2 hours post-load insulin [61]. These reference ranges appear to be skewed towards diabetes and are misleading for dermatologists. From an epidemiologic study in USA [63], Johnson et al concluded that a fasting insulin greater than 9 μIU/ml identified prediabetes in 80% of the cohort. A Japanese study has stated normal insulin level to be between 8 and 11 μIU/ml [64]. In a study of IR in severe acne vulgaris from Turkey, the mean fasting insulin in 156 controls (mean age 19.94 ± 4.77 years) was reported as 9.12 ± 3.55 μIU/ml versus 14.01 ± 11.99 μIU/ml for the acne subjects [29]. In a study of IR in children and youth with AN in India, the fasting insulin in 30 age-matched normal controls (age 16.06 ± 4.89 years) was reported as 10.17 ± 3.54 μIU/ml [65]. Postprandial insulin (and sugar) is typically not tested in younger subjects for compassionate reasons but is stated to be of particular relevance during puberty and adolescence when whole body IR naturally increases [66]. In a cohort of 132 IRAA patients (93 females, 39 males; 69 under 25 years), the mean fasting insulin was found to be 10.91 ± 6.44 μIU/ml and mean PP insulin 55.41 ± 38.99 (Kubba R, unpublished). After years of conducting insulin testing in acne patients, we have come to regard fasting serum insulin above 10 μIU/ml and a fourfold or greater jump in PP-insulin as suggestive of IR and, in the context of acne, the skin markers of IR, validating IRAA (clinical-laboratory correlation; CLC).

Treatment of IRAA

Diet and Lifestyle Modifications Additional therapeutic measures are warranted to address IR and associated systemic metabolic disturbances in IRAA patients. The prime therapeutic target is hyperinsulinemia (Fig. 9.13). The first step in this direction is lifestyle optimization in which weight

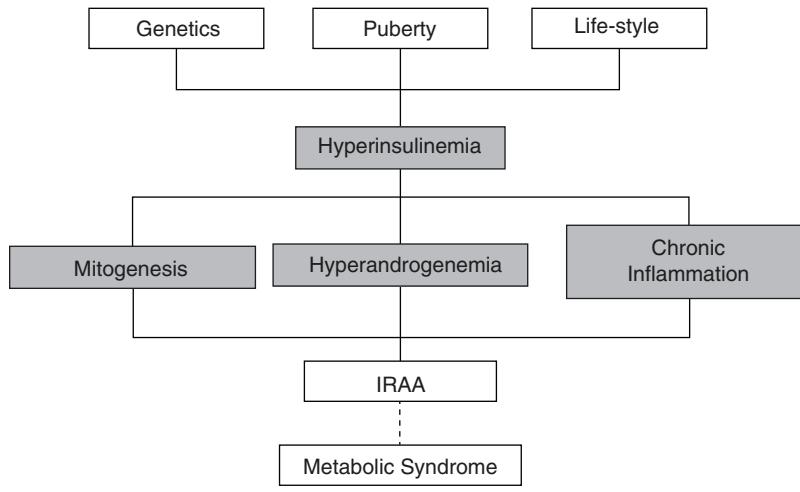

Fig. 9.13 Therapeutic approaches in IRAA

management and diet control are paramount. Weight reduction benefits acne by multiple mechanisms including increasing adiponectin levels [67], which in turn repress mTORC1/S6K1 signaling and lower IR [68]. Glycemic foods including milk and dairy products and saturated fats enhance insulin/IGF-1 signalling [69] and restricting them attenuates mTORC1 signalling [70]. In a 10 weeks long controlled study, low glycemic diet was shown to improve acne with reduction in size of the sebaceous glands, reduction in inflammation, lowering of SREBP-1, and lowering of IL-8 [71]. Enhanced physical activity and regular exercise is recommended. There are a number of therapeutic agents that are established in the management of diabetes, IR, PCOS, and obesity, suitable for repurposing in the treatment of IRAA (vide infra). The therapeutic rationale is that they all prevent activation of mTORC1 (Table 9.3).

Metformin A biguanide, an antidiabetic drug, is the sheet anchor of IRAA drug treatment. Metformin is an insulin-sensitizing drug and also an excellent mTORC1 inhibitor [72]. Metformin reduces glucose absorption from the gastrointestinal tract [73]. Metformin is antiandrogenic through mechanisms that are different than classical antiandrogens [74]. Metformin is anti-inflammatory through its effect on NF-κB signalling [75]. The beneficial effect of metformin in acne, an off-label indication, has been documented in several international clinical studies [76–78]. Metformin is administered orally in a daily dosage varying from 500 mg to 2500 mg.

Table 9.3 Miscellaneous therapeutic agents with potential to inhibit mTORC1 signalling and as possible adjuvants in the treatment of IRAA

EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid)
EGCG (Epigallocatechin-3-gallate)
Resveratrol
Curcumin
N-acetylcysteine
Alpha-lipoic acid
Myo-inositol
Vitamin D3

Data from: Melnik [2]

It can be given to patients above 10 years of age and also can be continued in female acne patients who are planning conception or have conceived. It is pregnancy category B. The dose of metformin is titrated according to therapeutic response and tolerance. About 20% of the subjects given metformin have G-I. intolerance and in some gradual escalation of dose may help overcome it [79]. Metformin has an excellent safety profile with sparse drug interactions. Metformin can be safely co-prescribed with systemic anti-acne drugs including antibiotics, retinoids, and antiandrogens. Metformin is unlikely to cause reactive hypoglycaemia in non-diabetics [80]. Prudence dictates that metformin pharmacology should be well learnt before starting to prescribe it for acne patients.

Other Drugs That Inhibit mTORC1 and Are Beneficial in IRAA EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) administered orally in a daily dose of 1–2 g were shown to decrease inflammatory and noninflammatory acne lesions [81], reportedly through inhibition of inflammasome activation and attenuation of mTORC1/SREBP1 signalling [82, 83]. EPA are also reported to reduce mTORC1 activity [84]. EGCG (epigallocatechin-3-gallate), derived from green tea, is another mTORC1 inhibitor [85]. Topically applied EGCG has been reported to improve acne by targeting sebaceous hyperplasia, *C. acnes* overcolonization, and inflammation [86]. Although the MAPK pathway is the most important, topical EGCG modulates multiple other molecular targets including inhibition of IGF-1/PI3K/Akt pathway [86]. Resveratrol, found in grapes and berries, inhibits mTORC1 [87]. Topical resveratrol also appears to have antimicrobial effects against *C. acnes* [88]. Curcumin, a derivative of turmeric, targets both mTORC1 and mTORC2 in a dose-dependent manner [89]. Turmeric may also improve acne through its antimicrobial, anti-inflammatory, and antidiabetic effects [90]. N-acetylcysteine, an antioxidant, that has been tried in acne both topically (for comedonal acne) and orally (for papulo-pustular acne) [91] is also an mTORC1 inhibitor [92]. Alpha-lipoic acid, yet another anti-

oxidant, is a recognized antihyperglycemic agent through its effect on insulin signalling, through increasing tyrosine phosphorylation of IRS-1, and through stimulation of GLUT4 translocation (via PI3K/Akt) and GLUT4 activation (via p38 MAPK) [93]. Alpha-lipoic acid has been shown to inhibit mTORC1 in animal experiments [94]. Myo-inositol (one of the nine isomers of inositol) is a component of the vitamin B complex, and a recognized insulin sensitizer; it improves insulin signalling, and reduces serum insulin [95]. Myo-inositol is recommended in PCOS (especially in adolescents) where it has an antiandrogenic effect comparable to OCPs, and improves metabolic parameters [96]. At the molecular level, inositol polyphosphates modulate activation of mTOR in response to essential amino acids, and also relate to AMPK signalling pathways [97].

Vitamin D3 and IRAA Hypovitaminosis D3 prevails in geographic areas besieged with air pollution and constitutes an important confounding factor in the pathogenesis of IRAA. Hypovitaminos D is associated with IR and ß-cell dysfunction [98]. Raising vitamin D level from 10 ng/dl to 30 ng/dl is stated to improve insulin sensitivity by 60% [99]. Correcting vitamin D deficiency in acne may attenuate mTORC1 signalling, increase the expression of antimicrobial peptide cathelicidin, and thus inhibit *C. acnes* [99, 100]. The aforementioned agents in this section (Table 9.3) are nutritional supplements available over the counter. They are adjuvants and offer scope for broader, creative, and tailored IRAA treatment plans.

Summary IRAA is a subset of insulin-driven acnes characterized by a distinctive clinical profile, attendant companion morphologies, multiple comorbidities, a persistent course, and hyperinsulinemia. IRAA appears to straddle genomics, proteomics, transcriptomics, and, metabolomics. Its metabolomic signature is scripted by mTORC1 [2]. IRAA has nutritional, metabolic, hormonal, and immune implications that are hitherto underrepresented in acne vulgaris literature. Being a systemic-metabolic condition, it requires comprehensive engagement, delineation, and management. It also offers a unique opportunity for dermatologists to "halt the march of MetS" [2].

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Acne Fulminans

10

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Introduction

Acne fulminans (AF), also known as "acute febrile ulcerating acne conglobate" or "acne maligna", is a rare severe form of inflammatory acne characterized by acute onset of painful, ulcerative and haemorrhagic nodules. It was originally described in 1959 in a young patient with severe conglobate acne and acute febrile illness [1], and later labelled as "acute febrile ulcerative conglobate acne with polyarthralgias" in 1971 [2]. In 1975, Plewig and Kligman [3] used the term "acne fulminans" to better define this disorder and to remark its acute onset and severity [4].

According to new findings, AF may or may not be associated with systemic symptoms including laboratory abnormalities, fever and polyarthritis [5].

Epidemiology

It is a rare disease with less than 200 documented cases in the literature [5]. Over the last decade, its incidence has been decreasing, probably because of early diagnosis and better therapeutic management [5]. AF typically affects Caucasian male teenagers aged 13–22 years, generally with a past 2-year history of acne preceding the onset of AF [6], although it has also less frequently been reported in East Asians and in females, usually with a milder course [5]. Other known risk factors include recent treatment with systemic isotretinoin at high starting doses or testosterone [5].

Pathogenesis

The sequence of events leading to AF is not established yet, although genetic factors, abnormal immunologic response, drugs intake, hormonal imbalance, and viral infections have been considered [5].

As regards genetic factors, several cases of AF in monozygotic twins [7, 8], and in siblings with identical Human Leucocyte Antigen (HLA) have been reported [9].

Some immunological findings supported the role of both innate and adaptive immune reactions, as well as autoinflammatory/inflammasone pathway alterations [5, 6]. In particular, it has been suggested that a genetically determined change in neutrophil activity causing a decrease of phagocytosis of *Cutibacterium* [*C.*] *acnes* (formerly *Propionibacterium acnes*) [10] may be responsible for the severe flare observed in

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some AF patients following treatment initiation with systemic isotretinoin [6]. A generalized hypersensitivity reaction (probably type III and/or IV) to *C. acnes* antigens has also been claimed, but no specific clues in qualitative or quantitative immunoglobulin assays have been found yet [5]. Although some findings, such as the rapid response to systemic steroids, the increase in γ-globulins and the decrease in C3 complement levels found in several AF patients point to a likely role of autoimmunity, this hypothesis has not been supported by the detection of specific circulating immune complexes in AF patients [5]. The assumption of an "exaggerated" autoimmune response is also suggested by the possible association, observed in a few cases, of AF with SAPHO syndrome, a complex disorder clinically characterized by any combination of synovitis, acne, pustulosis, and hyperostosis [11–13]. This occurrence supports the hypothesis that both diseases may share a common pathogenetic mechanism consisting in the release of cytokines, such as anti-tumour necrosis factor-α (TNF-α), triggered by *C. acnes* in genetically predisposed patients [11, 14]. The isolation of *C. acnes* in biopsy samples of sternal SAPHO osteitis [15] and the beneficial effects of anti-TNF-α agents on AF patients with SAPHO syndrome further support this supposition [6, 12]. Recently, some studies sustained the role of the nucleotide-binding oligomerization domain (NOD)-, leucine-rich repeat (LRR) domain- and pyrin domain-containing protein 3 (NLRP3) inflammasome activation (a multimeric protein complex located in the skin) in AF by a non-specific *C. acnes* phylotype [14] causing the release of pro-inflammatory interleukin-1β [5, 6, 16].

A possible triggering role of some drugs as systemic isotretinoin [17], and rarely doxycycline [18, 19], lymecycline [20], tetracycline [21], minocycline [22], or interferon-α-2a [23] has been observed. The reported inducing dose of isotretinoin is 1 mg/kg/day on average, with a lag time between treatment initiation and AF onset ranging from a few days to 4–8 weeks [17, 24]. It has been hypothesized that isotretinoin may act inducing an immunological reaction against *C. acnes* and its antigenic chemoattractans, released following the disruption of the pilosebaceous duct epithelium made fragile by the retinoid [6]. The chemotaxis of the neutrophils and an exacerbated immune response to their antigens could represent another possible triggering factor [25, 26].

Moreover, high doses of testosterone, either used during puberty for the management of genetic disorders characterized by tall stature or taken to increase muscle mass, may correlate with the higher incidence of AF in young patients with altered growth (Klinefeter, Marfan or Kallman syndrome) or in bodybuilders, respectively [27–31]. Their role in AF may consist in an increase of sebum level and *C. acnes* density that in turn may act as immune system triggers. Since androgen serum levels have been found to be within normal limits [32], an altered expression of androgen receptors on sebaceous glands and keratinocytes has been proposed [27]. Finally, based on the observation that AF related to androgen intake generally develops 3–18 months after initiating hormone therapy, it has been suggested that this lag time is probably necessary for *free* androgens to accumulate in the blood to a level able to trigger skin androgen receptors [27].

Viral infection by *Paramyxovirus morbillivirus* may also be a causative factor in selected cases, as suggested by the onset of AF after a measles infection that may be responsible of the release of inflammatory cytokines [33].

Associated Disorders

AF may occur as a single disease or may be associated with other inflammatory disorders, including erythema nodosum [21, 34–36], Crohn's disease [37], ulcerative colitis [38], or Wegener's granulomatosis [39]. The exact significance of these associations is still unclear [38].

AF can also occur in association with some genetic disorders, including Marfan syndrome [40] or late-onset congenital adrenal hyperplasia [40]. Association with SAPHO syndrome has also been reported (see pathogenesis section) [11–13, 41].

Classification

Traditionally, AF has been classified, on the basis of the presence of systemic involvement, in "acne fulminans" and in acne fulminans "sine fulminans", when no systemic involvement was present [42]. Recently, four clinical variants have been proposed: acne fulminans with systemic symptoms (AF-SS), acne fulminans without systemic symptoms (AF-WOSS), isotretinoin-induced acne fulminans with systemic symptoms (IIAF-SS), isotretinoin-induced acne fulminans without systemic symptoms (IIAF-WOSS) [5].

Clinical Presentation

Commonly, AF appears in male adolescents as a severe complication of a pre-existing mild or moderate acne [5]. The primary features of AF (Figs. 10.1a, b and 10.2a, b) include sudden onset of severe painful ulcerative nodules with haemorrhagic crusts, distributed mainly on the face, upper chest, back and shoulders [6]. These clinical manifestations may or may not be associated with systemic signs and symptoms that include: asthenia, fever, weight loss and polyarthritis [5]. Pain occurs mainly in large joints such as iliac, iliosacral, knees. Less frequently, patients with AF develop hepatosplenomegaly, myalgias, as well as aseptic osteolytic bone lesions (mostly localized in the clavicle, sternum and long bones of the extremities).

AF generally tends to persist for several months, with a quite slow healing and leaving extensive scarring [5, 6].

Histology

Early skin lesions show an intense dermal abscess, composed of granulocytes and occasional histiocytic cells, with destruction of the follicular wall and sebaceous glands. In a more advanced stage, haemorrhagic epidermal necrosis, dense mixed cellular infiltrate in the dermis, and hyalinization of the thrombotic vessels may be observed [43, 44].

Bone biopsies, performed in selected cases, show inflammatory changes, such as an infiltrate of neutrophils and mononuclear cells with granulation tissue that may mimic an osteomyelitis.

Laboratory Findings

No specific laboratory abnormalities characterize AF. However, frequently reported findings include leucocytosis, sometimes with leukemic-type reaction (up to 30,000/mm^2), normochromic and normocytic anaemia, increased percentage of polymorphonuclear leukocytes, elevated erythrocyte sedimentation rate (ESR), and high levels of C-reactive protein (CRP) and of liver enzymes. Serum proteins are generally normal, but decreased albumin or increased α-globulin and γ-globulin may be detected. Microscopic haematuria, proteinuria and other urinary abnormalities are sometimes found. Circulating immune complexes have been found in patients with both AF and erythema nodosum. Bacterial cultures from blood, joint fluid and skin are usually sterile [5, 6].

Imaging

In early stages, skeletal x-rays show reactive changes, including irregular cortical erosions of the right humeral mild shaft with periosteal reaction and obliteration of the sacro-iliac joints in about 50% of cases [6, 45]. Technetium-99 bone scan (scintigraphy) may reveal multiple areas of increased uptake spots in 70% of cases located at the mid-shaft humerus, median half of the clavicle, acromion and mid-sternum [45]. Ligamentous ossification or erosions are generally not seen. Computed tomography (CT) shows several osteolytic lesions most prominent at the proximal humerus, which correspond to specific images after administration of gadolinium-based contrast on magnetic resonance (MR) [45]. Radiologic AF imaging should mainly be differentiated from SAPHO skeletal alterations in which osteitis and hyperostosis are striking features that can be observed in any involved skeletal segments with or without concurrent dermatologic manifestations [46].

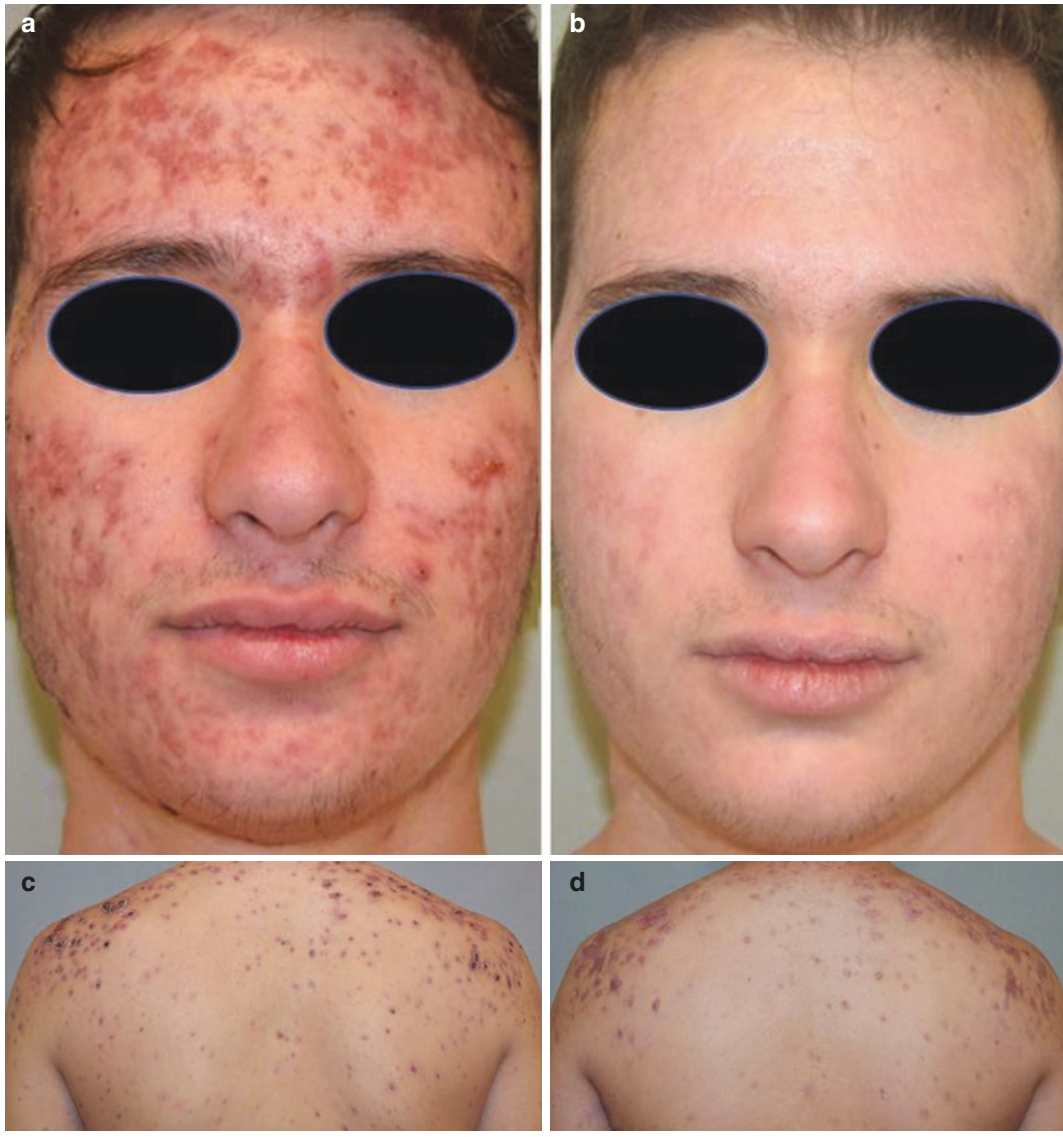

Fig. 10.1 (**a**, **b**) at baseline, patient under treatment with isotretinoin for moderate/severe acne since 1 month showing an abrupt onset of multiple, painful nodules on the face, chest and trunk. (**c**, **d**) same patient after 6 months of treatment with oral methylprednisolone (0.5 mg/kg/day for 2 months) and isotretinoin (0.5 mg/kg/day for 4 months progressively tapered within 12 months)

Differential Diagnosis

The diagnosis of AF is usually based on clinical history and physical examination. AF should mainly be differentiated from acne conglobate, rosacea fulminans and SAPHO syndrome.

Acne conglobate (AC) is a severe uncommon form of acne that may occur following the slow worsening of a pustular acne without systemic symptoms presenting with deep burrowing abscesses, painful nodules and multiple polyporous comedones [47].

Rosacea fulminans (RF) is a rare and severe variant of rosacea [48] that affects predominantly women aged 15–46 years. Although its aetiology remains unknown, hormonal, immunological and

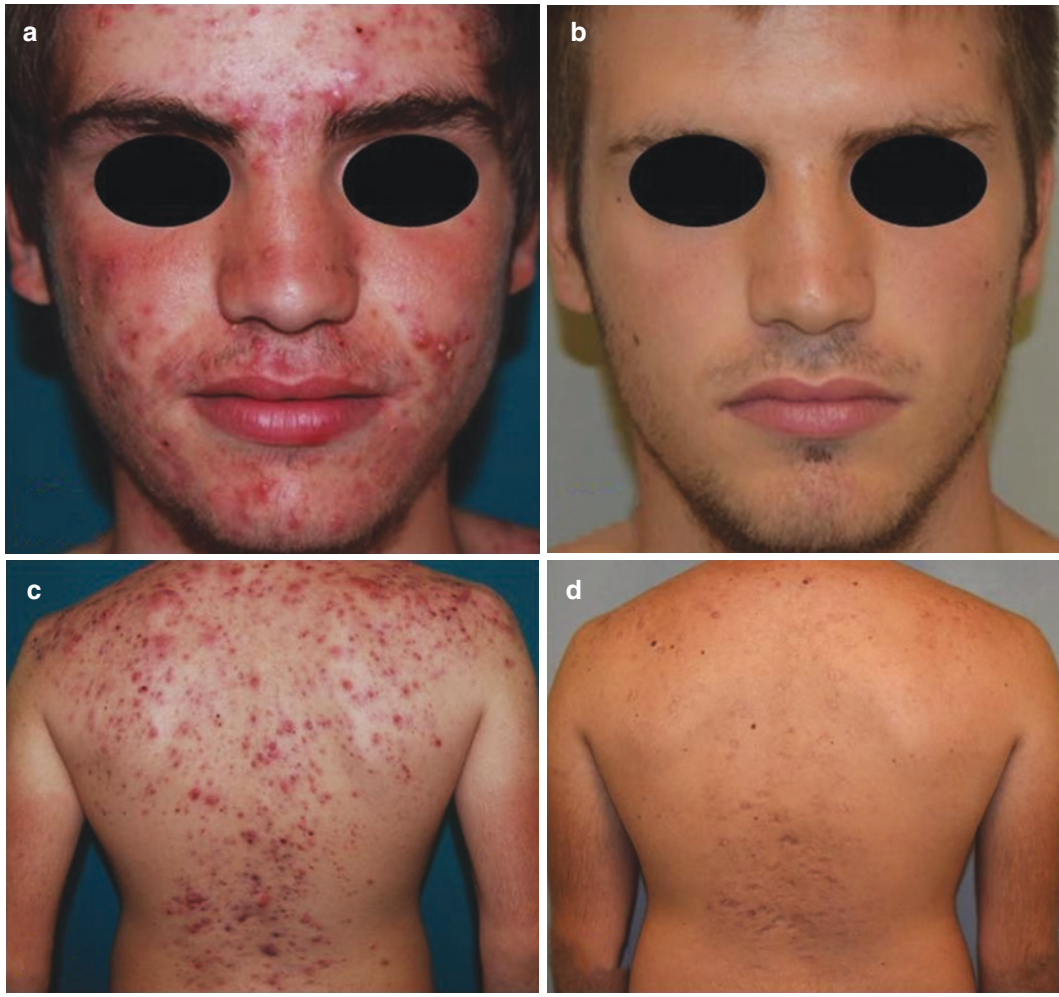

Fig. 10.2 (**a**, **b**) at baseline, patient with abrupt onset of ulcerative nodules with haemorrhagic crusts on the face, chest and trunk accompanied by systemic symptoms. (**c**, **d**) same patient after 6 months of treatment with oral prednisone (0.5 mg/kg/day for 8 months) and isotretinoin (0.5 mg/kg/day for 8 months)

vascular factors have been reported. The disease is characterized by sudden onset of inflammatory nodules, painful cysts, draining sinuses, abscess and/or oedema with red-cyanotic centrofacial erythema; extrafacial or systemic involvement are rare [49, 50].

SAPHO syndrome is clinically characterized by a combination of synovitis, severe acne, palmo-plantar pustulosis, hyperostosis and osteitis. Acne lesions in SAPHO syndrome may be initially mild but with time tend to become more severe, being generally classified as acne conglobate or confused with AF. SAPHO syndrome is primarily observed in young women [5, 41], and, similar to AF, may show systemic manifestations such as high fever and weight loss, although less frequently than AF [15]. Importantly, SAPHO syndrome shows different radiologic findings.

Treatment

The treatment of AF significantly differs from severe acne according to severity of clinical presentation and possible systemic involvement (Fig. 10.3). Currently, systemic corticosteroids

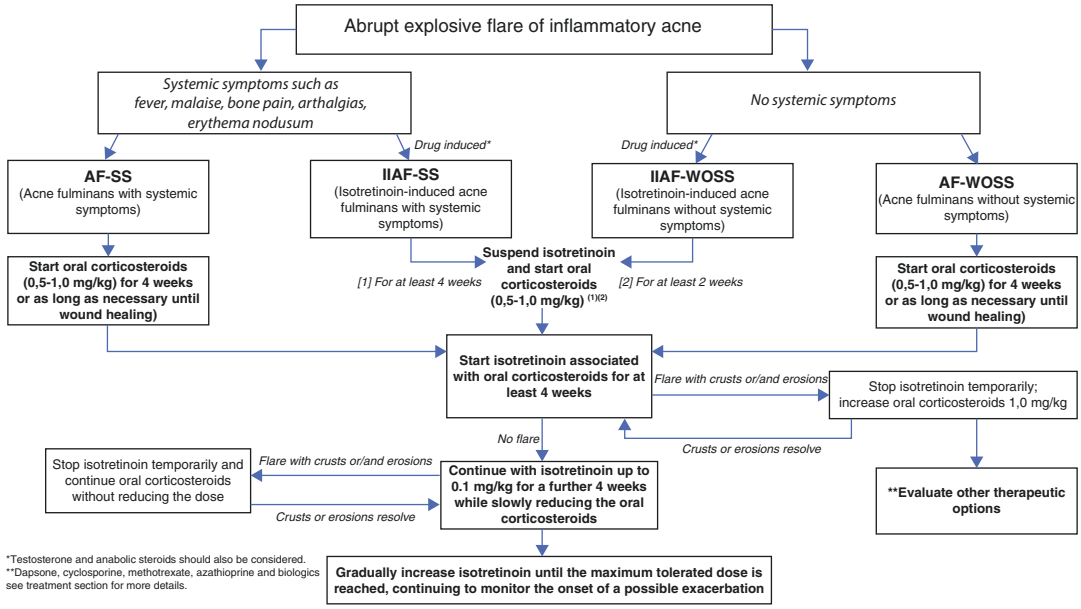

Fig. 10.3 Flowchart for the management of acne fulminans. (Modified from Greywal et al. [5], with permission)

(prednisolone) and retinoids (isotretinoin) represent the first choice of treatment (Figs. 10.1c, d and 10.2c, d). Sulfone (dapsone), immunosuppressive (cyclosporine A, methotrexate, azathioprine), immunomodulant (levamisole) and biological agents (anakinra, infliximab, adalimumab) may be considered as alternative systemic therapies in selected cases. Adjunctive therapies include topical and physical treatments.

Systemic Treatment

Systemic corticosteroids as monotherapy (prednisolone at a mean dose of 0.66 mg/kg/day; range: 0.25–1 mg/kg/day) [38] are indicated at the immediate onset of AF to quickly downsize systemic symptoms, including fever and/or musculoskeletal symptoms. Normally, treatment lasts longer than 4 weeks for AF-SS and 2 weeks for AF-WOSS [5]. Major contraindications for their use are active viral, fungal and tubercular skin infections, as well as peptic ulcer disease and hepatic dysfunction.

Systemic isotretinoin (13-*cis*-retinoic acid) is indicated in AF for its significant ability to reduce abnormal keratinization and sebaceous gland differentiation, although in some cases it paradoxically may precipitate AF with or without systemic symptoms (IIAF-SS, IIAF-WOSS) [51]. Risk factors for IIAF-SS or IIAF-WOSS are the presence of macrocomedones and higher initiating dose of isotretinoin [5, 52, 53]. In particular, large numbers of non-inflamed macrocomedones probably represent a "reservoir" of inflammatory mediators, transforming the macrocomedones into inflamed lesions [53]. Therefore, before the administration of isotretinoin, it would be appropriate to treat any macrocomedones with light cautery after applying a topical anaesthetic [52, 53].

To prevent IIAF-SS or IIAF-WOSS flares after the initial to 2–4 weeks of systemic corticosteroids in monotherapy, low dose of isotretinoin (0.1 mg/kg/day) should be added while continuing the corticosteroids. The dose of isotretinoin may be gradually increased not exceeding the cumulative dose of 120–150 mg/kg [5] with a slow corticosteroid taper. Treatment duration depends upon individual response and usually should not be less than 3–5 months. If acne flare (crusts and erosions) occurs during the course of isotretinoin therapy, its discontinuation is temporarily required and a prolonged use of systemic

steroids may be necessary [5]. Adverse effects from the use of isotretinoin are frequent and often dose-dependent. Drying of the mucosae of the mouth, nose, and eyes, cheilitis and skin desquamation are common. Disturbances in lipid metabolism, increase in creatinine phosphokinase, photosensitivity, as well as significant mood changes may also occur. Since isotretinoin is a well-known teratogen, in female patients the use of effective contraceptive measures is compulsory 1 month before starting therapy, during the entire period of treatment and 1 month after discontinuation.

Sulfones, especially diaminodiphenylsulfone (dapsone), for their antibacterial and anti-inflammatory properties may be used proficiently when isotretinoin is contraindicated or in case of AF in association with erythema nodosum [34] or ulcerative colitis [37]. Dapsone can be prescribed alone (usually 50–75 mg/day, rarely 100–200 mg/day) or in combination with prednisolone (20–30 mg/day) [54]. Adverse effects include severe haematological alterations such as methemoglobinemia, hemolysis and fatal agranulocytosis. A negative test for serum glucose-6-phosphate-dehydrogenase deficiency should be obtained before prescription.

Immunosuppressive agents, including cyclosporine A (CyA), methotrexate (MTX) and azathioprine (AZT), have been successfully used in selected cases in combination therapy with systemic prednisolone or isotretinoin. In particular, the effectiveness of CyA (5 mg/kg/day) plus prednisolone (10–40 mg/day) has been reported in AF presenting with severe pustules and pyoderma gangrenosum (PG)-like ulcerations [55]. It has also been used in combination with isotretinoin (30 mg/day) when systemic steroids were either ineffective or contraindicated [56]. The concomitant use of MTX (15 mg/weekly plus folate supplementation) with isotretinoin (0.25/mg/kg/day) [57] or AZT (1–3 mg/day) with systemic steroids in case of AF with bilateral osteomyelitis or with circulating immune complexes and leukaemoid reaction, respectively [58], may be also considered.

When AF do not respond to conventional therapies, several off-label alternative approaches, including levamisole [59, 60] and biologic agents, may be used. Among the latter, some reports have shown that recombinant IL-1 receptor antagonist (anakinra) and TNF-α inhibitors (infliximab, adalimumab) represent promising treatments for AF with severe osteoarticular involvement [61], or with bilateral acute sacroileitis and hip synovitis [62], or for AF associated with SAPHO syndrome [12] that do not respond to conventional therapies [63].

Miscellaneous

Generally, the response to broad-spectrum systemic antibiotic treatment (tetracyclines) is poor, but may be considered in cases in which the patient is intolerant to isotretinoin or oral corticosteroids, or to treat secondary infection when this occurs [6]. If tetracyclines are considered, the maximum dosing should be used (doxycycline 100 mg twice daily, minocycline 100 mg twice daily, oxytetracycline 500 mg to 1 g twice daily) [5, 22]. Possible adverse effects following the concurrent use of tetracyclines and isotretinoin include pseudotumor cerebri syndrome (PTCS) characterized by postural headache, transient visual disturbance, and diplopia [5]. The musculoskeletal symptoms (acute myalgia and arthritis) generally respond well to systemic non-steroidal anti-inflammatory drugs (salicylates), as well to intra-articular corticosteroids [6].

Topical Treatment

Topical agents should never be recommended as the only therapeutic option for their limited and unpredictable effect. Topical high-potency corticosteroids, applied on ulcerative nodules twice daily for 7–10 days, may be effective in the active phase to reduce the intensity of inflammation. Other adjunctive topical treatments include cleansing with antibacterial agents [6].

Physical Treatment

Surgical debridement, accompanied by frequent warm compresses with 20–40% urea solutions, is suggested before applying any topical agents to prevent crusting. Among the physical approaches, pulsed-dye laser (585–595 nm) [64] and 5-aminolevulinic acid photodynamic therapy (ALA-PDT) (red light of 635 nm at 100 mw/cm^2 irradiance for 20 min after 3 h occlusion with 20% ALA on all involved areas; 5 week-treatment) with systemic isotretinoin (20 mg/daily for 3 months) [65] have been used successfully in selected cases in order to reduce granulation tissue and acne scarring or follicular obstruction and hyperkeratosis, respectively.

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Acne and Environmental Factors

11

Ziyu Wei and Qiang Ju

Introduction

The skin is the largest organ of the human body and one of its main functions is to protect the body from noxious substances, whether they are ultraviolet radiation, toxic chemicals, or prolonged/repeated exposure to water, which are related to contact dermatitis, chemical depigmentation, connective tissue diseases, skin cancer, and acne [1–5]. Clinically, the etiology of acne consists of both endogenous factors such as androgen and exogenous factors. Environmental exposures are important exogenous factors in etiologies of acne, which leads to a group of environmental factors-induced acne including dioxin-induced chloracne, coal tar acne, cigarette smoking, and ultraviolet (UV) radiation [6]. The clinical features and mechanisms of environmental factors-induced acne are different from the endogenous acne, which still has a lot of myths until now. Environmental factors-induced chloracne, smoker's acne, coal tar acne, and UV-induced acne are introduced.

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Chloracne

Chloracne is normally the first manifestation of dioxins intoxication, caused by environmental chemicals such as chlorinated phenols, PCBs, and chlorinated naphthalenes, which has long half-life in human body [7]. Most cases of chloracne resulted from occupational and non-occupational exposures, such as the Seveso accident in Italy [8], 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) intoxication such as the famous toxic accident of Yushchenko, a former president of Ukraine [9], and herbicide [10].

Compared to the acne vulgaris, chloracne is different in clinical features characterized mainly by non-inflammatory pseudo-comedones, nodules, and comedo-like cysts. Disseminated lesions mostly involve face, chest, and back, as well as the neck, trunk, extremities, genitals, axillary, and other skin areas [7, 11] (Fig. 11.1). In addition, acute facial erythema, decreased sebum secretion and skin xerosis, pigmentation, porphyrinopathy, hirsutism, skin thickening, palmoplantar hidrosis, and palmoplantar hyperkeratosis can also be seen. Histopathologically, chloracne is mainly characterized by hyperplasia of epidermis, diminution and absence of sebaceous glands, and is totally different from the acne vulgaris [11, 12].

Although the skin lesions are historically summarized under the term "chloracne," they rather represent a functional hamartomatous adaptive process to this poison exposure [13],

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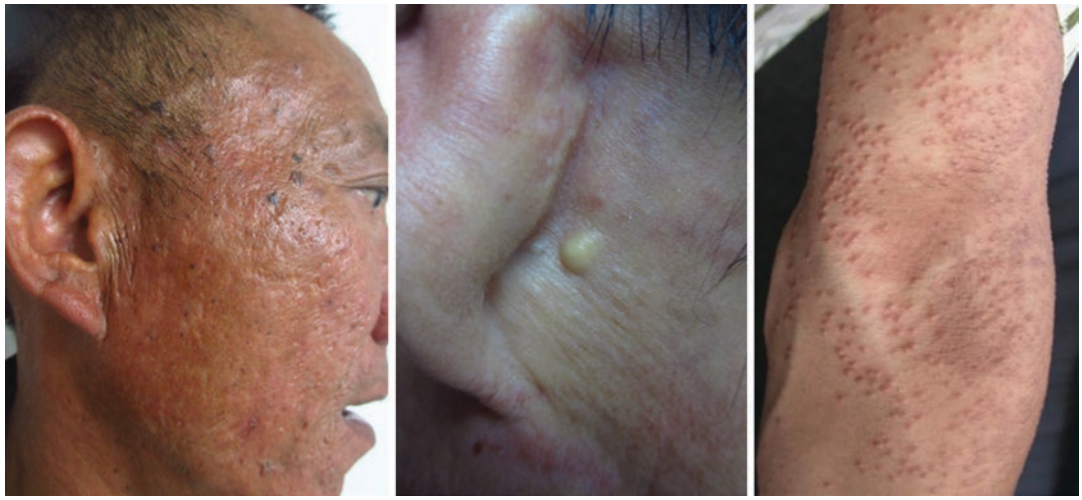

Fig. 11.1 The clinical manifestation of chloracne

which was named TCDD-induced skin lesions "metabolizing acquired dioxin-induced skin hamartomas" (MADISH) [14]. Actually, chloracne-like lesions have been found in other chemicals such as cigarette smoking [15] and medicines [12, 16], but if they belong to the same disease are still unclear, which needs more researches in the future.

The exact molecular mechanism of dioxins on human skin is still unclear. Chloracnegen-induced transformation of the pilosebaceous unit is driven by activation and accelerated exit of cells from the stem cell compartment coupled with a shift from a pilosebaceous differentiation pattern to an epidermal one, with a prominent epidermal/infundibular hyperplasia and hyperkeratinization, and diminution of sebaceous gland and hair follicle [17, 18]. The aryl hydrocarbon receptor(AhR) signaling pathway plays an important role in mediating the action of dioxins, especially the deregulation of pilosebaceous unit stem cell [19], including accelerating terminal differentiation of keratinocytes [20] and switching the differentiation of sebaceous gland cells into keratinocyte-like cells [21, 22] as well as reduced lipogenesis of sebaceous glands [23]. Downstream molecular targets of AhR are versatile, including influence of classical xenobiotic metabolizing enzymes (CYP), IL-1β, tumor growth factors, c-Myc, epidermal growth factor receptors, and B lymphocyte maturation protein 1 (Blimp1) et al. [21, 24].

Although some therapeutic agents have been used in the treatment of chloracne, it is quite resistant to conventional therapy. Inhibition of AHR-CYP1A1 signaling and activation of the NRF2-antioxidative axis were prospected [25]. Retinoids are commonly used in therapy of acneiform skin diseases; however, study in vitro suggests that retinoids not only were ineffective in treatment of TCDD-induced skin lesions in hairless mice, but also resulted in their exaggeration [26]. The only effective management is to remove the induced factors.

Cigarette Smoking and Acne

Several studies have been conducted to elucidate the relationship between smoking and acne, and the results are quite controversial. Some studies suggest no connection between tobacco consumption and acne [27–29]. A cross-sectional study indicate that an inverse correlation was seen between smoking and prevalence of acne; meanwhile, cigarette may exhibit anti-inflammatory property, resulting in the inhibition of papulopustular acne in girls [30, 31]. However, contrary observations that cigarette smoking may lead to the deterioration of acne are also reported [6, 32].

It seems that post-pubertal acne in females who have the habit of smoking are more prone to be affected by noninflammatory acne, which is characterized by micro- and macrocomedones, with few inflammatory lesions [33, 34]. The histological evaluation revealed that open and closed comedones and normal sebaceous glands can be found in the skin biopsies of smokers with acne [34].

Cigarette smoke contains more than 4000 chemicals that can be divided into two phases, that is, a particulate phase including nicotine, tar, and benzopyrene and a gaseous phase which includes carbon monoxide, oxides of nitrogen, and hydrogen cyanide [35]. Nicotine induced cutaneous hyperkeratinization through the activation of nicotine acetylcholine receptors (nACh-R) in human keratinocytes in vitro [36]. Meanwhile, chronic nicotine exposure results in an increase in sebum or altered sebum composition, which is mediated by nACh-R in sebaceous glands of acne lesions [37]. Nicotine and other components in cigarette smoke induce microcirculation alterations with consequent vasoconstriction and hypoxyemia [38, 39] and exhibit an inhibitory effect on the chemotaxis of neutrophils and lymphocytes [40]. Nicotine also inhibited inflammation through its effects on the central and peripheral nervous systems [41]. Benzo(a) pyrene (BaP) is an environmental contaminant found in cigarette smoke and one of polycyclic aromatic hydrocarbons (PAHs) [42]. Recent research shows that BaP can activate AhR signaling pathway and exhibits pro-inflammatory effects and inhibitory effects on sebum production in human sebocytes [43], thereby endorsing the data in another paper that BaP exhibited inflammatory and oxidative effects through the AhR signaling pathway in human keratinocytes [44]. A recent report showed that cigarette smoke exposure is also related to localized chloracne-like comedones, whereas BaP in cigarettes might be involved [15]. Moreover, smoking may prompt acne by inducing interleukin-1α (IL-1α) and exacerbate comedogenesis as well as inflammatory changes in comedones, which results in oxidative stress and the subsequent accumulation of lipid peroxide [6, 31, 34, 45]. Cigarette smoke exposure induced a scavenger receptor class B member 1 (SRB1 protein) posttranslational modifications and subsequently SRB1 protein loss, which caused an alteration of the lipid content in human sebocytes [46]. A wide range of water-insoluble PAHs in cigarette smoke may produce oxygen species and trigger the AhR signaling pathway, thereby inducing MMP-1 and CYP1B1, which were abolished by either AhR knockdown or AhR inhibitors [47, 48].

Coal Tar Acne

Coal tar is among the by-products of the destructive distillation of coal, which is an oily, dark brown-colored liquid, with high levels of PAHs, such as BaP, benzo[a]anthracene, and dibenz[a,h] anthracene [49]. Coal tar has been used in the treatment of skin disease including psoriasis, eczema, and dermatitis for many years [50]. Recently, it has been reported that coal tar modulated the cutaneous bacterial composition and restored the disrupted epidermal barrier via antimicrobial peptides produced by keratinocyte through the activation of AhR, which have explored the possible underlying mechanisms that could explain the therapeutic effect of coal tar against atopic dermatitis [51]. The short-term side effects are folliculitis, irritation, and contact allergy [52]. Animal studies [53–55] and studies in occupational settings [53, 56–58] showed the risk of non-melanoma skin cancer after chronic exposure to coal tar increased. However, a large cohort study including 13,200 patients with psoriasis and eczema found that coal tar treatment is not associated with an increased risk of cancer, which provided the basis for clinical application of coal tar in dermatological practice [59].

Acne has been frequently observed in industry workers after prolonged exposure to certain organic molecules, such as coal tar or crude oil, which is characterized by mainly black comedones and seldom papules on the exposed area [50, 60–63] (Fig. 11.2). There was an international patient survey that showed that some occupational factors like coal tar exposure were significantly more frequently reported for the acne group than

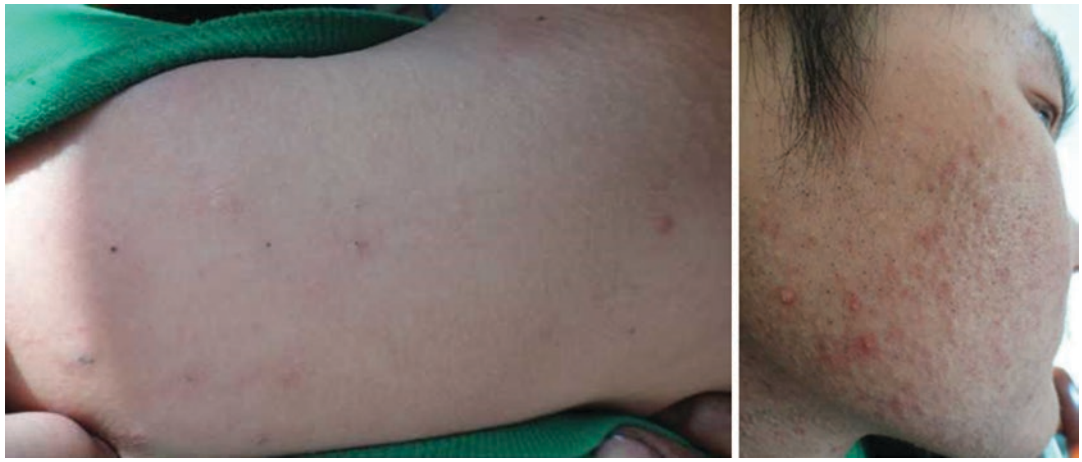

Fig. 11.2 The clinical manifestations of coal tar acne

the healthy control group [29]. Occupational exposure to PAHs is usually accompanied by very long duration at a low concentration level, whereas in dermatological practice exposure is high and short term. Also, the uptake route is quite different: with dermatological use, PAH uptake mainly occurs via the skin, while in occupational settings, the uptake route can also include the respiratory system. The variation in results found in studies on the risk of cancer after exposure to coal tar might be due to differences in PAH exposure levels and uptake routes [52].

There are few studies concerning the exact pathophysiology of coal tar-induced acne, and the PAHs in coal tar may mediate the pathogenesis of the disease through the activation of the AhR signaling pathway.

UV and Acne

Climatic conditions and seasonal variations often accompanied by a combination of heat, humidity, and intensive ultraviolet radiation (UVR) may trigger inflammatory acne flare-up, which is related to acne tropicana, acne majorca, or tropical acne [64–67]. A recent survey suggests that acne was significantly more frequent in hot and humid regions [29]. It is well established that UVR exposure has a great impact on our skin, such as UVR-induced skin cancer [68], epidermal barrier function [69], and skin aging [70]. There are some surveys observing the relationship between sun exposure and acne; nevertheless, the relationship between them remains controversial. A cross-sectional study on representative sample of 2516 schoolchildren in Serbia found that acne regression was more frequently perceived to be linked with sun exposure in girls [71]. However, another study included 110 patients above the age of 25 year diagnosed clinically as acne vulgaris indicated that 26.4% patients had exacerbations following sun exposure [72]. Similar results were recently reported by an international patient survey that acne was significantly more frequent in individuals with moderate or intensive sun exposure due to their work or daily activities [29].

A recent experiment has found that ultraviolet B (UVB) irradiation induced the sebum accumulation in the sebaceous glands of hamster skin [73]. Besides, heat induced by infrared (IR) radiation from sun exposure can stimulate sebum production and upregulate the expression of peroxisome proliferator-activated receptor (PPAR)γ and fatty acid synthase (FAS) in human sebocytes [74]. Squalene is an unsaturated fatty acid that represents ~10–15% of sebum produced by human sebaceous glands on the face and torso and is readily oxidized by ozone, long UV rays, and tobacco smoke [75]. High levels of squalene alter the redox balance

in the skin leading to an excessive generation of reactive oxygen species (ROS) and a state of oxidative stress. Oxidative stress and nitrosative stress play important role in acne [76] and may also be the trigger that sets off the acne cascade [77]. By-products produced from squalene peroxidation are known to be comedogenic and also exhibit proinflammatory properties [78, 79]. These oxidized sebum lipids cause keratinocyte hyperproliferation and inflammatory cytokine release, leading to the onset or worsening of acne [29]. In addition, UVB treatment in cultured sebocytes can directly induce the expression of inflammatory cytokines, especially IL-1β and IL-8 [80]. Besides, the relationship between UVR and skin microbiota was noted that the production of porphyrins by *Propionibacterium acnes* was decreased with increased doses of UVR, which indicate that facial bacteria are responsive to UVR [81].

Favre–Racouchot disease (FRD), also known as nodular cutaneous elastoidosis with cysts and comedones also named "solar comedone" (Fig. 11.3), is a disorder of cosmetic concern relatively common in middle-aged adults. Nearly 6% of adults aged above 50 years are affected, with a higher prevalence in white men [82]. Major risk factors of FRD includes excessive chronic UV exposure, cigarette smoking, and radiation therapy. Clinically, it is characterized by the presence of multiple open and closed comedones in an actinically damaged skin, with preferential localization to the periorbital and temporal areas. The eruption is usually symmetrical and no inflammation is present, which is different from acne vulgaris. Histologically, FRD is characterized by significant actinic elastosis and epidermal atrophy surrounding cystic lesions. Comedones similar to those of acne vulgaris can also be seen [83]. Hedelund and Wulf [84] had performed a provocation test utilizing both UV-A1 and UV-B irradiation. The test was positive, as UV irradiation (both with UV-A1 and with UV-B) resulted in comedones, with a stronger association between disease severity and UV-B rather than UV-A1 exposure.

According to recent findings, vitamin D and magnesium ascorbyl phosphate (MAP) inhibit the inflammation effects after *P. acnes* treatment and UVB irradiation in cultured sebocytes. Thus, they should be considered a complementary therapy for the regulation of inflammatory acne induced by UVR [85, 86]. Furthermore, sunlight exposure has been considered a quicker and safer alternative light source for photodynamic therapy(PDT). A clinical research suggests that DL-PDT seems to be an effective and tolerable therapy for the treatment of mild to-severe inflammatory acne [87]. In addition, the effectiveness of UVR, visible light, or infrared light

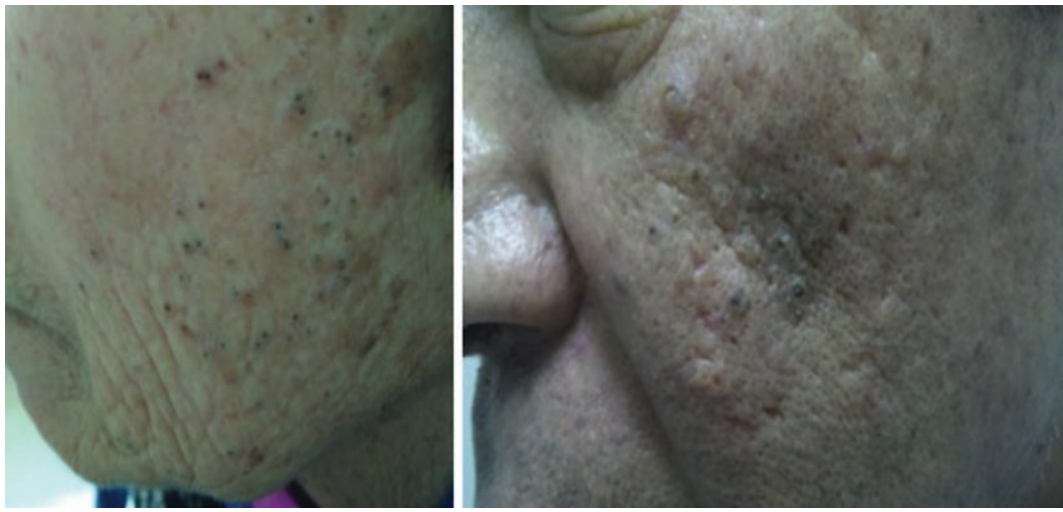

Fig. 11.3 The clinical manifestations of "solar comedones"

therapy for the treatment of acne has been proved, so that they can be used to target *P. acnes* for the treatment of acne, without an increase in the expression of inflammatory biomarkers and sebum production [88]. Conventional UV phototherapy may act beneficially in acne vulgaris by altering the skin microbiome and reducing *P. acnes* density [89].

Conclusions

Exogenous factors play important role in etiologies of acne, which leads to a group of environmental factors-induced acne including dioxin-induced chloracne, coal tar acne, cigarette smoking, and UV radiation. However, the pathophysiology of these physical and chemical factors on acne is still uncertain and controversial, which may have different mechanisms from endogenous factors-induced acne vulgaris. A better understanding of how these exogenous factors works and how they contribute to the physiological function of sebocytes, hyperkeratinization, modulation of skin microbiota, initiation of the innate immunity and inflammatory cascade, thus leading to the deterioration of acne will hopefully guide improvements in diagnosis and treatment of environmental factors-induced acne in the future.

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Acne on Pigmented Skin

12

Stefano Veraldi, Andrea Giuseppe Faraci, and Mauro Barbareschi

Sebaceous gland secretion was measured in 649 males and females, of whom 67 (10.3%) had pigmented skin. No significant differences in sebaceous gland activity were found between Caucasian and pigmented skin [1]. A study was carried out to compare lipid components of sebum in persons belonging to three different ethnicities: Caucasian, African American, and Asian. Healthy men and women in two age groups (18–25 years and 35–45 years, respectively) were enrolled. Two pairs of Sebutape™ applied on the forehead were used. African American women had more total lipid production than Asian and Caucasian women. Wax ester amount was higher in African American women, whereas the amount of free fatty acids and triglycerides was similar. Furthermore, six lipids were identified in the wax ester fractions that were significantly different in quantity between African Americans and Caucasians [2]. However, there is controversy about sebum synthesis and composition in different races [3].

Acne occurs in patients of all races and ethnicities. The incidence of acne in the black population would differ little from the incidence in the white population [1]. Acne is very common in patients with pigmented skin [4, 5]. In a group of 5.000 South African patients, eczemas were the commonest disease of the skin (29% of patients), followed by acne (11% of patients) [6]. Acne was the commonest skin disease observed in a private dermatology practice composed of predominantly black patients (27.7% of patients) [7, 8]. In 461 black patients (187 children and 274 adults) attending a dermatology clinic in London in the period January–March 1996, acne was diagnosed in 40 out of 274 patients (13.7%) [9]. In 3.795 Afro-Caribbeans patients, the main diagnosis was acne (19.5%) [10]. According to the US national survey data, acne was in 2014 the leading dermatologic diagnosis in African Americans, Hispanics, and Asians [11].

In an American study, it was observed that mean age of acne onset was 20.3 years in blacks, 15.9 years in Hispanics, and 18.9 years in Asians [12].

As far as morphology of acne lesions is concerned, no significant differences exist between Caucasian and non-Caucasian skin. Also the anatomic distribution of the lesions is similar in all races [13]. In the previously cited American study, papular lesions were observed in 70.7% of blacks, in 74.5% of Hispanics, and in 78.9% of Asians and pustular lesions in 26.4% of blacks, in 43.6% of Hispanics, and in

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21.1% of Asians. Finally, comedonal lesions were observed in 46.9% of blacks, in 50.9% of Hispanics, and in 52.6% of Asians [12]. Nodular acne is likely to be less frequent in patients with pigmented skin [3, 13–15] (Figs. 12.1, 12.2, and 12.3). In white and black prisoners aged 15–21 years, nodular acne was present in 5% of 893 white inmates versus 0.5% of 753 blacks [13].

A distinctive clinical variety of acne is pomade acne. It was first described by Plewig et al. in 1970. It is caused by the chronic use of oily products in order to smooth the hair. It is characterized by more or less numerous closed comedones, with rare papules and pustules, located mainly on the forehead and temples [16]. The existence of this entity has been subsequently confirmed by other authors [3, 8, 15, 17].

A very common and important complication of acne in patients with pigmented skin is postinflammatory hyperpigmentation (PIH) [3, 4, 11, 12, 15, 17–29]. It is characterized clinically by more or less numerous brown to black macules, of different morphology and size, located mainly on the face. Involvement of the neck, shoulders, chest, and back is less frequent. These macules are usually asymptomatic (Fig. 12.4). In an American study, PIH occurred in 65.3% of blacks, in 52.7% of Hispanics, and in 47.4% of Asians [12]. PIH is the final clinical result of (a) previous, long-lasting inflammatory lesions of acne, (b) chronic irritant contact dermatitis caused by topical products and drugs, (c) chronic scratching [25], and (d) chronic exposure to ultraviolet rays. In a survey published in 2002, the authors observed that sunscreens were used only by 31.4% of blacks with acne, in comparison with 57.9% of Asians [12]. Photoprotection is therefore mandatory in order to prevent PIH [3, 5, 17, 19]. Good-quality cosmetic camouflage is also very important [3]. Additional complications of acne in patients with pigmented skin are scars and keloids [3, 4, 15, 17, 19, 23, 26, 27, 29]. Scars usually occur as ice pick, boxcar, and rolling scars on the face, in particular the cheeks, and as hypertrophic scars in shoulders, chest, and back. The typical patient with scars and/or keloids is a male who suffered from long-lasting inflammatory and nodular acne located in the previously cited areas. Finally, not rare complications are skin lesions on the face caused by bleaching creams that represent 6% of all skin diseases in South Africa [6].

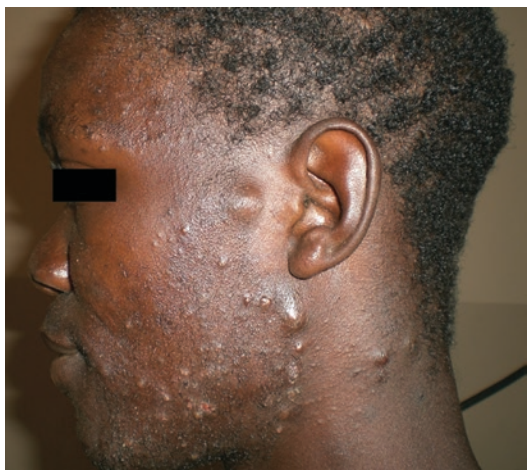

Fig. 12.1 Nodular acne in a patient with VI Fitzpatrick's phototype (Courtesy Dr. Federica Dassoni)

The treatment of acne is superimposable in all skin phototypes. In order to improve tolerability and compliance of topical anti-acne therapy in patients with pigmented skin, it is helpful (a) to begin the treatment with the lowest concentration of the drug, if it is possible; (b) to use a cream or an aqueous gel as vehicle; (c) to apply the drug every other day, with gradual increase to daily use; (d) to apply a moisturizer 2–3 times/day; and (e) to use a gentle cleanser [12, 19, 23]. A Web-based survey was administered to American females, aged 25–45 years, with acne of the face. Data collected included sociodemographics, self-reported clinical characteristics of their acne, treatment use, and treatment expectations and satisfaction. Three hundred twelve patients completed the survey, comprising blacks (30.8%), Hispanics (17.6%), Asians (17.3%), and Caucasians (34.3%). Treatment use was predominantly over-the-counter (OTC) (47.4%) versus prescription drugs (16.6%). OTC use was highest in white patients (blacks, 42.7%; Hispanic, 34.5%; Asians, 44.4%; Caucasians, 59.8%). The most frequently used OTC treat-

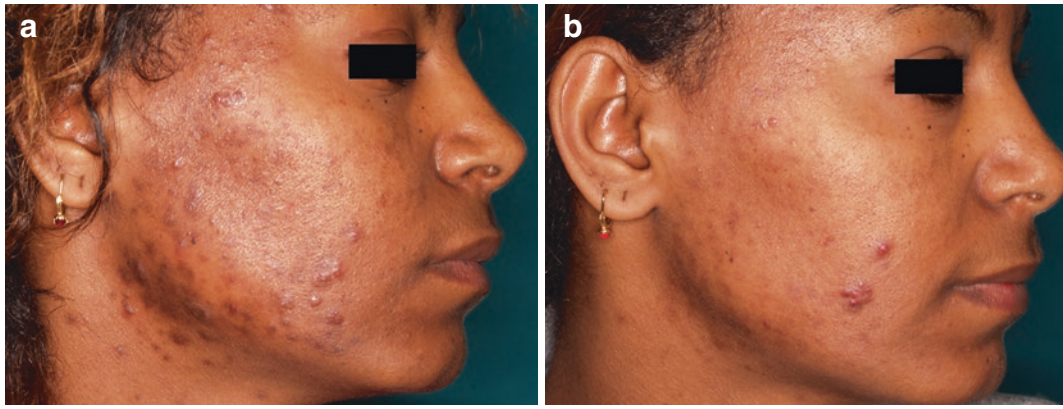

Fig. 12.2 (**a**, **b**) Severe acne before and after therapy with oral isotretinoin (right cheek)

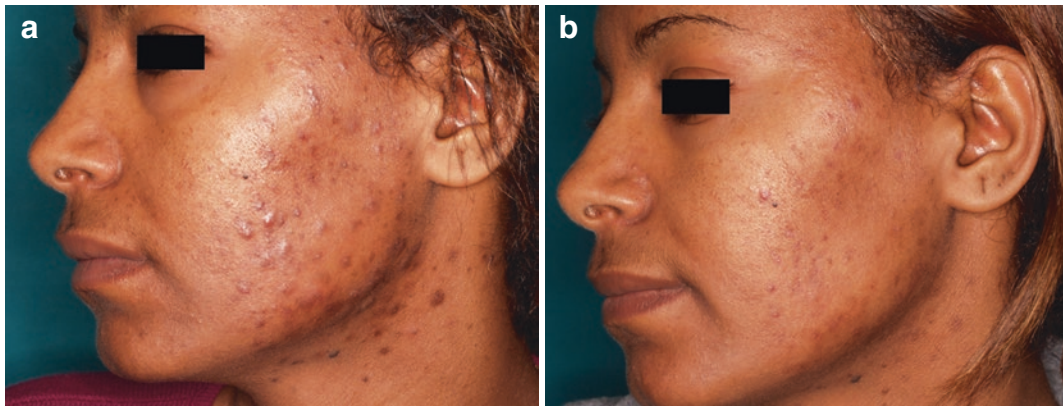

Fig. 12.3 (**a**, **b**) Severe acne before and after therapy with oral isotretinoin (left cheek)

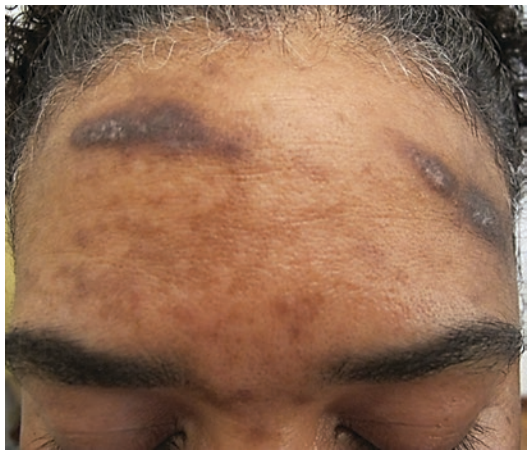

Fig. 12.4 Severe postinflammatory hyperpigmentation

ments in all racial/ethnic groups were salicylic acid (34.3%) and benzoyl peroxide (32.1%). Overall, compliance with acne therapy was highest in Caucasians versus blacks and Asians. Fewer than half of the patients were satisfied with OTC treatment (benzoyl peroxide, 47%; salicylic acid, 43%), often due to skin dryness (benzoyl peroxide, 26.3%; salicylic acid, 44.3%) [30]. The treatment of PIH should be started early [3]. Several topical products and drugs have been suggested for the treatment of PIH: retinoids [3, 19, 20, 23] (such as adapalene [3], tazarotene [3, 20], and tretinoin [3]), azelaic acid [3, 23], glycolic acid [23], kojic acid [3, 15, 23], salicylic acid [3], ascorbic acid [3], lactic acid

[15], arbutin [3], licorice root extracts [3], mequinol [3], N-acetyl glucosamine [3], nicotinamide [3], and soy [3]. Tazarotene 0.1% cream was studied by a double-blind, randomized, vehicle-controlled study in 74 patients with PIH. Once-daily application of the cream was effective, achieving significantly greater reductions compared with vehicle in the intensity and area of PIH within 18 weeks. Mean degrees of erythema, burning, and peeling were no more than trace in both groups, and mean levels of dryness were no more than mild in both groups [20]. In another study, two groups of subjects with PIH were treated with the combination 1% clindamycin/5% benzoyl peroxide gel versus this combination in addition to either a tretinoin microsphere gel at concentrations of either 0.04% or 0.1% or 0.1% adapalene gel. A better resolution of PIH was observed in subjects receiving the clindamycin-benzoyl peroxide in combination with 0.04% tretinoin microsphere [21]. The most effective topical treatment of PIH probably is hydroquinone [3, 15, 17–19, 23, 26]. It may be used at the concentration of 3–4% as cream, gel, or solution, also associated with 2–10% glycolic acid [17]. However, the most popular association is with 0.01% fluocinonide and tretinoin 0.05% cream, with hydroquinone at the concentration of 4–5% [24]. In our personal clinical experience, 15% azelaic acid as aqueous gel, applied twice/day for 4–6 months, is an effective and safe approach for PIH: only some cases of mild stinging and burning sensation are reported or observed. Chemical peelings include 30–50% glycolic acid solution or 70% gel or solution [29], 20–30% salicylic acid in ethanol [29], 10–35-50% trichloroacetic acid [29], and Jessner's solution [3, 15, 18, 23, 28, 29]. Twenty-five patients, 9 with acne and 5 with PIH, were pre-treated for 2 weeks with 4% hydroquinone prior to undergoing five 20–30% salicylic acid peels. These peels were performed at 2-week intervals. Moderate to significant improvement was observed in 88% of patients. Minimal to mild side effects (dryness, crusts, and transient hyper- and hypopigmentatiom) occurred in 16% of patients [18]. Other treatments of PIH include 20% aminolevulinic acid/blue light photodynamic therapy [3, 22], also associated with 4% hydroquinone [22], lasers [3, 30], microdermabrasion [15, 23], and microneedling [31].

The treatment of hypertrophic scars and keloids is based on the use of potent topical corticosteroids under occlusive dressing or intralesional corticosteroids [15]. CO2 laser was used in 30 patients with acne scars on the face. All patients were instructed to use 0.05% tretinoin cream, 5% hydroquinone, and 0.1% desonide cream nightly for 2–4 weeks before the laser treatment. The scars improved by 25–50% in all patients after one laser treatment. The most common side effect was erythema that resolved within 6 weeks. Hyperpigmentation occurred, but it was reduced by regular use of tretinoin, hydroquinone, and desonide cream, both pre- and postoperatively, along with use of broad-spectrum sunscreen [31]. Non-ablative fractional 1.550 nm and ablative fractional CO2 lasers were shown to be effective in treating acne scars in pigmented skin with good patient satisfaction rate and high safety profile [32]. Microneedling has also been used [33].

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13 Up-to-Date Therapeutic Approaches for Acne Scars in a Korean Dermatology Clinic

Hyuck Hoon Kwon

Introduction

As a dermatologist working in one of the largest dermatology clinics in Korea, treating patients with acne scars with satisfactory levels is one of the most important tasks. While the disease burden of acne scars from economic, social, and psychological perspectives is quite high even compared with other common dermatological conditions, treatment is still difficult [1–4]. Scars, ineffaceable reminders of acne, can compromise the self-esteem and psychological well-being of patients [1–3]. This dreaded outcome of acne has a wide variety of manifestations, from barely visible to severely disfiguring, and can be a consequence of even relatively mild acne; furthermore, it is currently impossible to predict which acne patient may scar and which may not [1, 5, 6].

Although acne scars create significant concerns for patients and clinicians alike, there are currently no standardized guidelines for the management of this condition [3, 7]. This is, in part, a result of the variable morphological character of acne scars. Acne scars are classified as atrophic, hypertrophic, or keloidal, with atrophic being the most common. Atrophic scars are further subdivided into ice pick, boxcar, and rolling scars [8–10]. In addition, these various types of scars can be erythematous, hyperpigmented, or hypopigmented. While management approaches have been rapidly developing with the aid of related biotechnology including resurfacing instruments, dermal fillers, and surgical methods, most single treatment modalities for acne scars have less than ideal results. Therefore, a customized treatment based on scar subtype and severity as well as the size of the involved area is needed for optimal treatment outcomes [7, 11, 12].

In Korea, aesthetic dermatology is flourishing, and patients' interests in acne scar treatments are also high. Furthermore, related industry has introduced novel therapeutic modalities to treat acne scars. Generally following a universal regimen [1, 13], we also apply cutting-edge techniques for scar improvement. In this chapter, we will briefly review each widely used treatment modality and then focus on practical perspectives for acne scar treatments.

Treatment Modalities

Overview of Fractional Laser Technology

Fractional lasers are currently the first-line therapy for almost all cases of acne scar [12, 14]. In contrast to traditional lasers, fractional lasers create numerous, discrete columns of thermal damage with intervening untreated areas. Treated areas, known as micro-ablative columns (MAC) in ablative fractional laser (AFL) treatment or micro thermal zones (MTZ)

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in non-ablative fractional laser (NAFL), span an area of 100–300 mm and penetrate deeply into the tissue, up to 1500 μm [15–17]. Through the creation of these MAC/MTZs, fractional lasers induce dermal remodeling and re-epithelialization. Healing is further augmented by migration of unaffected keratinocytes away from untreated areas [18, 19].

Non-ablative Fractional Laser (NAFL)

NAFL, such as fractional 1550 nm erbium-doped or 1540 nm erbium glass lasers, leave the epidermis intact, minimizing the incidence of post-procedure erythema, bleeding, and crusting compared with AFL [20]. While multiple treatment sessions are required to achieve a satisfactory level of clinical improvement, they are attractive since most patients' concern is posttreatment social downtime [20, 21]. It is known to be effective and safe in all skin types and can also be used for acne scar-associated erythema [17, 22]. As related mechanisms, the infrared wavelength of these lasers allows deep penetration into the dermis. It induces thermally coagulated microscopic columns in regularly spaced arrays over a fraction of the skin surface, leading to the upregulation of novel collagen production with no epidermal ablation. Leaving intact tissue bridges between minute cores of coagulation necrosis results in faster healing, and epithelialization from the unharmed surrounding tissue occurs within 1–2 days [23]. In my clinic, I usually use this laser as first-line therapy with other modalities in the treatment of acne scars, enlarged pores, and skin texture issues.

Ablative Fractional Laser (AFL)

Outcomes of ablative fractional CO_2 laser nearly rival those of traditional ablative lasers but with a more favorable safety profile. It is generally more effective than any other single modality with only 2–3 treatment sessions, while there is a higher incidence of adverse effects compared with NAFL [24, 25]. Fractional 10,600 CO_2 laser, 2940 nm Er:YAG laser, and 2790 YSGG laser are commonly used. Different wavelengths produce distinct degrees of absorbed thermal energy, and choosing which one to use depends on the balance between efficacy and adverse effects [26]. By vaporizing microdiameter columns of the epidermis and dermis and exerting a heat effect on the surrounding tissue, AFL has a stronger effect than NAFLs [27, 28]. Previous studies have shown consistent results that AFL has more robust effects than NAFL for both immediate skin tightness and shrinkage through dermal stimulation and gradual collagen production in the deeper target [29, 30]. I frequently use this laser in the treatment of moderate to severe acne scars for patients not seriously concerned with concomitant social downtime.

Picosecond Lasers with a Diffractive Optic Element (P-DOE)

Picosecond lasers represent a novel group of laser devices characterized by ultrashort, picosecond pulse duration [31]. An innovative incorporation of a diffractive optic element redistributes the beam into peaks of high fluence surrounded by a low fluence background to the treatment area [32, 33] and creates a grid of focused, high-intensity micro-injury zones present as upper dermal vacuoles through the process called laser-induced optical breakdown (LIOB) [34, 35]. LIOB is a nonlinear absorption process related to plasma generation, followed by mechanical expansion in the dermis, the physical principle of which is fundamentally different from selective photothermolysis [36]. With the initiation of wound repair processes and stimulation of dermal remodeling, these micro-injury zones have been shown to clinically improve skin texture, atrophic scars, and wrinkles [34, 35, 37, 38]. Histological analysis has revealed elongation and increased density of elastic and collagen fibers, without notable damage to the epidermis [32, 33, 39]. Our group first reported that picosecond lasers afforded better clinical outcomes and fewer side-effects in the treatment of acne scarring in Asian patients compared with NAFL [40]. Since this technology is relatively superior for pain and posttreatment complications such as hyperpigmentation compared with conventional fractional lasers, picosecond lasers may provide a novel paradigm as a promising alternative non-ablative device in the future scar treatment regimen [33, 41, 42].

Fractional Microneedling Radiofrequency (FMR)

Various radiofrequency (RF) devices have been used in acne scar treatment [43–45]. While lasers generate heat by delivering energy to chromophores through photothermolysis, the heat produced by RF device originates from electron movement and conductivity of the target tissue. In addition, as RF is originally not ablative, it rarely results in a transient interruption of epidermal integrity, which is usually seen with ablative lasers. Among the various RF methods, fractional microneedling radiofrequency (FMR) is widely used as the main component of acne scar treatment in Korea. FMR delivers bipolar RF directly to the dermis using an array of microneedles reaching multiple depths [46–49]. FMR has been recently reported to improve skin laxity, wrinkles, and acne scars [50]. Given its association with epidermal preservation and a rapid recovery time, it has become more popular. Microneedles have been reported to stimulate the migration and proliferation of keratinocytes and fibroblasts by inducing the release of several growth factors [50, 51]. FMR delivers high volumetric heating and deeper heat diffusion for profound neocollagenesis, consolidating the effects of dermal remodeling when combined with MAC/MTZs of fractional lasers. In fact, the combination of these two devices demonstrates synergistic efficacy with reasonable safety profiles [52–54], as confirmed for Asian patients in our study [50].

Chemical Peeling

While chemical peeling is less widely used for scar treatment after the advent of sophisticated devices, medium-depth chemical peels are still useful for correcting small depressed scars; this approach should not be used for ice pick scars or deep fibrotic scars. Repeated light peels with Jessner solution or 20–35% trichloroacetic acid (TCA), or glycolic acid peels, can improve mild scars [55, 56]. A technique called chemical reconstruction of skin scars (CROSS), which incorporates focal application of TCA using sharp stick for ice pick and deep boxcar scars, is widely used as a component of a multimodality approach [57]. The procedure is associated with good clinical response in the majority of patients, but it should be performed with caution in dark-skinned individuals because of the high risk of prolonged post-inflammatory hyperpigmentation.

Mini-surgical Techniques

There are three representative mini-surgical techniques for acne scars: subcision, punch elevation, and excision. In many cases, additional improvement may be achieved when surgical techniques are combined with resurfacing procedures.

Subcision, or subcutaneous incision, is commonly used for rolling scars [58, 59]. This technique releases fibrotic strands that tether the scar to the underlying tissue. A sharp needle is inserted under the skin with the blade parallel to the skin surface and then moved in a sweeping motion to cut the subcutaneous fibrotic strands [59]. Associated pooling of blood in the subcutaneous space probably reduces the likelihood of new tethers forming. Temporary bruising and swelling are expected, but severe complications are rare.

Punch elevation uses partial lateral round excision of the borders of the scar, leaving the deep part of the scar adherent to the fat layer. After the scar has been isolated from the surrounding skin, it is elevated enough to be slightly raised against the bordering tissue. During healing, the tissue retracts and a level surface is achieved. There is no risk of skin color or texture mismatch. Elevation should only be used on boxcar scars with sharp edges and normal-looking base [5].

Scattered individual ice pick scars may be removed by punch excision of each scar [5]. The scar is excised down to the layer of subcutaneous fat; the resulting hole in the skin is then repaired with sutures or with a small skin graft [5]. Punch excision may be used for ice pick and narrow, deep boxcar scars. The tool should be carefully sized to the inner diameter of the scar. This is a relatively easy technique that usually produces a good result, while in some cases, secondary widening of the scar occurs.

Transcutaneous Pneumatic Injection of Solutions

Pressure- and dose-controlled, needle-free transcutaneous pneumatic injection technology was recently reported to be safe and effective for treating various cutaneous scars and wrinkles [60–63]. Jet-infiltrated solutions including hyaluronic acid, or high concentration glucose solution, generated after a high-pressure pneumatic energy in the dermis, elicit immediate tissue shrinkage, mechanical stimulation, and later wound healing. It has a much lower risk of bleeding compared with traditional subcision. High-velocity solutions induce controlled trauma, acting as "nano-bullets" and initiating a wound-healing process throughout the mid to low dermis, with a relatively wide space, where fractional lasers do not fully cover. The triggered healing process stimulates growth factors and the formation of new collagen fibers. In addition, these solutions promote secondary collagen production in the long term, potentiating dermal remodeling with distinct mechanisms [64–66].

Fillers

In addition to the steady induction of dermal regeneration with various devices, atrophic acne scars can be directly filled with various artificial dermal fillers. Dermal hyaluronic acid-based fillers with varying degrees of cross-linking are effectively used for the treatment of various atrophic scar types [55]. Clinicians sometimes find that certain kinds of acne scars are resistant to the aforementioned "skin remodeling" modalities. In those cases, filler injection could produce immediate improvement, plumping up atrophic scars. These products have themselves been shown to stimulate endogenous collagen formation over time, which could contribute to sustained volumetric corrections [67–69]. It has variable duration of effect (6–12 months), depending on the agent chosen [70]. While filler injections must be repeated to maintain the effect, they are generally safe with a low risk of adverse effects. In addition, semipermanent (lasting up to 24 months: Poly-L-Lactic acid and calcium hydroxylapatite) and permanent (lasting many years if not lifelong; silicon, polyacrylamide, and polymethacrylate) may be used as dermal fillers for acne scar treatment [71]. Generally, fillers are used to fill certain types of superficial and deep soft scars, particularly those with gently sloping walls, but are not a preferred option for fibrotic scars.

Autologous Fibroblast Transplantation

While not clinically performed yet, autologous fibroblast transplantation has been tried for acne scar treatment [72]. It can be a fundamental method for correcting dermal defects, involving in vivo injection of autologous fibroblasts into contour defects. Autologous fibroblasts may have the ability to produce human collagen in vivo, which obviates the need for skin testing. While the exact mechanism has not been elucidated, previous data suggest that new collagen production and remodeling of pre-existing extracellular matrix in the scarred tissue may be associated with the clinically observed improvement [72, 73]. While further studies evaluating its efficacy and long-term safety are definitely needed for practical application, this cellular approach could provide a novel option in future acne scar treatment.

Biologic Materials

While not solely used as a scar-treatment method, an adjuvant application of biologic materials enhances tissue regeneration and increases the wound healing process after resurfacing treatments. Platelet-rich plasma (PRP), epidermal growth factor (EGF), and stem cell-conditioned medium (SCM) are representative components of a combination regimen. Platelets are known to contain diverse growth factors. Activated PRP contains high concentrations of various growth factors, and it is often used in the postoperative care of problematic wounds. The growth factors in PRP are assumed to increase the regenerative ability of controlled-damaged tissue formed after resurfacing treatments, increasing both efficacy

and safety [74–76]. EGF also has comparable effects, without the course of blood sampling [77, 78]. In addition, human mesenchymal stem cells, with paracrine effects, have been introduced as an alternative source of growth factors that promote wound regeneration [79]. SCM has emerged as a promising cell-free modality for therapeutic applications in scar treatment by containing functional exosomes [80–84]. Our group first confirmed that the combined use of adipose tissue stem cell-derived exosomes with resurfacing devices could provide synergistic effects on the efficacy and safety of atrophic acne scar treatments [85], possibly by promoting de novo synthesis of ceramides as key lipid molecules for skin wound healing [86]. These biologic materials are helpful for enhanced efficacy and fast wound recovery, but further refined technology needs to be developed.

Treatments for Hypertrophic Scars and Keloidal Acne Scars

While various modalities have been used for hypertrophic and keloidal acne scars, complete improvement does not seem feasible. For hypertrophic scars, surgical excision was used early on, but was associated with a high recurrence rate. Radiation therapy has also been used, alone and in combination with surgical excision [87, 88]. Optical treatments offer good potential, with pulse dye laser (PDL) emerging as a good option [89]. The 585- or 595-nm PDL has been used with good results to treat hypertrophic scars and keloids, reducing erythema, pliability, bulk, and dysesthesia with few side effects. Thick keloids may respond best to PDL plus intralesional corticosteroid or 5-fluorouracil injections [90, 91]. Cryotherapy has also been used, but may be undesirable in patients with sensitive skin because of the potential for hypopigmentation and postoperative pain. Pressure and occlusive dressings can be used alone or with surgical excision. To date, no optimal treatment has been identified, and investigation into pharmacologic agents and combination of various treatment modalities is encouraged [89].

Practical Perspectives for "Real-World" Treatments: Author's Opinion

Multimodal Approaches for Individual Atrophic Scar Subtypes

Since most single treatment modalities for acne scars yield less than ideal results, a customized treatment with various therapeutic modalities is needed for optimal outcomes. I believe that an individualized approach based on scar subtype is most practical and reliable. In addition, dermatologists should carefully consider the balance between efficacy and safety, since many techniques also have associated side effects such as hyperpigmentation, prolonged erythema, or poor healing. In this section, I will briefly introduce "real-world" combination protocols for acne scars based on scar subtype (Fig. 13.1).

Common Procedures

While there are variations in treatment regimen depending on many variables, I generally use about three to seven sessions of combination treatment with fractional lasers and FMR per month for almost all cases. I prefer NAFL for most cases, but I sometimes use AFL for severe scars. Picosecond lasers with a diffractive optic lens are also selected as the first choice, instead of NAFL. In this regimen, superficial layers are mainly covered by fractional/picosecond lasers and deep layers by FMR. These common steps provide therapeutic efficacy not only for scar lesions but also for concomitant improvement of wrinkles, sun damage, and enlarged pores [28, 52, 92]. Our group has reported synergistic efficacy of the combination of two modalities through a prospective, randomized split-face study, consistent with this practice [50]. After finishing this common step, I then routinely concentrate on treatment of individual scar subtypes as a step for all-in-one multiple strategies (Fig. 13.2).

Ice Pick Scars

Ice pick scars are deep narrow (<2 mm) cylindrical depressions that occur at the infundibulum. Because of the depth and shape of these

scars, they are often resistant to common device-based procedures, compared with other subtypes. In my practice, CROSS is the first step in this case with moderate efficacy. If results of CROSS are not satisfactory, I resort to punch excision and suture closure. In patients with multiple ice pick scars, focal AFL or erbium resurfacing is also recommended. They remove and blend the pitted scars.

Rolling Scars

Rolling scars are characterized as scar bands extending from the dermis to the subcutaneous tissue resulting in dimpling of the skin. Common

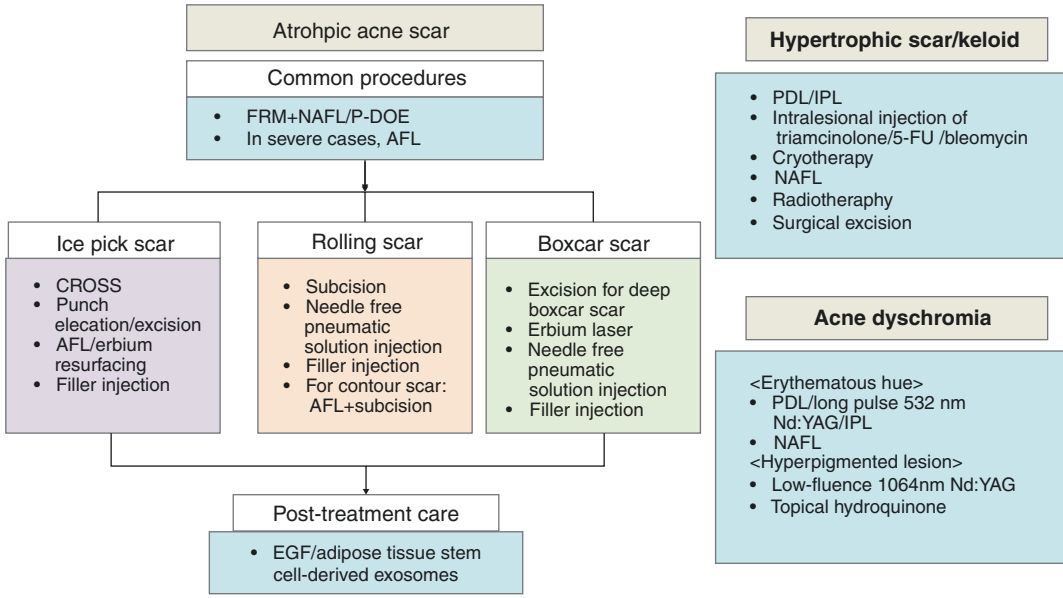

Fig. 13.1 Dr. Kwon's acne treatment regimen

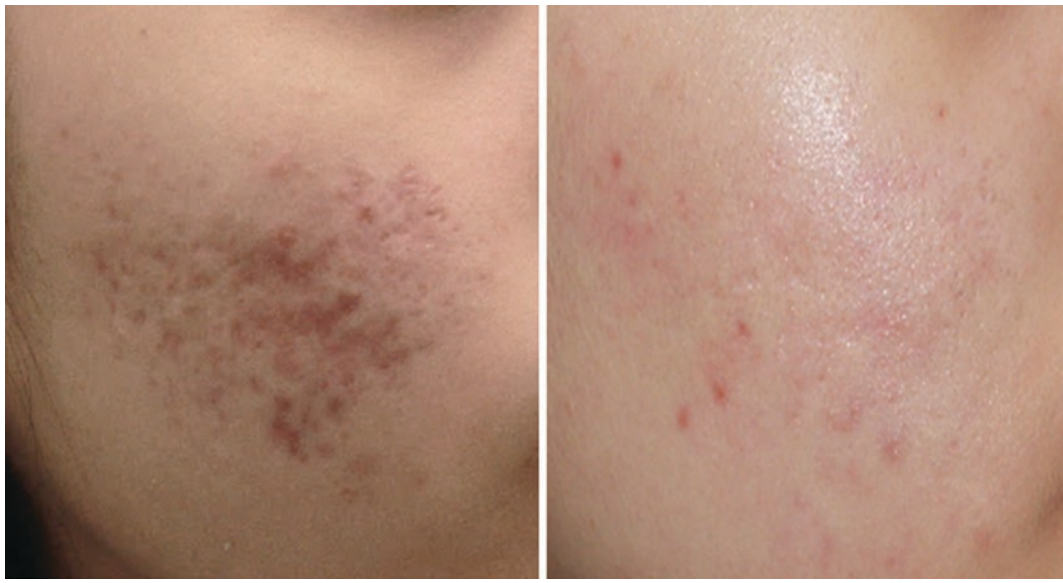

Fig. 13.2 A 27-year-old female patient visited our clinic for her atrophic acne scars around the cheeks. After receiving four sessions of FMR & NAFL followed by CROSS, subcision, filler injection, and needle-free pneumatic hyaluronic acid injection with a month interval, there was considerable improvement after 4 months

procedures are generally effective, and subcision is especially helpful for this subtype. It lifts the skin depression by the releasing action of the procedure, as well as from novel connective tissue that forms during the course of normal wound healing. To partly overcome the accompanying side effects of subcision such as pain and hematoma, pneumatic solution infusion is sometimes used with subcision-like effects. In severe or treatment-recalcitrant cases, hyaluronic acid filler injections are placed intradermally as small depots of about 0.1–0.3 mL under each residual rolling scar. Contoured scars improve significantly with both subcision and AFL with a synergistic effect seen when combined on the same day.

Boxcar Scars

Boxcar scars are round to rectangular depressions with a well-demarcated vertical edge and a 1.5- to 4-mm diameter. Deep boxcar scars may require a punch removal or excision if larger than 3 mm in diameter, whereas superficial boxcar scars may be treated using common procedures. Excision is the most dramatic and cost-effective treatment for deep boxcar scars. If a boxcar scar is not excisable or if there are a small number of scars, ablative laser resurfacing can be done with the erbium laser shot tangentially across the skin to vaporize and smooth raised areas of scars. On the basis of our recent experiences, pneumatic infusion or filler injection is also helpful to regenerate this subtype of scar, combined with skin remodeling devices.

Hypertrophic and Keloidal Scars

Hypertrophic scars have excessive collagen deposition and remain within the borders of the original injury. Keloidal scars are thick bundles of hyalinized acellular collagen and proliferate beyond the borders of the original injury. Usually, I treat hypertrophic scars first with PDL for erythematous lesions followed by intralesional injection of triamcinolone. Sometimes, the addition of 5-fluorouracil or bleomycin in the injection mixture is helpful. The injection technique includes firm pressure applied to the scar after insertion of a 30-gauge needle to prevent lateral spread and atrophy with a retrograde injection. Cryotherapy or NAFL treatment is sometimes helpful to improve the texture of treatment-refractory lesions. The use of a silicone sheet after intralesional steroids is also helpful. Radiotherapy is sometimes applied for recalcitrant ones.

Acne Scar Related to Dyschromia

For many acne patients, erythematous hues are often left. They are generally improved with light-based treatments including PDL, long pulse 532-nm neodymium-doped yttrium aluminum garnet laser (Nd:YAG), or intense pulse light. Combination treatments with NAFL, FMR, and PDL often demonstrate synergistic effects. For hyperpigmented lesions, caused by either acne inflammation or posttreatment induced hyperpigmentation, repeated applications of a low-fluence 1064-nm Q-switched Nd:YAG, which is commonly used for the treatment of melasma in the Asian population [93–95], yield promising results. Topical hydroquinone is also helpful in this case.

Concurrent Treatments with Active Acne

In many cases, patients receiving acne scar treatments still have active acne [96, 97]. About 90% of acne patients are known to have at least “mini” scars (<2 mm in diameter) [98, 99]. While there is some debate, I personally believe that concurrent treatments for moderate to severe degrees of acne and acne scar could have many advantages (Fig. 13.3). First of all, major treatments targeting acne scars, enhancing dermal remodeling by conveying energy through TGF-β-dominant pathways, also seem to improve acne inflammation. With relatively shorter downtime compared with traditional AFL, NAFL alone is even used for active acne treatments only [100]. Our group also confirmed that FMR is effective for acne improvement [101]. An appropriately inserted needle around sebaceous glands could induce heat mainly around acne lesions since sebaceous lipids are electrically resistant to RF integrated circuits, leading to functional and structural damage. The microneedle itself also induces secretion of growth factors and migration of adjacent cells, which not only lead to extracellular matrix formation but also affect sebaceous glands. In fact, selective sebaceous gland electrothermolysis by micro-insulated needles with RF is currently used as a treatment for active acne [102, 103]. When patients severely

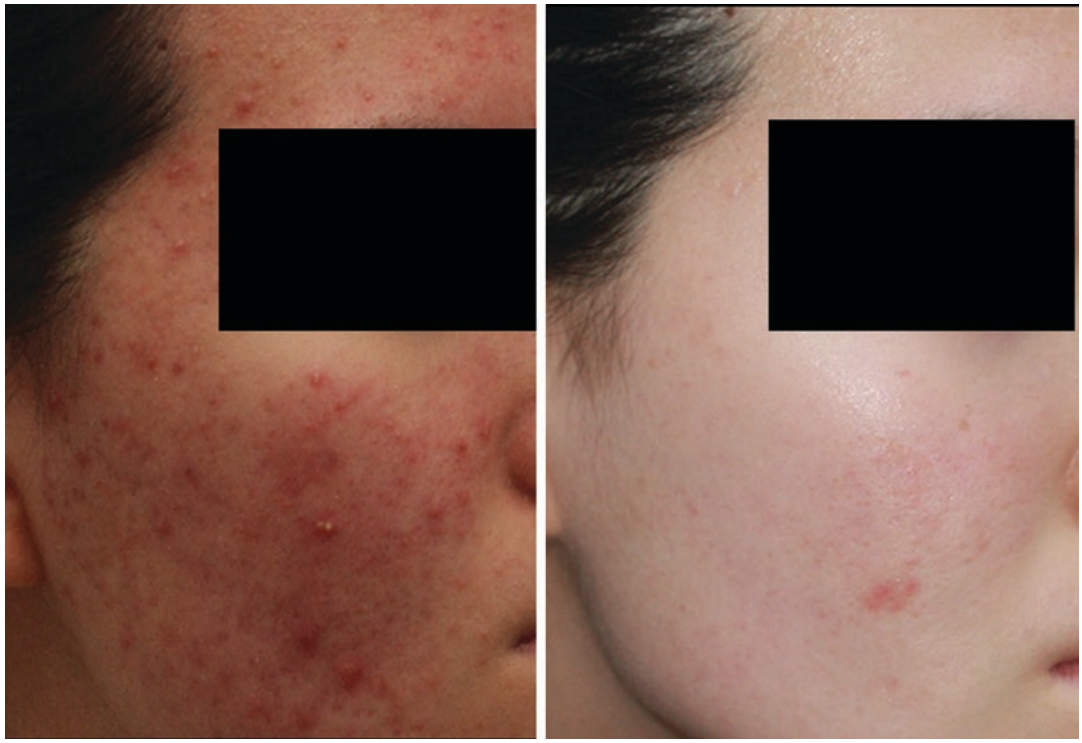

Fig. 13.3 A 21-year-old female patient visited our clinic for her acne, erythematous dyschromia, and atrophic scars. After taking 10 mg oral isotretinoin daily for 3 months, she received three sessions of FMR & NAFL followed by subcision, filler injection, and two sessions of PDL. All lesions showed considerable improvement after 3 months

concern with hyperseborrhea, incorporation of 1,450 diode lasers with scar treatment regimens can be also effective [104, 105].

In addition, oral isotretinoin within 6–12 months of cutaneous surgery, the most effective medication for moderate to severe acne, has been previously considered to contribute to abnormal scarring or delayed wound healing. However, recent studies demonstrated through systemic reviews or randomized controlled studies that there is insufficient evidence to support delaying superficial chemical peels, cutaneous surgery, and fractional laser procedures for patients simultaneously receiving isotretinoin [106–109]. While I usually prescribe low-dose isotretinoin (e.g., 10–20 mg/day) for acne patients receiving scar treatments concurrently, I have rarely experienced any need to delay treatment for scar improvement or related adverse effects, even compared with patients solely receiving scar treatments. In this way, patients usually experience rapid improvement of both acne and scars. Future studies may definitely reveal the synergistic relationship between acne and scar treatments.

Conclusion

While the development of acne scars is a frequent complication of acne vulgaris, predicting their occurrence is difficult. Therefore, the best method of managing acne scars is to prevent them by managing acne early enough. For the treatment of scars, several therapeutic options can be used to achieve significant cosmetic improvement, but it must be noted that none of the currently available single treatments achieve complete resolution. Customizing the treatment regimen depending on a patient's individual status may provide additional improvement compared with single method only.

A large variety of laser and RF modalities exist for treating acne scars. Ablative treatments, such as CO_2 and Er:YAG lasers, are most efficacious for atrophic scars; however, I definitely believe that safety profile, posttreatment downtime, age, individual skin status, timeframe, financial situation, and patient's subjective opinions are as important as efficacy itself in acne scar treatments. Therefore, combination treatments for acne scars are highly creative procedures considering many factors altogether.

Additional studies examining combinatorial acne scar treatments are warranted, and more academic and industry efforts are required to resolve this unmet medical need. Active application of cutting-edge treatment methods should be especially encouraged in this field. As a dermatologist engaged in various research and clinical practice focusing on acne and acne scars, I want to emphasize the following point again. Suitable training of dermatologists with regard to acne patients is critical in this field since treating acne is much easier than treating scars.

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Innate and Adaptive Immunity in Acne Vulgaris

14

Lajos Kemény and Kornélia Szabó

Abbreviations

AIM2	Absent in melanoma 2
AP-1	Activator protein 1
C. acnes	*Cutibacterium acnes*
C. albicans	*Candida albicans*
CAMP (LL37)	Cathelicidin antimicrobial peptide
CAMP factor	Christie-Atkins-Munch Peterson factor
CXCL8	C-X-C motif chemokine ligand 8
GM-CSF	Granulocyte-macrophage colony-stimulating factor
hBD2	Human beta-defensin 2
IFNγ	Interferon-gamma
IGF-1	Insulin-like growth factor 1
IL-1, 6, 10, 12	Interleukin-1,6, 10, 12
LPS	Lipopolysaccharide
LTA	Lipoteichoic acid
MAPK	Mitogen-activated protein kinase
MMP1, 3, 9	Matrix metalloproteinase-1, 3, 9
NF-κB	Nuclear factor kappa B
NLRP1, 3	NLR Family Pyrin Domain Containing 1, 3
P. acnes	*Propionibacterium acnes*
PAPA syndrome	Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome
PAR2	Proteinase-activated receptor 2
PRR	Pattern recognition receptor
PSU	Pilosebaceous unit
ROS	Reactive oxygen species
SAPHO syndrome	Synovitis, acne, pustulosis, hyperostosis, and osteitis
SCFA	Short-chain fatty acids
TLR2, 4	Toll-like receptor 2, 4
TNFα	Tumor necrosis factor-alpha
TNIP1	TNFAIP3-interacting protein 1
VCAM1	Vascular cell adhesion molecule 1

Introduction

Acne vulgaris is a prevalent and clinically well-characterized skin disease. In the last three decades, the rapid advancement of experimental dermatology significantly improved our view, but there are still open questions regarding its exact molecular pathogenesis. This chapter aims to

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highlight the role of the skin immune system in the pathogenesis of acne.

Immune Events Are Crucial in All Stages of Acne Pathogenesis

According to the classical view, the most important pathogenic factors in the development of this skin condition includes a hormonal trigger, follicular epidermal hyperproliferation of the ductal keratinocytes within the pilosebaceous unit (PSU), excess and altered sebum production, presence and activity of the skin commensal *Cutibacterium acnes* (*C. acnes*, formerly known as *Propionibacterium acnes*, *P. acnes*), and inflammation [1–3]. Although the exact sequence of events and the primary cause is still not known, initial steps of acne pathogenesis may include microcomedo formations. These are clinically not yet visible precursor lesions that later often develop into comedones (open or closed), papules, pustules, nodules, or cysts [1].

Earlier it was thought that androgen imbalance, follicular hyperkeratinization, and reduced desquamation lead to the formation of a keratin plug at the infundibulum part of the PSU [4]. Below the obstruction, increasingly anaerobic conditions favor the growth of *C. acnes*, resulting in enhanced immune activation and more pronounced inflammation and the formation of inflammatory acne lesions. The severity of inflammation is also enhanced by the frequent rupturing of the follicle wall, the leakage of bacterial antigens, cellular debris, and immunogenic sebum components into the surrounding tissues, where these greatly enhance inflammation [5].

Results, however, of detailed clinical investigations started to challenge this concept (reviewed by Kircik et al.,) [6]. It became accepted that hyperproliferation and increased retention of infundibular keratinocytes were among the main initiators of microcomedo formation [7], and interleukin (IL)-1 appeared as an important molecule inducing keratinocyte hypercornification [8, 9]. More than one study described signs of inflammation and immune activation, which preceded or occurred parallel with the keratinization process during microcomedo formation, and researchers identified leukocytes, mostly CD4+ T cells, polymorphonuclear cells, and CD68+ macrophages in the immune infiltrate around these early structures [5, 10]. Later studies also detected a higher number of CD3+ and CD4+ T cells already in the clinically uninvolved skin of acne patients, where the levels of different molecules related to inflammation (e.g., IL-1, E-selectin, vascular adhesion molecule 1 – VCAM1) were also elevated [9]. Early in lesion formation, CD1+ dendritic cells were also identified around the PSUs, while neutrophils only appeared in increasing numbers in the more advanced states, around the forming pustules. Finally, CD8+ cells have also been recognized in the early infiltrate around the affected follicles [5, 10]. These data strongly argue that inflammation, and parallel with that immune activation, is already present even before lesion formation and throughout all the subsequent steps during lesion development [11]. What are the initial driving forces, however, is still a question that remains uncertain. Altogether, these results strongly argue that acne is a prototypic chronic inflammatory, rather than a hyperproliferative disorder [6, 12], and the classical distinction of non-inflammatory (microcomedos, comedones) and inflammatory (papules, pustules, nodules, cysts) lesions theory needs to be revised.

Discovery of the Immune Properties of Keratinocytes

As opposed to vertebrates, where immune recognition is provided by the organized efforts of the two arms of their immune system, the innate and the acquired ones, in less evolved organisms, their protection relies only on the former type. Research efforts toward the end of the twentieth century led to the discovery of Toll, a protein in fruitfly (*Drosophila melanogaster*), which plays a role not only early in develop-

ment in a process called embryonic segmentation [13] but also in antifungal responses in adults [14]. Soon after that, members of this protein family were also discovered in humans (Toll-like receptors, TLRs), and their importance in vertebrate immune recognition was proposed [15].

During the 1980s, epidermal keratinocytes have been considered passive building blocks of the human skin, which serves as the very first line of defense and an essential delimiter between the outside world and our body. However, studies beginning in these years started to question this static view and suggested for the first time that our epithelial cells can actively identify sources of danger in the external environment and initiate active defense processes. The discovery that human keratinocytes not only recognize the presence of *Candida albicans* (*C. albicans*) in their culture but also actively kill this fungus opened a new path for subsequent research studies. These results suggested that keratinocytes, although does not belong to professional immune cells, still possess some functional properties allowing them to identify and respond to the presence of harmful foreign invaders [16–19].

Around the turning of the century, different research laboratories reported the presence of TLRs in epidermal keratinocytes, and it was also proved that these receptors are functional in this epithelial cell type. Challenge with microbial ligand resulted in the activation of the known, downstream signaling cascades in these cells, too, resulting in innate immune and inflammation activation due to the organized expression changes of pro-inflammatory cytokines, chemokines, antimicrobial peptides, and other factors [20–22]. It also became clear that not only pathogenic microbes but different members of the commensal microflora or their conserved structural molecules (e.g., *C. acnes*, *C. albicans*, lipopolysaccharide (LPS), lipoteichoic acid (LTA)) are recognized by these pattern recognition receptors (PRRs); thus it may contribute to the molecular pathogenesis of different chronic inflammatory diseases [22].

Innate Immune Events

The Role of Keratinocytes in Acne Pathogenesis

Immune activation and inflammation are central events in acne pathogenesis. Nevertheless, what are the exact driving forces of these reactions during the different phases in lesion development is still not clear. Etiopathogenic role of *C. acnes* in these processes was suggested for the first time more than 100 years ago, but since its first mention, a long-standing scientific debate formed about the exact role the bacterium plays in the disease [23, 24], reviewed by Dessinioti and Katsambas [25]. In the early 2000s, studies, investigating the keratinocyte – *C. acnes* interaction identified TLR2 as the major receptor playing indispensable roles in bacterial recognition. TLR4 has also been implicated in these processes [20–22], and the expression of both receptors was found to be increased in acne lesions [26]. Studies showed that receptor activation led to innate immune and inflammation activation, and the central mediator of these events was MAPK, NF-kB, and AP-1 transcription factor-dependent [21, 27]. As a result, coordinated expression changes of different pro-inflammatory mediators, among them cytokines (IL-1α, IL-6, IL-10, IL-12, GM-CSF, TNFα), chemokines (CXCL8), antimicrobial peptides (hBD2, CAMP(LL37)), matrix remodeling proteins (MMP-1, MMP-3, MMP-9), and other factors were detected [9, 20–22, 28–32]. Apart from these molecules, PRR activation also leads to the generation and elevated expression of factors (e.g., TNIP1) exhibiting negative regulatory effects on innate immune activation [33].

PRR activation is not restricted to keratinocytes, but monocytes and freshly isolated peripheral blood mononuclear cells from healthy controls and acne patients also reacted very similarly to the bacterium [20, 34–36].

The question that remains is how and exactly at which steps are these processes play a role in acne pathogenesis? The presence of IL-1α-like activity in the comedonal extracts [37], together

with the fact that the same cytokine may cause hyperkeratinization of infundibular keratinocytes, suggests that IL-1α may be one of the initiators or early factors in microcomedo formation [8, 38]. The source of the cytokine is not clear, but in vitro data suggests the role of keratinocytes, which are close to *C. acnes* in the still intact PSU [36, 39].

Parallel with TLR activation, another system capable of inflammation activation may also play a role in acne pathogenesis, the inflammasomes. Immunohistochemical studies around the turning of the century revealed the presence of lymphocytes and macrophages around the healthy-looking follicles of acne patients and in early acne lesions [9, 10]. Later, Qin and colleagues detected mature caspase-1 and NLRP3 molecules in the proteasome of macrophages. These data suggest a role of the NLRP3 inflammasome pathway and IL-1β in disease pathogenesis, particularly in shaping the innate receptors-induced immune and inflammatory reactions [35]. At this point, essential sources of secreted IL-1β are the monocytes, which may also play a role in the induction of neutrophilic inflammatory responses [36, 40]. Different inflammasomes (NLRP1, NLRP3, and AIM2) are also present in keratinocytes [41, 42], but whether and how they contribute to acne pathogenesis and if they react to the presence of *C. acnes* are not clear. It is a rather interesting fact that in various autoinflammatory diseases (e.g., PAPA, SAPHO syndrome), skin involvement often includes severe acne [42].

C. acnes also enhances the production of reactive oxygen species (ROS), in particular, superoxide anions ($O_2^{\cdot-}$) by keratinocytes, and these functions depend on the scavenger receptor, CD36. This pathway may also function as an important modulator of bacterially induced TLR signaling events in several different levels; among others, $O_2^{\cdot-}$ itself can induce inflammation, modulates the production of the CXCL8 chemokine, and directly inhibits *C. acnes* bacterial growth [30].

Bacterially secreted enzymes, including lipases, proteases, and hyaluronidases [32, 43–46], may also exert different biologic functions that contribute to acne inflammation and lesion development. *C. acnes*-produced proteases can generate tissue injury, by weakening and subsequently rupturing the follicular epithelium. However, the same enzymes may also be recognized by PAR-2 (protease-activated receptor-2), and these events can modulate the production of inflammatory mediators [32].

These results argue for the role of microbes, especially *C. acnes* itself and/or bacterially secreted metabolic products in innate immune and inflammation induction in acne vulgaris pathogenesis. Opposers question its role because this bacterium is one of the most prominent commensal microbes, especially in the sebum-rich skin regions. Thus it is rather difficult to consider the same microbe as a prototypic pathogen [47]. Ongoing research still aims to find a definite answer and explain a seemingly dual role this bacterium plays in skin physiology.

Sebocytes Are Active Players in Acne Immunity Too

The fact that acne mostly present in skin regions (face, shoulders, upper chest, and back), which are sebaceous gland rich [31], already suggests that besides keratinocytes, another cell type that may play a key role in disease pathogenesis is the sebocytes. Hyperseborrhea and altered sebum composition have long been considered as important factors in the pathophysiology of this disease. The cause of enhanced sebum secretion, however, may be complex; hormonal and genetic factors, together with dietary habits, may influence it [48].

Earlier, sebum was considered as a substance playing important roles in the moisturization of the skin surface. It is also an important food source for the *C. acnes* bacterium, which uses sebaceous triglycerides for its growth [49]. It is clear now that sebum composition and secretion rate rapidly change together with the changing environment, and specific lipids may exert antimicrobial and pro- or anti-inflammatory properties. Through their sebum production, sebocytes may also act as important modifiers of the inflammatory processes [48, 50, 51].

Nevertheless, sebocyte functions are not restricted to sebum production [52, 53]. These cells are also immunocompetent, actively respond to different external signals, and produce inflammatory cytokines and other mediators, similarly to keratinocytes [20, 54–56]. *C. acnes* recognition in sebocytes, similarly to keratinocytes, takes place through the activation of, among others, TLR2, CD14 and CD1, and inflammasomes. As a result, this cell type also plays an essential role in immune and inflammation activation in the PSU [54, 57–59]. On the other hand, through these signaling pathways, the bacterium also influences sebocyte viability and differentiation [54] and directly enhances lipogenesis, and sebum secretion rates tend to correlate with the severity of skin symptoms [60, 61].

These data suggest that this cell type may act as an important regulator of a complex equilibrium. By regulating the amount and composition of sebum, sebocytes may promote the growth and metabolism of the skin commensals. They, on the other hand, may also limit bacterial viability during bacterial dysbiosis and pathogenic events and enhance microbial clearance by contributing to innate immune and inflammation activation.

This cell type is regulated by many factors (reviewed by Makrantonaki et al., [48]), among them, sex hormones. Pubertal hormonal changes, especially local androgen synthesis, are markedly higher in acne patients, which results in increased sebocyte activity and hyperseborrhea [48, 62, 63]. Recently, another hormone has emerged with complex roles in acne, the insulin-like growth factor 1 (IGF-1). In sebocytes, it induces increased lipid synthesis, while in keratinocytes, it also acts as a mitogen [64, 65], and in in vivo studies, IGF-1 levels were elevated in acne patients [66, 67]. The levels of this hormone are also increased in individuals following a Westernized lifestyle and diet (decreased physical activity, consuming high glycemic index food and milk products), which would explain how diet and acne may be linked [68].

One crucial point that should be mentioned is that it is still not clear whether and how sebocyte-*C. acnes* interaction takes place in the skin. Sebaceous glands usually are free from bacteria [69], so direct interaction in intact PSU may not happen. It is possible, though, that bacterially derived structural proteins, enzymes, and other secreted molecules and metabolic products reach the sebaceous glands and the sebocytes in the distance. In this way, the bacterium may still exert a biologic function on these cells [70].

Adaptive Immune Regulation in Acne

Microscopic identification of different adaptive immune cells around the affected follicles suggested that this arm of our immune system is also involved in acne pathogenesis. The findings that higher number of CD3+ and CD4+ T cells are present in the uninvolved skin of acne patients supported this idea, but what is the main initiator of such T cell infiltration remains to be unknown [5, 9, 10].

Another line of evidence suggested that *C. acnes* exhibited a potent immunostimulatory activity and the induction of T helper 1 immune responses in animal models [71, 72]. Finally, these data led to the identification of a T cell subpopulation in early inflamed acne lesions that exhibited increased cell proliferation in response to *C. acnes* extract, possibly as a result of the recognition of bacterial antigens. These T cells also exhibited a characteristic Th1 cytokine pattern and expressed IFNγ in high whereas IL-4 in low quantities [73]. Further studies also identified essential roles for Th17 activation in acne pathogenesis, and IL-1β, IL-6, and TGF-β appeared as key activators of this arm of the adaptive immune responses, similar to other systems. As proof of this concept, IL-17 expressing lymphoid cells were found around inflamed follicles by immunohistochemical analysis [74, 75]. Finally, CD4+ T cells expressing IL-17 together with IFNγ were also identified, characteristic of mixed Th1/Th17 differentiation [40].

Based on these results, *C. acnes* appears as one factor playing important roles in the initiation of the above adaptive immune responses. Nevertheless, apart from the bacterium, sebocytes may also act as critical factors, as the super-

natant of these cells induces Th17 differentiation of naïve T cells. The resulting cell population is suggested to exhibit a dual function; it not only mediates host defense but can also actively participate in disease pathogenesis [56].

These data altogether clearly indicate that Th1, Th17, and mixed Th1/Th17-type adaptive immune responses play important roles in the cutaneous response to *C. acnes* and through that in acne pathogenesis [40, 73, 74]. However, there are still many open questions remains. Why acne vulgaris mostly affect the adolescent population? Why is it a self-limiting condition? What happens before, during, and after puberty? According to the current view, acne may be viewed as a transient arrest of homeostatic host-microbial dialogue between two phases of microbial tolerance [76]. This is a novel and intriguing concept, which suggests the crucial role of adaptive immune regulation in the maintenance of skin homeostasis in child- and adulthood and the lack or disturbance of these events as a critical pathogenic factor in puberty.

Not All *C. acnes* Strains Are Created to Be Equal?

Within the *C. acnes* species, different subtypes have long been identified, and currently, six major phylotypes are recognized: IA1, IA2, IB, IC, II, and III [77, 78]. A hot topic of the recent investigations is whether various *C. acnes* strains differ in their microbiological, metabolical, genetic, pathogenic, and other properties. The origin of these investigations comes from early findings, suggesting that various strains may differ in their innate immune induction properties in keratinocytes and sebocytes [22, 54], and differences in the internalization rates were also noted [79]. Selected strains might have different growth properties. They also exhibit variations in their metabolic traits, among them the production of short-chain fatty acids (SCFA), including acetic, propionic, and butyric acid, some of which exhibiting potent immunomodulatory properties [80–82].

According to the current knowledge, one of the most significant, differentially expressed molecules by the *C. acnes* strains are the CAMP (Christie-Atkins-Munch-Peterson) factors, cohemolytic enzymes involved in pore formation processes [83]. These are secretory virulence factors, and genomic analysis revealed five different genes belonging to this family in *C. acnes* [80]. Recent studies indicate that TLR2 may directly recognize CAMP-1 [84], which would suggest that strains producing more virulence factors also are more potent innate immune activators.

Recently, it was identified that selected strains (IA, IC), and within that specific ribotypes (IB-1, IB-2, IC-2, IC-3), were frequently associated with acne [77, 85, 86], and variations in the ability of selected strains to induce adaptive immune responses have been described [87].

Acne Has a Complex Pathogenesis

Inflammation is vital in all stages of acne pathogenesis, in which *C. acnes* plays essential roles. What is still not clear is the initiator, the first step that pushes the delicate balance between the bacterium and the cutaneous cells to microbial dysbiosis. Or in other words, why and how exactly an important member of the skin microbiota turns into a microbe exhibiting opportunistic pathogen features? One idea is that loss of microbial diversity plays essential roles. Whether this means the loss of various species that were part of the cutaneous microbiota during human evolution [33] or the loss of the diversity of various *C. acnes* phylotypes [88] requires further investigations. One thing is clear; acne is an intriguingly interesting and complex skin disease. By uncovering its exact pathogenesis, we will not only gain more in-depth knowledge on the pathogenesis of the most common prototypic inflammatory skin disease but may also have more excellent knowledge on how the human body and our microbes interact to generate a healthy ecosystem.

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15 Clinical Features and Differential Diagnosis of Acne Vulgaris

Nobukazu Hayashi

The Purpose of This Chapter

More than 85% of teenagers experience acne vulgaris [1], which also affects people in post adolescent age. The diagnosis of acne is generally easy, and many patients with acne self-diagnose before seeing a doctor. They visit not only dermatologists but also other doctors including general physicians, pediatricians, plastic surgeons, and gynecologists who are not familiar with other follicular or facial skin diseases. Care must be taken, especially in the nonresponsive cases for standard acne treatments. The purpose of this chapter is to highlight the need to recognize differential diagnosis.

Clinical Features of Acne Vulgaris

Acne eruptions are distributed on the face, chest, upper back, and shoulders where sebaceous grand follicles are located. The initial, primary lesion of acne is comedones, caused by an increase in sebum secretions and plugging of hair follicles with keratin. Clinically this condition looks like whitehead and blackhead, which are referred to as closed comedone and open comedone, respectively. These are noninflammatory lesions. Increasing *Cutibacterium acnes* in hair follicles and other factors cause inflammation, and comedones become inflammatory eruptions such as papules and pustules. At the younger age, the major eruptions are comedones located on the forehead and gradually expand to the lower parts of the face with inflammatory eruptions. If inflammation occurs at deeper places, cysts and nodules are induced. Some of these inflammatory eruptions cause post-inflammatory erythema and post-inflammatory hyperpigmentation. Superficial and deep inflammatory eruptions can be atrophic, hypertrophic, and keloidal scars. Acne patients may have atrophic and hypertrophic scars, even if they have mild acne [2].

Typical acne vulgaris have a polymorphous feature, which includes not only inflammatory eruptions but also noninflammatory comedones. Important points used to diagnose acne vulgaris are follicular distribution and the existence of comedones.

Special Forms of Acne

Neonatal Acne, Acne Neonatorum (Fig. 15.1)

Neonatal acne may be evident at birth or appear during the first 4 weeks of life. It is commonly seen in boys than in girls and mainly affects the forehead, nose, and cheeks [3]. It is usually closed comedones and papulopustular eruptions. In the

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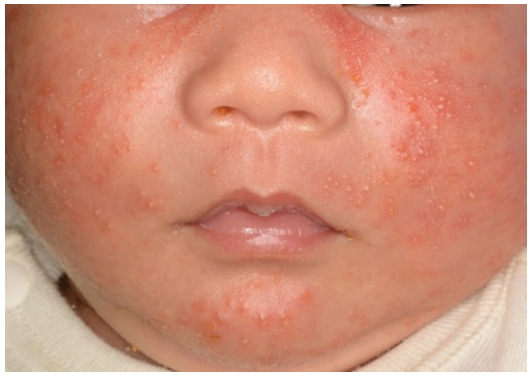

Fig. 15.1 Neonatal acne, acne neonatorum

etiology of neonatal acne, the main factor is thought to be increased sebum excretion caused by stimulation of the sebaceous glands by maternal or neonatal androgens. The differential diagnosis of neonatal acne is neonatal cephalic pustulosis, which may be caused by an inflammatory reaction to *Malassezia* species on the seborrheic neonatal skin.

After 6 months of age, the size of the sebaceous glands and the sebum excretion rate decrease [3]. In most of the acne neonatorum cases, the eruptions are generally mild and regress spontaneously within several months without any treatment.

Acne Conglobata

Acne conglobata is a severe form of acne that has nodules, cysts, abscesses, and sinuses with truncal involvement. Some of these eruptions result in hypertrophic and atrophic scars. It mainly occurs in males and may continue after adolescence. The most common treatment is isotretinoin and oral antibiotics in combination with topical retinoids. If they are not effective, prednisolone and dapsone may be used with informed consents of adverse effects. For inflammatory cysts, corticosteroids such as triamcinolone may be injected into the cysts.

Acne Fulminans

Acne fulminans presents as an abrupt onset with rapid development of ulcerative craters with hemorrhagic crusts that leads to severe scars on the upper chest and back, with variable involvement of the face. Cases with only skin symptoms are classified as acne fulminans without systemic symptoms. Acne fulminans with systemic symptoms may have one of the following symptoms: fever, malaise, bone pain, arthralgias, and leukocytosis. Isotretinoin therapy might trigger acne fulminans in patients with severe acne, particularly when high-dose treatment is initiated. Recently, cases of acne fulminans are classified into four categories, acne fulminans with systemic syndrome (AF-SS), acne fulminans without systemic syndrome (AF-WOSS), isotretinoin-induced acne fulminans with systemic syndrome (IIAF-SS), and isotretinoin-induced acne fulminans without systemic syndrome (IIAF-WOSS) [4]. SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis), PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne), PASH (pyoderma gangrenosum, acne, and suppurative hidradenitis), and PAPASH (pyogenic arthritis, pyoderma gangrenosum, acne, suppurative hidradenitis) syndromes are associated syndromes that have common manifestations of chronic inflammatory disease with severe acne. For the treatment of acne fulminans, systemic corticosteroids given immediately, at the onset of acne fulminans, followed by low dose of isotretinoin (0.1 mg/kg/day) are recommended. If flare persists, introducing dapsone, cyclosporine, and biologics is considered [4].

Cosmetic Acne Including Pomade Acne

In the 1970s, pomade acne [5] was reported as the appearance of acne along the hairline after the usage of hair pomade. Some cosmetics [6] were also recognized to induce similar acne eruptions, which are called cosmetic acne. Later, comedogenicity of cosmetics was identified using rabbit ears [7] and the back of humans [8]. Patients with acne should use non-comedogenic skin care materials including moisturizer, emollient, and sunscreen.

There are several studies which showed the merit of camouflage including foundation and cheek color, which improves quality of life of

patients with acne [9, 10]. Camouflage should not be prohibited for the social activities of patients with acne. The important points are to use non-comedogenic cosmetics and remove cosmetics perfectly and gently every day.

The clinical picture of cosmetic acne is almost indistinguishable from acne vulgaris. Comedones may be more conspicuous, especially on the neck where less numbers of sebaceous glands exist compared to other parts of the face. Papules and pustules may be present, but deeper lesions such as cysts or induration are rare. For the diagnosis of cosmetic acne, interview of patients about their skin care products is the most important.

Many acne patients in some Asian countries, including Japan, have recently believed the hypothesis that excessive dryness is one of the aggravating factors of acne, and they use moisturizing cosmetics to treat acne without consideration of comedogenesis. Although moisturizers are useful to prevent side effects of topical retinoids [11, 12], it should not be used with aim of expecting an improvement in acne, especially on the oily skin of teenagers.

Acne Excoriee (Fig. 15.2)

Some of the patients with acne squeeze or scratch comedones, pustules, and papules. But most of them can stop doing these actions because they know excoriation makes acne worse. Patients with acne excoriee excessively scratch and prick all their eruptions although their symptoms are mild. Consequently, they have no active acne lesion and complain of acne with only polymorphic excoriated ulcers, oozing excoriations, hemorrhagic crusts, hyperpigmented spots, and scars. Most of these patients are adult females and have associated psychiatric symptoms such as depression.

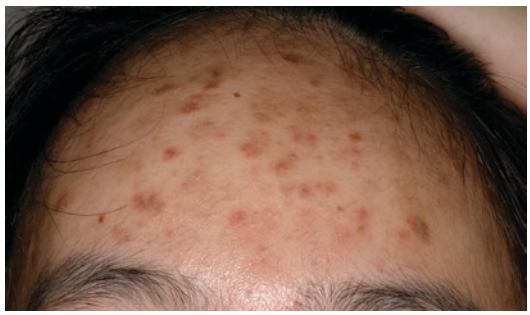

Fig. 15.2 Acne excoriee

In general, topical therapy is ineffective for these patients. The most important treatment is mental or psychological care. Early consultation by psychotherapists or psychiatrists to find out their stress, depression, or psychological disease is required. Some of them need psychological therapy and psychotropic drug treatments. Their skin manifestations will disappear by stopping excoriation.

Steroid Acne

Steroid acne is the most frequent form of drug-induced acne that appears as a side effect of short-term or long-term corticosteroid therapy. It may occur after aggressive use of systemic steroids, especially in the treatment of autoimmune diseases or after transplantation of organs like kidney or bone marrow. Topical potent steroid also causes steroid acne at the application site when it is used inadequately.

Steroid acne more often occurs in the younger generation, although elderly people may rarely experience it. High dose and long-term medium dose of systemic steroid mainly affects the face, chest, upper back, shoulders, and upper arms where sebaceous hair follicles are distributed. Clinically, each lesion is uniformly milia-sized, dull-red, smooth, dome-shaped papules. The exact pathogenesis of steroid acne is still uncertain [13].

Steroid acne spontaneously improves with the reduction or withdrawal of systemic and topical steroids. However, if treatment is required, topical use of benzoyl peroxide and retinoids including adapalene is recommended. If symptoms are severe, oral antibacterial agents such as doxycycline may be used. The clinical feature of steroid acne is similar with *Malassezia* folliculitis, which will disappear within 2 or 3 weeks with the use of antifungals treatments for *Malassezia*.

Chloracne Including Dioxin Acne

Chloracnes are induced by halogenated compounds such as iodide, bromide, chloronaphthalenes (CNs), polychlorinated biphenyls (PCBs), polychlorinated dibenzofurans (PCDFs), chlorobenzenes, and contaminants of chlorophenols including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), hexachlorodibenzo-p-dioxin, and tetrachlorodibenzofuran. Skin symptoms present as acne-like eruption of comedones, cysts, and pustules on cheeks, back of the ears, axilla, and groin region. The peculiar symptoms of this type of acne are comedo-like lesions and yellowish cysts on the face, which can spread to the trunk and other body parts [13].

The comedogenesis of chloracne is thought to be induced by cytochrome p450 1 A1, caused by activation of the aryl hydrocarbon receptor. These lesions are known as chloracne/metabolizing acquired dioxin-induced skin hamartomas (MADISH) [13].

Other Drug-Induced Acnes

Some drugs other than corticosteroids or halogens (e.g., iodide, bromide) induce acne-like eruptions. Representative medicines are isoniazid; vitamins B1, 6, and 12; cyclosporin; thiouracil; tetracyclines; antidepressants (e.g., lithium, amineptine); anticonvulsive; disulfiram; chinin; azathioprine; phenobarbiturate; phenytoin; anabolic steroids; dactinomycin; gold; phenytoin; and so on. To improve the acne-like eruptions, discontinuation or reduction of these medicines works. If the medicine is essential, standard acne treatments should be applied.

Hormonal Acne (Fig. 15.3)

Adult female patients who have persistent acne with no menstruation for more than 3 months may be suffering from polycystic ovary syndrome (PCOS). In patients with PCOS, hypersecretion of androgen from ovary causes irregularity or absence of menstruation. Its skin symptoms are acne and hypertrichosis. Serum elevated blood levels of androgens and/or the high ratio of luteinizing hormone to follicle-stimulating hormone (LH/FSH) in designated dates in the menstrual cycle is helpful for diagnosis, and gynecologic ultrasonography reveals appearance of "string of pearls." In cases of acne with PCOS, hormonal treatment should be given with regular acne treatments.

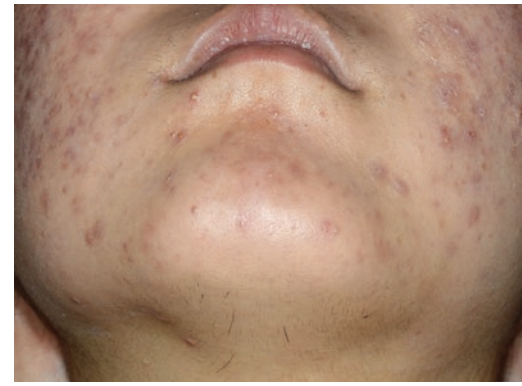

Fig. 15.3 Hormonal acne

SAPHO, PAPA, PASH, and PAPASH Syndromes

SAPHO syndrome is one of the inflammatory bone disorders that may be associated with skin changes. The name SAPHO is derived from the initials of synovitis, acne, pustulosis, hyperostosis, and osteomyelitis. Its skin symptoms include palmoplantar pustulosis, pustular psoriasis, and severe acne. Higher prevalence of HLA B27 [14, 15] has been reported in patients with SAPHO compared with the normal population, and genetic background might be involved.

PAPA syndrome is an acronym for pyogenic arthritis, pyoderma gangrenosum, and acne. It is inherited from an autosomal dominant pattern. PASH (pyoderma gangrenosum, acne, and suppurative hidradenitis) or PAPASH (pyogenic arthritis, acne, pyoderma gangrenosum, and suppurative hidradenitis) are also similar syndromes.

Currently, biologics including anti-TNF-alpha antibody and anti-IL-17 antibody are candidates of effective treatment for these syndromes.

Clinical Differential Diagnosis of Acne

Rosacea (Fig. 15.4)

The most important differential diagnosis of acne is the papulopustular type of rosacea, which usually occurs in older patients and presents as papules and pustules with facial erythema and/or telangiectasia without comedones, nodules, cysts, or scarring. Occasionally patients may have both rosacea and acne. The presence of facial flushing, which is induced by heat, alcohol, or spicy food, is a useful point toward a diagnosis of rosacea. On the other hand, patients with acne have comedones because the primary lesion of acne is comedones. Some of the treatments for rosacea, such as oral antibiotics and topical azelaic acids, are also used to treat acne. But there are many specific treatments for acne, such as topical retinoids and benzyl-peroxide. On the other hand, topical metronidazole and ivermectin are used for rosacea.

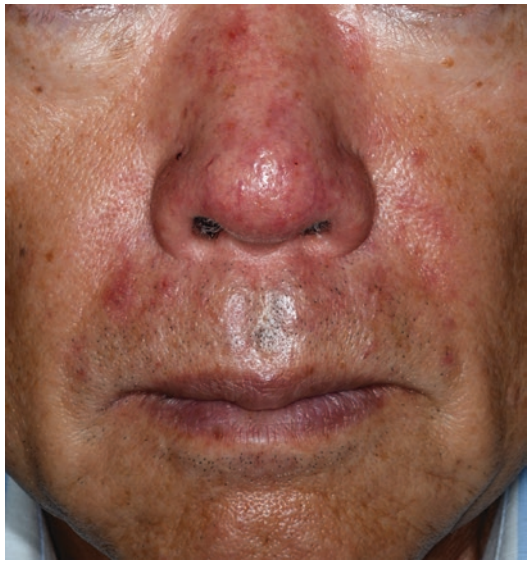

Fig. 15.4 Rosacea

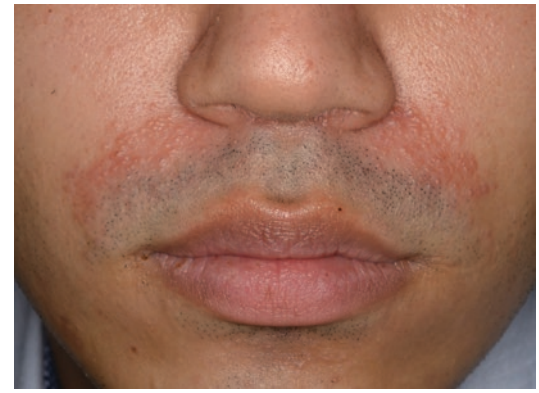

Fig. 15.5 Perioral dermatitis

Perioral Dermatitis (Fig. 15.5)

Perioral dermatitis is characterized by a facial eruption of milia-sized erythematous papules around a narrow zone of the perioral area and sparingly around the vermilion border of the lips. Erythematous papules and papulopustules may occur around the chin, perinasal, and perioral areas. The lesions are usually accompanied by a diffuse erythema and scaling. Patients may also complain of burning sensations and pruritus. Potent topical corticosteroid application to the facial skin may cause similar symptoms as perioral dermatitis. Some people classified these symptoms as rosacea-like dermatitis.

Folliculitis

Folliculitis is an infectious disease of the hair follicles caused by bacteria such as *Staphylococcus aureus*. Solitary or scattered multiple pustules without comedones are typical clinical feature. Folliculitis may appear on the face, trunk, and extremities except the palm and soles. Oral and/or topical antibiotics usually work very well.

***Malassezia* Folliculitis** (Fig. 15.6)

Malassezia folliculitis, also called pityrosporum folliculitis, is an inflammation in the hair follicles as a result of overgrowth of *Malassezia*,

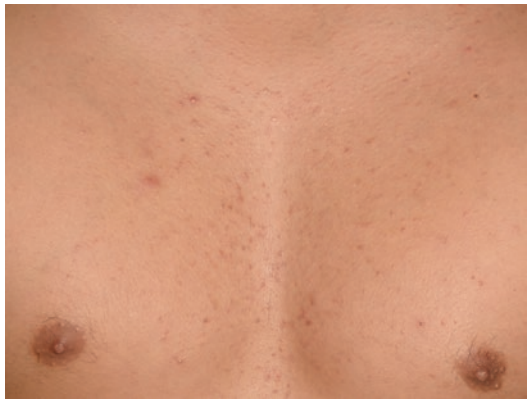

Fig. 15.6 *Malassezia* folliculitis

which is a lipophilic yeast and prefers seborrheic conditions. *Malassezia* folliculitis may occur in specific conditions, for example, on the back or chest of adolescent and young adult males in humid hot climates or in immunosuppressive patients who use oral and/or topical steroids.

Clinically, *Malassezia* folliculitis presents as small uniform itchy papules and pustules on the trunk and the extensors of the upper limbs. Detection of *Malassezia* has little implications, because it is part of the normal skin flora. It usually responds well to oral treatment with itraconazole or fluconazole.

Demodicosis (Fig. 15.7)

Demodex folliculorum and *Demodex brevis* are resident organisms in hair follicles of humans. Demodicosis is one of the facial diseases caused by overgrowth of demodex. The symptoms look like rosacea or rosacea-like dermatitis. Patients with demodicosis complain of follicular papules, pustules, scales, redness of cheeks, and itching. *Demodex* may be found in the pustule or scale of the lesion by microscopic examination. Demodicosis is diagnosed by the increased number of demodex. For its treatment, avoiding oil-based skin care is most important, and topical use of permethrin, sulfur, crotamiton, metronidazole, and ivermectin are recommended.

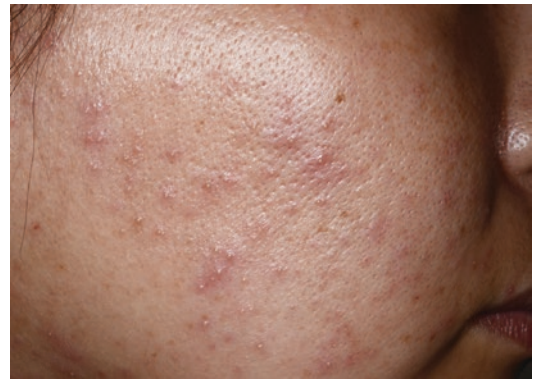

Fig. 15.7 Demodicosis

Folliculitis Barbae

Folliculitis barbae, also called sycosis barbae or sycosis vulgaris, are folliculitis of the area around the beard of males due to bacterial infection, mainly *Staphylococcus aureus*. Sycosis barbae has inflammation at deeper places of the hair follicles and may cause larger nodules and scars. Topical antibiotics for mild to moderate cases and oral antibiotics for more severe cases are usually effective.

Pseudofolliculitis Barbae

Pseudofolliculitis barbae is a foreign-body inflammatory reaction due to an ingrowth of hair occurring around the beard. Secondary infections may occur. Avoiding shaving and growing a beard is the most efficient preventive measure.

Eosinophilic Pustular Folliculitis (Ofuji Disease)

Eosinophilic pustular folliculitis (EPF) is a chronic pruritic dermatosis showing repeated pruritic follicular papules and sterile pustules arranged in arcuate plaques with central healing and peripheral spread with a histopathological finding of folliculotropic infiltration of eosinophils [16]. There are no comedones. The eruptions mostly appear on the face, scalp, neck, and

trunk and may persist for weeks or months. Palms and soles may rarely be involved, although there are no hair follicles in these areas. There are several types of eosinophilic pustular folliculitis: (1) classic type, which mostly occurs in Japan, (2) immunosuppression-associated eosinophilic folliculitis including human immunodeficiency virus infection-associated one, and (3) infantile eosinophilic pustular folliculitis.

The etiology of EPF is unknown. Indomethacin and its metabolites are generally effective against EPF, and cyclooxygenase metabolites are assumed to be involved in the pathomechanism of EPF [17].

Acneiform Eruption Due to Anti-EGFR Drugs or Other Anticancer Drugs (Figs. 15.8 and 15.9)

Epidermal growth factor receptor (EGFR) inhibitors and some other anticancer medications often cause adverse reactions on the skin, including acneiform eruptions. Sterile inflammatory follicular papules and pustules are seen predominantly on the seborrheic area of the face and can be more widely spread to the scalp, trunk, legs, and other parts of body. For treatment and sometimes prevention, oral tetracyclines including doxycycline or minocycline are prescribed. Topical steroids, retinoids, and antibiotics are also used. In severe cases, change or discontinuation of anticancer drug is required.

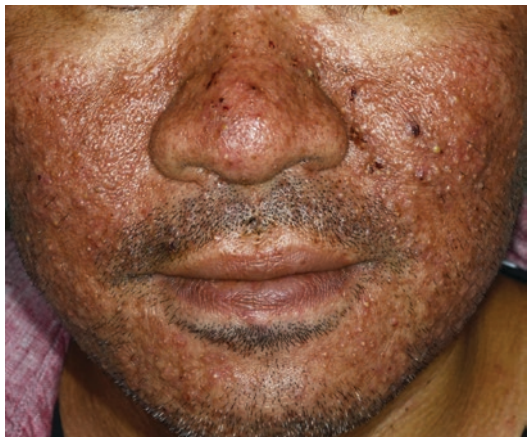

Fig. 15.8 Acneiform eruption due to EGFR inhibitors

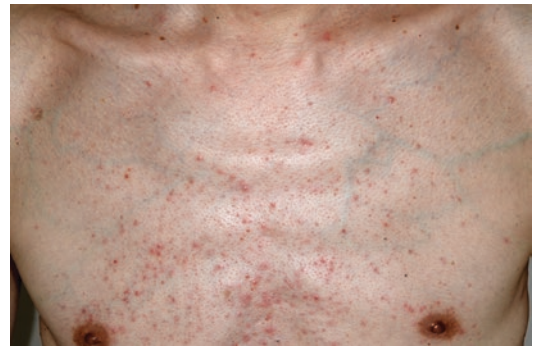

Fig. 15.9 Acneiform eruption due to EGFR inhibitors

Lupus Miliaris Disseminatus Faciei

The histology of lupus miliaris disseminatus faciei (LMDF) shows epithelioid granuloma with caseous necrosis. LMDF was once considered a tuberculoid, but now it is considered as a variant of granulomatous rosacea. The etiology of LMDF is still unclear.

Clinically it consists of faint reddish or yellowish papules on the cheeks, particularly on and around the eyelids. For treatment, oral tetracyclines, minocycline and doxycycline, or oral macrolides are usually used, and they work effectively.

Milium

Milium is a small keratin-filled cyst located at the superficial dermis. It is sometimes misdiagnosed as a closed comedone. Clinically, milium is often located around the eyes and nose of adult females. It usually does not cause inflammation.

Angiofibroma (Tuberous Sclerosis) (Fig. 15.10)

Angiofibroma is one of the symptoms of tuberous sclerosis which mainly develops around the nose and on the face of patients with tuberous sclerosis at puberty and is rarely misdiagnosed as acne. It is not located on the hair follicle and is usually a 2–3-mm elastic hard papules, and it does not have any pustules nor comedones.

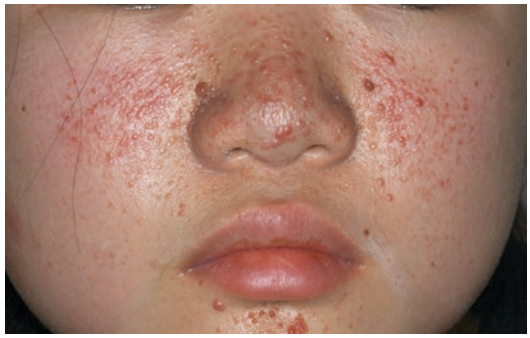

Fig. 15.10 Angiofibroma (tuberous sclerosis)

Topical sirolimus is effective in treating this condition.

Syringomas

Syringomas are benign eccrine sweat duct tumors, typically found clustered on eyelids, which are skin-colored or yellowish firm papules, 1–3 mm in diameter, and are more common in females. It does not show any follicular distribution. Carbon dioxide lasers are the most common modalities used for treatment.

Flat Warts (Fig. 15.11)

Flat warts, also called juvenile warts, are pinhead-sized, round or oval in shape, smooth, flat-topped, flesh- or brownish-yellow-colored papules caused by human papilloma virus mainly types 3 and 10. Flat warts usually disappear by themselves and require no treatment. An aggressive treatment like liquid nitrogen cryotherapy is not the first choice because of the risk of post-inflammatory hyperpigmentation. Topical treatment with retinoic acid or imiquimod may be used. Before they disappear, flat warts become inflamed and turn into reddish color. Few weeks later, they disappear without any scaring.

Others

There are many other rare diseases, which presents as acne and could be misdiagnosed as acne, for example, dental sinus, bilateral nevus comedonicus, molluscum contagiosum, and lymphoma (Fig. 15.12).

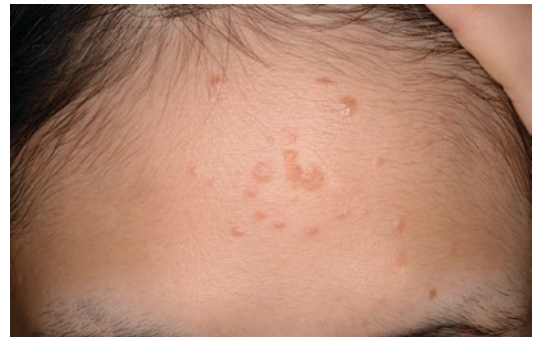

Fig. 15.11 Flat warts

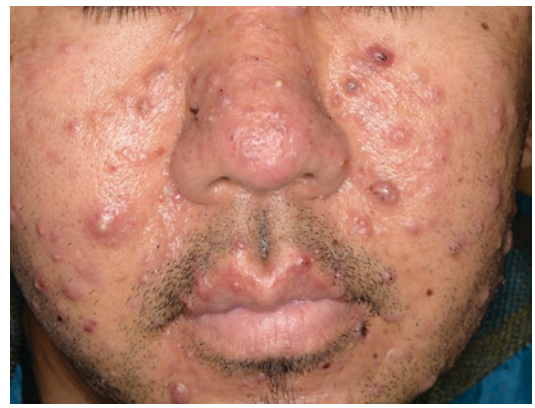

Fig. 15.12 Cutaneous manifestations of chronic myelomonocytic leukemia

Conclusion

Acne is one of the most common skin diseases. But there are still many associated differential diagnoses. To prevent misdiagnosis, primary evaluation of comedones and consideration of differential diagnoses for the cases without comedones should be carried out.

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16 Epidemiology of Acne in Latin America and Research News from Brazil

Ediléia Bagatin, Marco Rocha, and Caroline Sousa Costa

Acne Vulgaris

Inflammation

Acne is a multifactorial disease, and inflammation has been considered to be the central etiopathogenic factor. Histologic and immunohistochemical studies have been showing that a variety of cytokines are detected in the skin before development of clinical inflammatory lesions. The main triggers of inflammation include sebocyte activation by androgen linking to nuclear receptor; qualitative changes in sebum; and recognition of *Cutibacterium acnes* by Toll-like receptor (TLR) 2 and 4 in sebocytes, keratinocytes, and monocytes. The presence of pro-inflammatory mediators in acne lesions, as well as in perilesional area, had already been demonstrated. If the inflammation precedes comedone formation, it may be less likely that *C. acnes* is driving the early influx of inflammatory cells. Different inflammatory mediators are involved, such as IL-1 and IL-1R, IL-6, TNF-α, IGF-1 and IGF-1R, PPARs, and T helper cells (Th1 and 17) [1].

The role of IGF-1 and IGF-1R in acne has been suggested in studies about the influence of occidental insulinogenic diet with high glycemic load. Therefore there is a raising discussion about the association between severe acne and metabolic syndrome [1]. Our research group evaluated 85 patients under treatment for metabolic syndrome looking for acne scars on face, thorax, and back, in a pilot study. We have asked for behaviors like smoking and alcohol consumption and performed clinical examination, measurement of abdominal circumference, blood pressure, weight, height, and body mass index. Laboratory tests, such as fasting glucose, complete blood count, and serum levels of insulin, lipids, ALT, AST, urea, and creatinine were assessed. Medical history of acne was detected in 52/85 (61%) patients and 27/52 (52%) presented acne scars. As they were under treatment for metabolic syndrome, only triglyceride levels were significantly higher in patients with acne scars. The correlation between acne and metabolic syndrome could be suggested considering the elevated number of patients with acne history and scars. This result pointed out the value of clinical and laboratorial investigation to evaluate the metabolic syndrome risk, especially in prolonged and severe inflammatory acne [2].

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Classification

Since 1931, many classifications for acne vulgaris have been proposed. A group of dermatologists, members of the Iberian-Latin American College of Dermatology (CILAD) and well-known acne specialists, created the Latin American Group for Acne Study (GLEA). They discussed the subject during 1 year and published a classification, in 2007, considering the morphology and severity of acne lesions. Four years later, a revision included the number of each type of lesions in order to classify any clinical presentation of acne in mild, moderate, and severe. Classification according to age was added. Acne *fulminans* and conglobate were included as special forms. The final classification was published in 2015 (Table 16.1) [3].

Prevalence and Clinical Forms

A cross-sectional study, published in 2014, analyzed prevalence and acne degree in adolescents from Sao Paulo City, as well as socio-demographic factors, family history, and lifestyle [4]. A total of 452 adolescents, aged between 10 and 17 (mean = 13.3yo), from elementary and high school were examined by three independent evaluators: 62.4% were female and 85.8% white and 6.4% aged 14. The prevalence of acne was 96.0%, increased with age, and 100% presented acne over 14 years old. The most prevalent form was comedonal (61.1%), followed by mild (30.6%) and moderate (7.6%) papular/pustular, affecting mostly the face (97.5%). About half of the adolescents reported family history, and only 20.6% were previously treated. There was a high prevalence of acne in adolescents from Sao Paulo City, predominantly comedonal, on face, with higher chance of presenting non-comedonal acne as age increased. In a previous study, we have evaluated the prevalence and clinical forms of acne in adolescents with Down's syndrome, in the same city. A high prevalence was also observed, with predominance of noninflammatory lesions. Interestingly, the patients didn't care about the disease, and no excoriations were observed [5].

Table 16.1 Acne classification – according to age of onset, predominant lesion, severity and special forms

Age of onset	Predominant lesion and severity degree[a]	Special forms
Newborn (0–30 days)	Comedonal	Fulminans
Lactant (1–24 months)	Papular/pustular	Conglobate
Childhood (2–7 yo)		Nodular/ cystic
Pre-adolescent (8–11 yo)		
Adolescent (12–24 yo)		
Adult (>25 yo)		

Data from: Kaminsky et al. [3]
[a]Light: <20 lesions; Moderate: 20–50 lesions; Severe: >50 lesions

Quality of Life

The negative impact of acne in quality of life (QoL) with psychological, social, and relationship impairment is largely documented, indicating that clinical trials should always include this evaluation as efficacy outcome. For this purpose, the use of specific instruments, like "Acne-specific Quality of Life Questionnaire (Acne-Qol)," is recommended. The original English questionnaire, after author authorization, was translated, adapted to cultural aspects, and validated into Brazilian-Portuguese language. It was published in 2014 in a Brazilian journal and has been used in researches about acne vulgaris as well as adult female acne, showing parallel results with other efficacy parameters [6].

Algorithm of Treatment

The acne treatment involves topical and systemic drugs, as well as adjuvants cosmeceuticals products and procedures. An evidence-based review showed that the following substances have their indication supported by good studies. Topical therapy include 2.5%, 4%, 5%, and 8% benzoyl peroxide; 0.025% and 0.05% tretinoin; 0.1% adapalene; 15% and 20% azelaic acid; clindamycin,

preferably in combination with benzoyl peroxide or tretinoin or adapalene; and combination of benzoyl peroxide and adapalene. There are few options for systemic treatment: antibiotics (cyclins, macrolides, and sulphonamides), never as monotherapy, during 6 to 12 weeks; hormones (for women, like oral contraceptives and spironolactone); and oral isotretinoin (ISO) [7].

A group of 33 dermatologists from CILAD and acne experts expanded the GLEA, including doctors from Spain and Portugal and created the Iberian-Latin American Group for Study of Acne – GILEA. All the available scientific evidence was carefully selected, and several questions were discussed in face-to-face meetings to determine the classification and gradation of acne and subsequently create a guideline for treatment, as a therapeutic algorithm, published in 2017 (Fig. 16.1) [8].

Oral Isotretinoin

The efficacy and safety of ISO for treatment of moderate to severe acne unresponsive to conventional therapy with negative impact in QoL and tendency to scars is well documented after about 40 years of use, around the globe, with millions of patients treated. This drug is the unique option to achieve prolonged remission or cure of acne in 70 to 80% of patients after one or more cycles. The most frequent and common adverse effects are mucocutaneous (cheilitis, dry eyes, nose, and skin). They are predictable and easily controllable with lubricants. Teratogenicity, the major safety concern, makes pregnancy test and use of two safe contraceptive methods mandatory. Laboratorial monitoring, regarding liver function and lipid profile, is necessary and should be done before and after 2 months of treatment. Future evaluations are needed just if tests show significative alterations. The label daily dose is 0.5 to 1 mg/kg until the total of 120–150 mg/kg. Nevertheless, lower daily doses (such as 0.2 or 0.3 mg/kg/day, 5 mg/day), for longer periods, have been described with the same efficacy, less adverse events, and better adherence [9].

We published a Cochrane's systematic review in 2018 [10]. The conclusion confirmed the safety of the drug, as severe adverse event, depression, suicide, and inflammatory bowel disease were not found in association with ISO therapy for

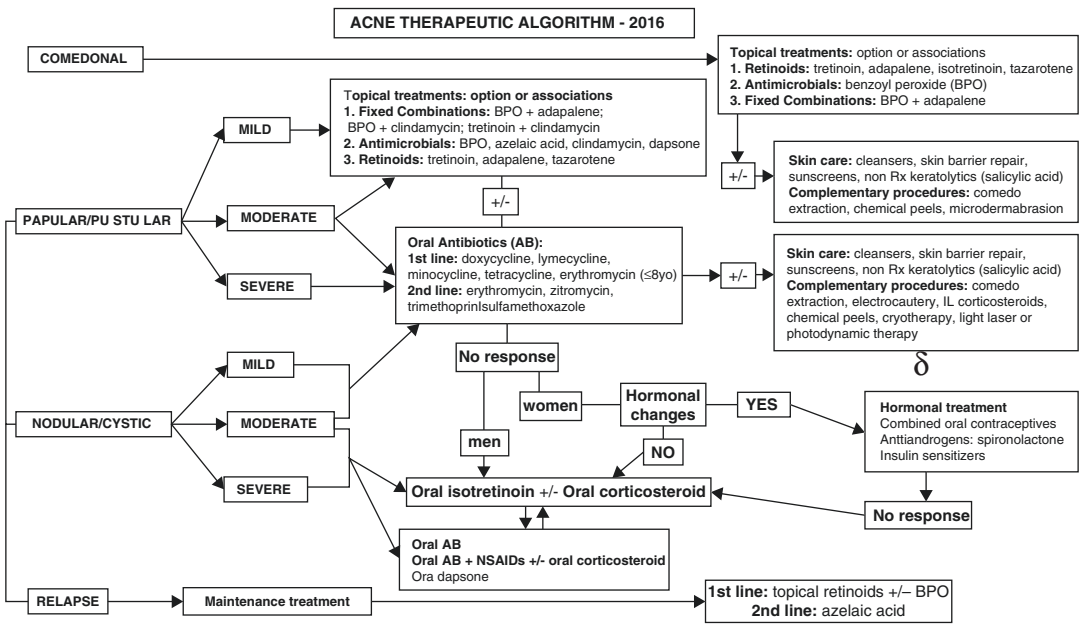

Fig. 16.1 Acne therapeutic algorithm – 2016 (Data from: Bagatin et al. [8])

acne. Nevertheless, as the efficacy studies are old, with low-quality methodology and short-term follow-up period, ISO superiority when compared with oral antibiotics plus topical agents, which is observed in clinical practice, could not be demonstrated [10].

A survey published in 2015 showed that doctors from private offices in Brazil prescribe ISO as first therapeutic option for 76.7% of patients with moderate acne and 94.6% with severe acne [11]. Public Health System in Brazil freely provides ISO for selected patients. We analyzed its prescription in a Brazilian Institutional Public Hospital, in a retrospective and observational study, by using medical records of patients treated or under treatment during 7 years. From 1526 medical records of acne patients, only 279 (18.28%) were treated with ISO, which differs from private offices reality. Regarding acne severity, 1.19% were mild, 57.37% moderate, 35.85% severe, and 5.57% conglobate. The majority of patients presented sequelae (scars and hyperpigmentation) when the treatment was initiated, meaning a delayed indication. Initial daily dose was 20 mg; average according to weight was 0.33 mg/kg and 127.61 mg/kg for daily and total dose, respectively. Few cases developed mild laboratory abnormalities, and no severe adverse event was recorded, confirming the drug safety. We emphasize the prescription for moderate forms of acne and indication of lower daily doses. This corroborates the current tendency for prescription in order to reduce side effects, prevent scars, and increase the adherence [12].

Controversies About Oral Isotretinoin

We are absolutely sure about efficacy and safety of ISO. It should be considered the best and gold standard treatment for acne. However, the continuous raise of controversies about new adverse events has been causing unnecessary concerns and prejudice to patients with severe acne. Case reports published in the 1980s and 1990s associated its use with occurrence of hypertrophic scars and keloids, after mechanical dermabrasion and argon laser in patients undergoing or previously treated with ISO. Since then, the label warns patients to avoid skin resurfacing procedures during and for at least 6 months after treatment due to risk of atypical scarring. In 2010, our research group published a case series about dermabrasion test in a small area of the face for acne scars revision during treatment with oral ISO and observed normal healing in all patients [13]. We also evaluated chemodermabrasion with medium depth peel (Jessner's solution plus TCA 35%) in the whole face followed by dermabrasion in areas with atrophic scars, performed 1 to 3 months after treatment with normal reepithelialization (Fig. 16.2) [14]. An additional observational retrospective study suggested that this association

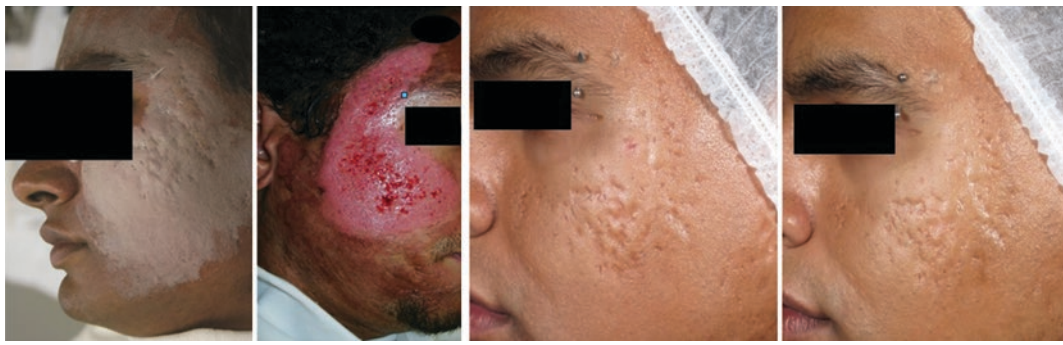

Fig. 16.2 Chemodermabrasion with medium depth peel (Jessner's solution plus TCA 35%) in the whole face plus dermabrasion in atrophic scars. (**a**) Immediate effect of medium depth peel; (**b**) Immediate effect of dermabrasion; (**c**) Atrophic acne scars before chemodermabrasion (one session); (**d**) Normal reepithelialization and moderate effect for acne scars revision

might be a rare undesirable event, which depends on individual response, and probably related to acne. So, up to date, our results in accordance with recent publications about the use of lasers during the use of ISO point out that there is no robust evidence about negative impact in wound healing. We agree that for full-face dermabrasion or ablative laser or microneedling, additional caution should be recommended [15].

There are approximately 500 case reports of depression in patients treated with ISO. The prevalence of depression among adolescents is estimated around 3–11% and associated to this drug, between 1% and 11%. In Brazil, these numbers are 3–10% and 0.06%, respectively. The drug is liposoluble, crosses the blood-brain barrier, and may interact with retinoid receptors in the brain. On the other hand, it is well-known that moderate and severe acne vulgaris have the same psychosocial impact as neurofibromatosis and epilepsy and is related to stigma, shame, guilt, and low self-esteem. Therefore, the high rates of depression, mental issues, and suicidal ideation in adolescents, who are candidate for treatment with ISO, might reflect, at least partially, the effect of acne. A systematic review and meta-analysis evaluated 31 studies and observed that the prevalence of depression after the treatment diminished, with a relative risk of 0.588. Nowadays, occurrence of depression during ISO has been considered an idiosyncratic reaction. There is consensus that ISO probably cures more than causes depression, and there is no psychiatric contraindication for its prescription. We conducted an observational study with 53 men and women who were about to complete treatment by using Beck's Depression Inventory. Our data, despite the small sample size, supports the idea that there is no negative impact of the drug on depression [16].

According to FAERS – Food and Drug Administration Adverse Event Reporting System – 2214 cases of inflammatory bowel disease (IBD) related to oral ISO had been reported from 2003 to 2011, the majority (87.7%) being reported by lawyers. On the contrary, lawyers reported 3.6% of adverse events related to other drugs in the same period, which highlights a possible medico-legal distortion. Populational case-control studies didn't confirm that association. The correlation between acne itself, as well as the prior use of oral antibiotics, and IBD has been considered a possible bias. We conducted an observational study including 64 subjects who were about to complete treatment with ISO and detected a low prevalence of intestinal symptoms, corroborating the no association between the drug and IBD [17].

Brazilian Similar Product

Considering the safe and effectiveness of the reference product, we evaluated a similar product developed in Brazil in an open study. Fifty patients with moderate to severe acne, aged from 13 to 35 years old (mean = 20 years old), received 0.5 mg/kg/day to complete 120 mg/kg. Lesions count showed a 99% reduction and complete remission in 91.5% of patients (Fig. 16.3). Investigator Global Assessment (IGA), patient's satisfaction, and scores of AcneQoL presented similar results compared to published data about the reference product. Safety and tolerability were also similar [18].

Adult Female Acne

Recent epidemiological data revealed particularities in adults affected by acne. Women have a high and increasing prevalence when compared to men, especially after 25 years of age, and the disease can persist after 50 years old. Besides genetic, hormonal, and inflammatory factors, several triggers have been postulated, such as ultraviolet radiation, modern lifestyle, stress, obesity, diet, supplements, smoking, sleep disorders, cosmetics, medications, exogenous hormones, and excessive skin washing. The damage of epidermal barrier with increase of transepidermal water loss is also responsible for onset of the inflammatory cascade. Adult female acne (AFA) may represent a persistence of adolescent acne or emerge in adult life. It has been considered a different disease as it is more chronic, resistant to treatment, recalcitrant, and predominantly in the

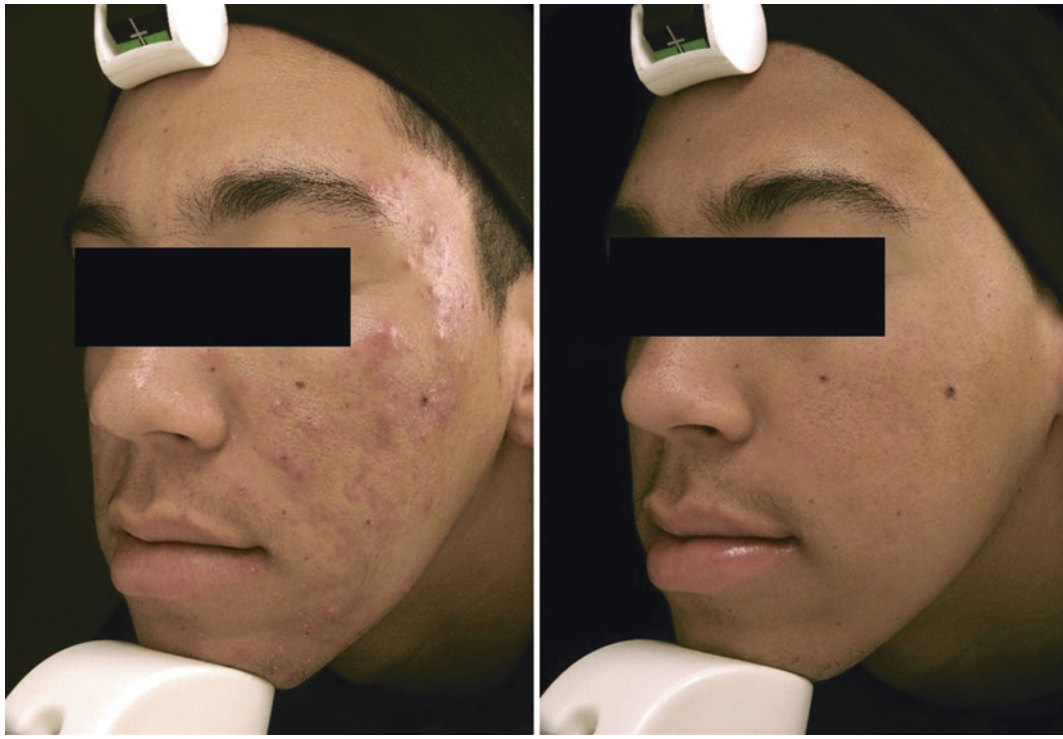

Fig. 16.3 Treatment of moderate inflammatory acne with oral isotretinoin (Brazilian similar product). (**a**) At baseline; (**b**) after 6-month treatment

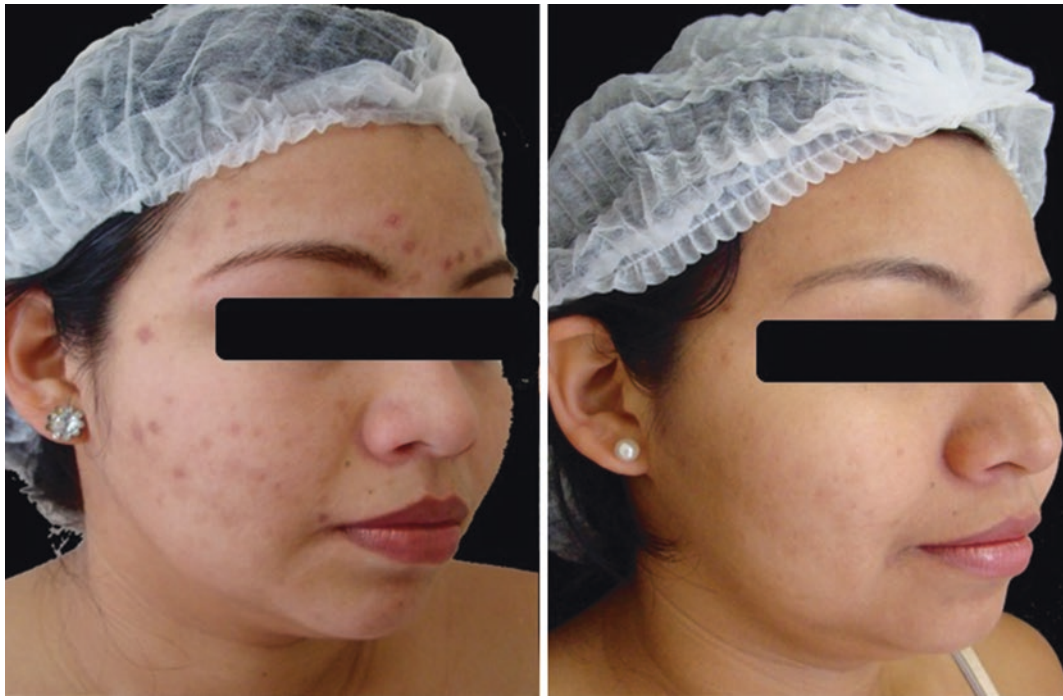

Fig. 16.4 Patient 29 years old at baseline and after 6-month treatment with combined oral contraceptive

face with inflammatory lesions and occurs in a more sensitive skin (Fig. 16.4). In contrast to what was thought, most of women do not present endocrinopathy, i.e., they have normal levels of androgens. When present, polycystic ovarian syndrome is the main cause, also presenting menstrual irregularity, hirsutism, and acanthosis nigricans. There is high negative impact on QoL; anxiety and depression may be present even in mild acne [19, 20].

Epidemiology in Latin America

Researchers from Latin America and Iberian Peninsula assessed the demographic and clinical characteristics of 1384 (1105 women and 279 men) acne patients from 21 countries, aged from 25 to 60 (mean age for men = 33.35 ± 8.42; women = 33.62 ± 7.26). The purpose was to identify triggers and parameters for severity according to demographic, biological, social, and environmental factors. Family history of acne was detected in 828 (60%) of patients. Gender differences regarding severity and lesions distribution were identified. The majority of patients had mild or moderate acne. Nevertheless, severe acne was more frequent in men than women (15% versus 3.9%). The lesions were predominant on face, but men had lesions on face, chest, and back more frequently than women (12.3% versus 5.7%). The lesions were predominant in lower face in women and whole face in men. Univariate analysis demonstrated that male gender, cosmetics use, onset at adolescence, and other signs of hyperandrogenism were associated with severity. Similarities and differences with previous epidemiological researches were detected, possibly related to lifestyle and geographic characteristics [21].

Quality of Life

The influence of some physiological responses derived from the surroundings, such as mechanical, physical, or chemical stimuli, and mental disorders are commonly observed in AFA. Poor sleep quality may act as a stressor promoting release of hormones and affecting immune system, with relevant role in AFA. We have evaluated the effect on QoL of acne treatment with 15% azelaic acid gel, twice a day or combined oral contraceptive (20ug of ethinylestradiol and 3 mg drospirenone), measured by AcneQoL, in 38 adult and normoandrogenic women. Before treatment, a significant impact on QoL was detected, and both treatments produced a score reduction. Considering the four domains, patients treated with oral contraceptive showed greater improvement in self-perception and acne symptoms compared to azelaic acid [22]. The sleep quality was also investigated in the same two groups of women. A significant improvement was observed after the acne control, regardless of the use of monotherapy and oral versus topical drugs [23].

Inflammation: Molecular Mechanism

Recent investigations about the role of innate immunity, through activation of TLRs by the commensal bacteria, *C. acnes*, have explained the prolonged course of acne as well as the mechanism of action of drugs used for treatment. After recognition of *C. acnes* molecules by TLR-2, an inflammatory response, through *nuclear factor kappa* B pathway, is initiated. We have investigated the role of an oral contraceptive (drospirenone 3 mg /ethinylestradiol. 02 mg) or 15% azelaic acid gel, for 6 months, in an open, randomized (two parallel groups), evaluator-blinded, and comparative trial including 38 adult women with moderate facial acne and 10 age-matched controls, aging from 26 to 44 years old. TLR-2 expression by immunohistochemistry was investigated at baseline (control group, lesion, and perilesional area) and at end of treatment (lesion and perilesional area). There was no difference in lesion and perilesional area, but controls had lower expression. Despite moderate clinical improvement in both groups, significant reduc-

tion of TLR-2 expression was observed after treatment, with no difference (Fig. 16.5), suggesting an anti-inflammatory effect of oral contraceptive and azelaic acid in AFA [24].

Hormonal Metabolism

Serum dosage of sexual hormones usually shows normal results and is not useful to evaluate the skin androgen production. We conducted a study to investigate the possible usefulness of an androgenic metabolite as a biomarker in AFA. A population of 38 women presenting AFA and no other signals of hyperandrogenism and a control group were submitted to hormonal dosages, including total and free testosterone, dehydroepiandrosterone sulfate, and androsterone glucoronate (ADT-G) which is an androgen metabolite from peripheric tissues. Before treatment with oral contraceptive (drospirenone 3 mg /ethinylestradiol. 02 mg), only ADT-G was high (above the normal values) in the acne group. After treatment, there was a reduction in free testosterone and ADT-G. Therefore, we believe that it may be useful for monitoring the peripheral hyperandrogenism, which has been suggested as main trigger for development and chronicity of AFA [25].

Practical Guide for Management

A team of five experts with extensive experience in acne conducted a literature review searching for scientific evidence and discussed the best therapeutic approaches and personal experiences to develop a practical guide for the management of AFA. A consensus was reached, and detailed recommendations for best clinical practices were summarized and published in 2019. The final treatment algorithm for adult female acne is presented in Fig. 16.6 [26].

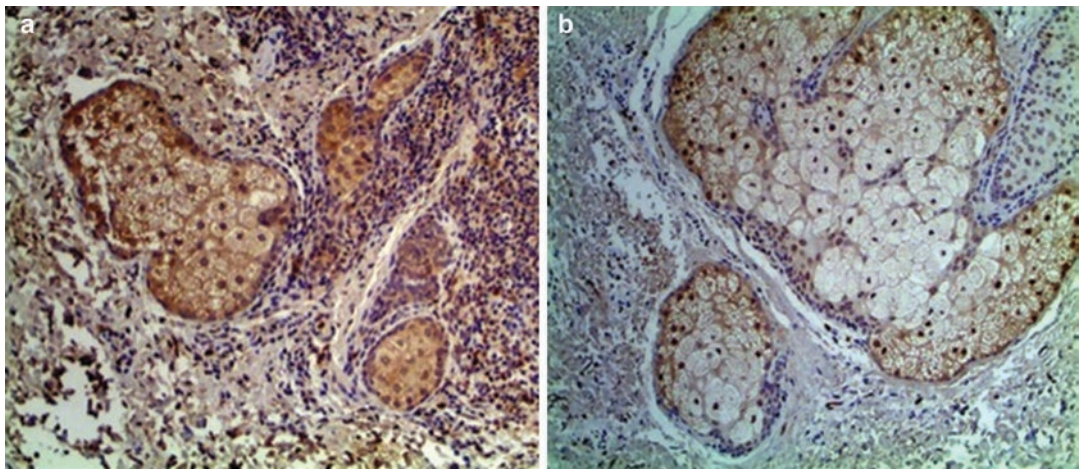

Fig. 16.5 TLR2 expression sebaceous gland from adult female acne lesion (**a**) At baseline; (**b**) after 6-month treatment with combined oral contraceptive (immunohistochemical staining, Å ~ 100)

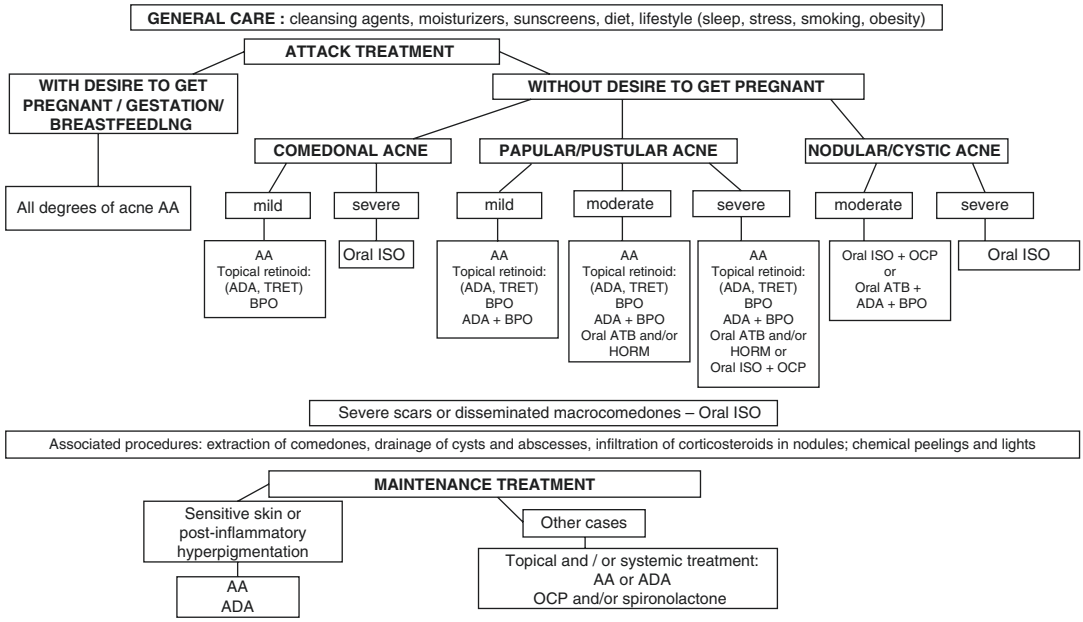

Fig. 16.6 Treatment algorithm for adult female acne (Data from: Bagatin et al. [26]). AA = azelaic acid (15%, 20%); ADA = adapalene (0.1%); TRET = tretinoin (0.025%, 0.05%); BPO (benzoyl peroxide (2.5%, 5%); ISO = isotretinoin (low dose or medical criteria/off label); ATB = antibiotics (tetracycline 500 mg, twice a day; doxycycline 100 g/day; lymecycline 300 mg/day; minocycline 100 mg/day); HORM = hormonal treatment (spironolactone 50–150 mg/day; OCP = oral contraceptives – ethinylestradiol + drospirenone or cyproterone acetate or chlormadinone or dienogest)

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Androgens and Acne

17

Chanat Kumtornrut and Nopadon Noppakun

Introduction

Acne vulgaris (AV) is the most common folliculosebaceous disorder. The main pathogenesis of AV are abnormal sebum production and composition of sebaceous glands (SGs), follicular dyskeratinization, as well as skin inflammation, and microbiome dysbalance [1]. Circulating and local cutaneous androgens play important roles in SG differentiation and function and in follicular dyskeratinization and inflammation. Thus, androgens are directly and indirectly involved in AV formation. Effective treatments with antiandrogenic agents confirm the role of androgen in acne pathogenesis. This review mainly focuses on androgen-related pathophysiology and clinical implications of androgens in AV.

Androgen-Related Pathophysiology of AV

Androgens are steroid hormones mainly produced in testes, ovaries, and adrenal glands [2]. However, the SG can also synthesize androgens de novo from endogenous cholesterol and circulating adrenal dehydroepiandrosterone-sulfate (DHEA-S) [3–5]. The most potent androgen is dihydrotestosterone (DHT), which can be metabolized from testosterone by 5α-reductase found in SG and hair follicles of the skin [6]. Androgen action relies principally on the intracellular androgen receptor (AR), which is a member of the steroid hormone nuclear receptor superfamily [7]. Androgen receptor actions are mediated via specific binding to DNA sequences that regulate genes involved in several important cellular pathways [2]. Also, a non-DNA-binding-dependent mechanism is present, shown by the rapid onset of AR-dependent actions [8]. In the skin, ARs are expressed in apocrine excretory cells, dermal papilla cells, fibroblasts, inflammatory cells, keratinocytes, sebocytes, and vascular endothelial cells [5]. Several enzymes and coregulators tightly regulate androgen/AR metabolism and actions [2].

Androgens and Altered Sebum Production and Composition

Androgens, mainly DHT, are involved throughout the SG cell cycle, especially in sebaceous differentiation and sebum production. Androgen actions modulate SG size and morphology and stimulate sebocyte maturation, lipogenesis, and the apoptotic process, which is involved in the ultimate process of sebaceous differentiation known as holocrine secretion [9]. Sebum

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production and lipogenesis are also influenced by other factors, such as peroxisome proliferator-associated receptor gamma (PPARγ) [10], TGF-β [11], insulin/insulin-like growth factor-1 [12], and fibroblast growth factor receptor 2 [13].

Changes in the levels or sensitivity of androgens/AR in SG affect sebaceous activity. During puberty, sebum production dramatically increases, especially in men, due to increased androgen production [14]. Castrated patients and those with complete androgen insensitivity exhibit remarkably reduced sebum production [14, 15], and testosterone replacement in castrated men exhibits significantly increased SG activity; however, testosterone replacement in normal men did not increase SG activity [14]. The sebum excretion rate was diminished in patients receiving systemic medications with antiandrogenic effects [16]. Recently, a novel AR antagonist, cortexolone 17α-propionate, showed an inhibitory effect on sebocyte lipid production [17]. In addition, regional variation of AR expression in SGs determines the sebum levels found on different areas of human facial skin, higher on the T-zone (forehead, nose, chin) compared with the U-zone (both cheeks) [18].

The sebum is composed mainly of free fatty acids (FFAs), squalene, triglyceride (TG), wax esters, cholesterol, and cholesterol ester [19]. Among several types of lipids in sebum, TG and FFAs are the most abundant, but squalene and wax ester are the most characteristic and not found in other parts of the human body [19]. Some unsaturated FFAs are uniquely produced in human SG, namely, sapienic (16:1, Δ6) and sebaleic (18:2, Δ5,8) acid, and considered markers of sebocyte differentiation [20]. In normal conditions, the sebum composition maintains a constant ratio of FFAs [20, 21].

Androgen modulates the sebum composition. Androgen levels in urine were positively correlated with the level of monounsaturated fatty acid in sebum [22]. Sebum components and skin surface lipids are related to androgen-induced sebum production and secretion. One study demonstrated an inverse relationship between sebum secretion and linoleic acid levels [21], and linoleic acid levels were significantly lower in acne patients [23]. Other studies showed that changes in sebum content, especially monounsaturated fatty acids, regulated sebocyte differentiation and sebum production via PPARs [24, 25].

Numerous epidemiological and clinical studies have investigated the relationship between AV, altered sebum production and composition, and androgens. Pochi et al. reported higher levels of sebum production in male acne patients compared with normal, especially in those with severe acne, but no significant differences in plasma and urine testosterone or 17-ketosteroid levels were found between acne patients and controls [26, 27]. Khondker and Khan found that DHEA-S levels correlated with prepubertal acne development in girls and severity of acne and sebum production in both sexes; however, androgen levels in all subjects were within normal ranges [28]. Aizawa et al. reported increased levels of DHEA-S in adolescent females with acne, but no differences in androgen levels in both sexes exhibiting acne, noting that no sebum measurements were reported [29, 30]. After treatment with the combined oral contraceptive pill (ethinyl estradiol combined with either drospirenone or cyproterone acetate), van Vloten found that the decreased testosterone, androstenedione, and DHEA-S levels paralleled the reduction of acne counts and sebum production [31].

Although several studies indicated that androgens are directly or indirectly associated with sebum levels and composition, the interconnection between androgens, sebum, and AV remains complex and inconclusive. This may reflect the involvement of various factors regulating SG activity and homeostasis and the multifactorial nature of AV.

Androgens in Epidermal Dyskeratinization in Hair Follicles

The expression AR was found in epidermal keratinocytes by immunohistochemistry studies [32–34], but the functional status was questionable since no mRNA was detected by PCR [35]. However, the effects of androgen on epidermal keratinocytes have been demonstrated in several

studies. Androgens were found to be involved in epidermal hyperproliferation [36], differentiation [37], and lamellar body formation and secretion [38]. AR expression is predominantly found in dermal fibroblasts, which are located closely to the epidermal keratinocytes in the skin. Evidence from in vitro cultures and skin samples from acne patients indicated that androgens indirectly modulated keratinocyte differentiation via androgen-dependent fibroblast-derived growth factor production [39].

Certain lipid components, mainly unsaturated fatty acid and peroxide forms of squalene, in SG were related to abnormal keratinization and comedo formation [40, 41]. This mechanism may involve abnormal calcium metabolism in keratinocytes [42]. The net effects of androgen and lipid disturbance were reported to cause an abnormal skin barrier, which is usually found in acne patients [43, 44].

Androgens in Cutaneous Inflammation

ARs are expressed in inflammatory cells found in the skin [5]. Androgens produce different effects on distinct types of inflammatory cells. For example, androgen actions increased monocyte chemotaxis and numbers, resulting in localized tumor necrosis factor (TNF)-α expression. Blockage of AR by flutamide in macrophages suppressed the expression of tissue TNF-α [45]. In contrast, androgens inhibited superoxide anion release from neutrophils [46], as well as interleukin (IL)-6 and prostaglandin E2 expression in peripheral blood monocytes [47]. Therefore, androgens may induce both pro- and anti-inflammatory responses in the skin [48]. In AV, androgens promote pro-inflammatory actions.

Androgens indirectly modify cutaneous inflammation, through the sebocyte and sebum, in the pathogenesis of acne. Dihydrotestosterone upregulated the expression of pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-α, in cultured sebocytes [49]. Abnormally elevated levels of FFAs in sebum can trigger the inflammation process, through the induction of IL-6 and IL-8 [25], and human beta-defensin 2 expression via the NF-κB pathway [50]. The pro-inflammatory effect of androgens in acne patients was augmented by elevated levels of squalene, especially in the oxidized form [41, 51]. This evidence suggested that lipid disturbance under androgen influence could trigger the initiation of inflammation and comedo formation in acne [52, 53]. The modification of androgen actions and lipid abnormalities could provide new avenues for future acne treatments [17, 52].

Androgen-Related Clinical Implications

Anabolic-Androgenic Steroid-Induced Acne in Bodybuilders

Anabolic-androgenic steroids (AAS) are used for the therapeutic treatment of medical indications; however, AAS are commonly abused by bodybuilders and sportsmen in fitness centers and studios, exhibiting a high prevalence in many countries [54]. Abusers were predominantly males and their average age was 21–25 years old [54].

The clinical manifestations of AAS-induced acne, sometimes called “doping acne” or “bodybuilder acne,” range from acneiform eruption to the exacerbation of inflammation and total numbers of acne, including acne conglobata or acne fulminans [54, 55]. This condition may be worsened by administration of vitamin B2, 6, and 12 [56]. Other cutaneous side effects include striae distensae, delayed wound healing, hirsutism, and edema [54, 57].

The most common systemic side effects of AAS are personality and behavioral disorders, namely, aggression and depression; mood swing and sleep disturbance were also reported [54]. These psychiatric side effects are dose-dependent [58]. Endocrinological abnormalities include gynecomastia, impotence, and testicular atrophy [54]. Long-term complications for prolonged abuse of AAS include cardiovascular toxicity with sudden cardiac death [59], cardiomyopathy [60], hepatotoxicity [61], as well as psychiatric distress and suicide [54].

The treatment of choice is to stop the use of AAS. Systemic retinoids must be cautiously prescribed, since they may aggravate severer forms of acne [55, 62], pyogenic granuloma-like tissue [62], and hepatotoxicity. Alternative treatments include systemic steroids and antibiotics. Concomitant wound debridement and dressing and topical benzoyl peroxide were also recommended treatments [55].

Androgen-Induced Acne in Transgender Men

Transgenders exhibit a gender identity/expression that is different from that assigned at birth [63]. For transgender men, the first-line medical therapy is exogenous androgen (mainly testosterone), together with surgical intervention and psychological management. The aim of the treatment focuses on the masculine secondary sexual appearance, including male-pattern facial and body hair, deepening of the voice, change of body composition, and sense of masculinity [64]. To date, there is no standard protocol for testosterone therapy for this group of patients. In general, testosterone is prescribed at a lower dose at the initiation of therapy and then gradually titrated until the serum testosterone levels of patients reach the male reference range [63]. At this level, cutaneous and extracutaneous side effects are observed [63, 64].

AV is one of the most common cutaneous manifestations in transgender men after androgen administration. One study showed that 82.4% of subjects developed AV during the first 6 months of androgen therapy. The acne usually involved the face, upper chest, and back with mild severity in majority of cases; severe cases were randomly reported [65]. The total number of acne lesions and severity of acne peaked at 6 months and declined spontaneously 12 months after treatment [66].

The treatments for androgen-induced acne in transgender men are similar to the standard AV treatment with several noteworthy issues. Antiandrogens should be avoided since they antagonize the effect of exogenous hormonal administration. The potential of pregnancy and risk of teratogenicity, in some patients, should be addressed. And the increased risk of hepatotoxicity and emotional disorders from both androgens and systemic retinoids should be monitored. Topical and systemic treatments should be chosen according to the severity of AV, ensuring the response of the treatment is acceptable [67]. Long-term maintenance therapy should be continued, and multiple courses of systemic retinoids may be required [65].

Acne in Androgen-Mediated Conditions (Polycystic Ovarian Syndrome, PCOS)

PCOS is a multifactorial and complex disease. The exact pathophysiology of this disease remains inconclusive, but an abnormal excess of androgens is an important factor in PCOS. The clinical constellation of PCOS involves multiple organs, with gynecological, endocrinological and metabolic, and dermatological systems all interacting in a complex disease network [68].

Several groups have proposed diagnostic criteria for PCOS, with debatable benefits and limitations, especially among subgroups of the PCOS population [69–71]. According to different definitions in several studies, the prevalence of PCOS varied between 6% and 10% of the unselected populations [72]. The age range for PCOS is wide, from adolescent to peri- and postmenopausal females [71]. The most common clinical manifestation is the polycystic ovary, and the reported prevalence of AV was 8–26% [72].

AV is one of the cutaneous signs of virilization. In PCOS, the distribution of inflammatory acne on the lower face, neck, upper chest, and back may be more predominant when compared with normal AV, and usually the degree of acne is moderate to severe. Other clinical clues prompting PCOS diagnosis include the resistance of AV to conventional therapies and a personal history of menstrual irregularity [73]. Apart from AV, other signs of hyperandrogenism, such as

seborrhea, hirsutism, androgenetic alopecia, and signs of insulin resistance, for example, acanthosis nigricans and acrochordon, may be found in PCOS patients [73].

Other important manifestations and comorbidities of PCOS include chronic anovulation, irregular menstruation, polycystic ovaries identified by ultrasonography, obesity, metabolic syndrome, and insulin resistance. The long-term complications include an increased risk of endometrial cancer, infertility, cardiovascular events, obstructive sleep apnea, nonalcoholic steatohepatitis, and psychiatric problems [73].

The management of PCOS requires a multidisciplinary approach reflecting the heterogeneous nature of the disorder [74, 75]. The primary treatment of acne in PCOS involves systemic hormonal and/or non-hormonal therapy. The hormonal treatments include those with antiandrogenic effects and will be discussed later in the next section. An anti-insulin resistance medication, metformin, may be used to treat PCOS, but studies revealed its benefit on acne were limited. Studies found that 500 mg metformin three times daily for 8–12 weeks improved acne in PCOS patients; however, 20–60% of patients exhibited treatment-related side effects, including reduced appetite, diarrhea, nausea, and abdominal discomfort [76, 77]. Also, isotretinoin proved to be useful in acne treatment at a daily dose of 0.5–1 mg/kg and total accumulative dose of 120–150 mg/kg. Its efficacy was similar for patients with and without PCOS but had a slightly higher rate of relapse in the PCOS group [78].

Antiandrogenic Treatments in AV

Antiandrogen use in AV has become more widely accepted, due to the global increase of antibiotic resistance. Antiandrogens can be broadly categorized into oral contraceptive pills (OCPs) and non-OCPs. The actions of antiandrogens are mediated via several mechanisms, i.e., blockage of androgen synthesis, reduction of free-form androgens in the circulation, suppression of androgen conversion, and AR blockers. Many medications exhibit more than one mechanism of action.

- Oral contraceptive pills

The OCPs are the only antiandrogens approved for the treatment of AV by the Food and Drug Administration (FDA) in the USA [79]. The form of OCPs must be a combination of an estrogen, usually ethinyl-estradiol, and a progestin, either norethindrone, norgestimate, or drospirenone. Drospirenone is a fourth-generation progestin not derived from testosterone that shows the least androgenic activity [80]. Cyproterone acetate (CA) and levonorgestrel, which is another type of progesterone, are approved by other countries [81]. The suppression of androgen production and induction of sex hormone-binding globulin (SHBG) by estrogen [82], and the competitive inhibition of 5 α-reductase by progestins [83], result in the overall antiandrogen effect [80]. The efficacy of OCP therapy has been demonstrated in several studies, for both facial and truncal acne [84–87], and efficacies were similar for different OCP preparations [88]. Since the onset of action takes a few months, treatment with OCP should initially be combined with other modalities [80].

The hormone-related adverse events have been a major concern for OCP use in the past, but recent data suggest that serious side effects may now be lower than previously experienced. This may be due to reduced levels of estrogen being used in OCPs, availability of long-term follow-up data, and risk factor modification for some comorbidities. A working group in the USA recommended the use OCPs as a first-line treatment for moderate to severe acne in women with or without signs of hyperandrogenism who desire contraception and have neither contraindications nor serious drug interactions [80].

- Spironolactone (SPL)

Spironolactone is a potassium-sparing diuretic that acts as an aldosterone antagonist and is indicated in hypertension and congestive

heart failure. It also exerts antiandrogenic effects through AR blockage, inhibition of 5α-reductase, and SHBG upregulation [81]. Although it is wildly used to treat AV, especially in adult women, it is not approved by the FDA in the USA because of lack of evidence using well-designed studies [80]. According to the limited data, acne experts suggested that the efficacy of SPL in AV treatment was comparable to systemic antibiotics or OCPs [80]. The therapeutic dose of SPL ranges from 25 to 100 mg daily [89] to a maximum dose of 200 mg daily [90]. Its onset of action takes 6–8 weeks. Spironolactone was considered a rational choice for adult female acne [81, 89].

In general, the side effects of SPL are acceptable and well-tolerated; diuresis is the most common. Other side effects include headache and dizziness, orthostatic hypotension, and hormone-related conditions, such as menstrual irregularity and breast tenderness. Most side effects are transient and mild and positively correlated with the dose [80, 81]. The monitoring of serum potassium levels was not mandatory when SPL was used in young and healthy individuals [80, 91]. Spironolactone can be safely combined with OCPs, especially in those who experience irregular menstruation as a side effect of SPL [92]. Previous data from animal studies with megadoses of SPL reported associations with several types of adenoma and carcinoma; however, recent data from large human studies found no equivalent associations [93, 94].

- Novel topical AR blocker

Cortexolone 17α-propionate (clascoterone) is a novel potent AR blocker that provides an interesting candidate for acne treatment. In SG, it demonstrated a higher potency in the suppression of androgen-dependent lipogenesis and inflammatory cytokine production than SPL [17]. As a topical cream, clascoterone showed a significantly higher success rate of facial acne treatment at week 12 than placebo in a phase 2b clinical trial, and it was effective for both inflammatory and non-inflammatory acne. The reported side effects were mild; erythema was the most common [95].

Conclusion

Androgens are directly and indirectly involved in AV pathogenesis, namely, in regulating sebum production and composition, epidermal dyskeratinization, and skin inflammation. Clinical evidence confirms the effects of exogenous and endogenous androgen on AV. The high potency and limited side effects of antiandrogens, both systemic and topical forms, in acne treatment provide a valuable therapeutic avenue for AV patients, especially in the era of antibiotic resistance.

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Index

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