

Dermatology

Acne

Symposium at the
World Congress of Dermatology
Paris, July, 2002

Editors

Ch.C. Zouboulis, Berlin

M.I. Herane, Santiago de Chile

D. Thiboutot, Hershey, Pa.

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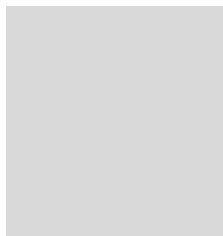
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24 figures, 16 in color, and 18 tables, 2003



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Editors:

Christos C. Zouboulis Department of Dermatology
University Medical Center Benjamin Franklin
The Free University of Berlin
Fabeckstrasse 60–62
14195 Berlin (Germany)
Tel. 49-30-84456910
Fax 49-30-84456908
E-mail zouboulis@medizin.fu-berlin.de

Maria Isabel Herane Department of Dermatology
West Unit
University of Chile
Hospital San Juan de Dios
Guardia Vieja 255 of. 901
Providencia, Santiago (Chile)
Tel. 56-2-3310449
Fax 56-2-3310450
E-mail giderm@yahoo.es

Diane Thiboutot Department of Dermatology
Milton Hershey Medical Center
Pennsylvania State University
P.O. Box 850
Hershey, PA 17033 (USA)
Tel. 1-717-531-8307
Fax 1-171-531-4821
E-mail dthiboutot@psu.edu

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Dear colleagues and friends,

It is a great pleasure to present the Proceedings of the Symposium on Acne held at the 20th World Congress of Dermatology, July 1–5, 2002 in Paris. The topics discussed have been selected to address current and future aspects of research, clinical entities and treatment of the most common human disease.

The manuscripts represent a cooperative effort of 20 experts on acne from literally all around the globe. They are state-of-the-art reports including data on the increasing evidence of acne occurrence in a considerable amount of adults, especially females, the cycling of normal follicles and of comedones that may explain the natural resolution of comedones and, in the longer term, of the disease itself, evidence that cutaneous neurogenic factors contribute to the onset and/or exacerbation of acne inflammation, first data that chromosomal abnormalities, HLA phenotypes, polymorphism of human cytochrome P-450 1A1 and the MUC1 gene may be involved in the pathogenesis of acne, new topical therapeutic regimens, systemic drugs, and concepts for their use, in association to the need of developing strategies to minimize use of antibiotics in acne therapy, the endocrine aspects of acne and their selective treatment, and effective acne medication alternatives for countries which cannot afford modern treatments. In addition, Prof. John S. Strauss, Iowa City, wrote a comprehensive summary of the most important data and highlighted concepts for pathogenesis-tailored acne treatment.

This publication addresses equally clinicians and scientists interested in acne and determines the revolution which occurred recently in acne research and will probably continue in the future.

We express our sincere thanks to Prof. Jean-Hilaire Saurat, Geneva, Switzerland, Editor-in-Chief of *Dermatology* and Mr. Thomas Karger, Ms. Susanna Ludwig, and Ms. Elisabeth Anyawike from S. Karger AG for their help in the realization of this project as a peer-reviewed publication under most favorable conditions.

Hoping that you will find this *Dermatology* thematic issue interesting, informative, and stimulating, we wish you a pleasant reading.

Prof. Dr. *Christos C. Zouboulis*, Berlin

Prof. Dr. *Maria Isabel Herane*, Santiago de Chile

Prof. Dr. *Diane Thiboutot*, Hershey, Pa., USA



Prof. Dr. *Christos C. Zouboulis*, Berlin



Prof. Dr. *Maria Isabel Herane*, Santiago de Chile



Prof. Dr. *Diane Thiboutot*, Hershey, Pa., USA

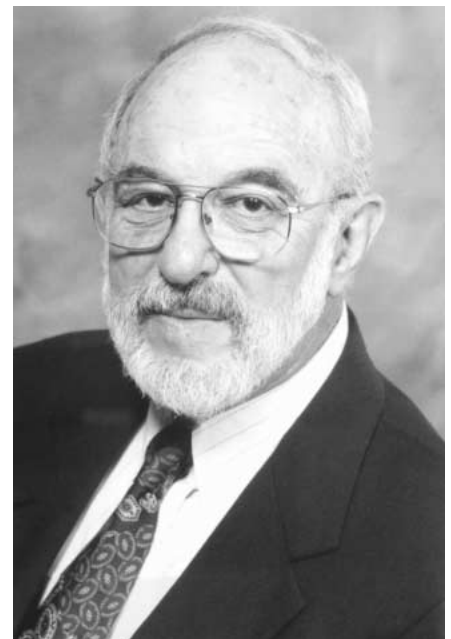
Foreword and Critical Remarks

John S. Strauss

Department of Dermatology, University of Iowa, Iowa City, Iowa, USA

The acne symposium held at the 20th World Congress in Paris in July 2002 was an opportunity for some of those working in the field to present their findings on a wide selection of topics related to the pathogenesis and treatment of acne. The presentations were indeed world-wide, including investigators from Argentina, Chile, France, Germany, Japan, Taiwan, United Kingdom, United States, and Venezuela. As is appropriate for the World Congress which is held every 5 years, these papers are a comprehensive review of the past, present, and future. The publication of these nine papers as a unit in this journal covers varying points of view, and is an excellent reference source for all those interested in acne. There is a need to focus our attention on acne, as it should not be forgotten that in developed countries, it is still responsible for more visits to the dermatologist than any other skin disease.

A basic theme that runs throughout the nine papers is the importance of the four principles of treating acne, proposed many years ago by Kligman and myself. These include correcting the altered pattern of keratinization, the inhibition of *Propionibacterium acnes* and the production of extra-cellular pro-inflammatory products, the inhibition of sebum, and producing an anti-inflammatory effect. Almost all of the therapeutic approaches summarized in the presentations are related to these principles, and as is often mentioned, while we have made tremendous strides and are eminently successful in the management of acne, we cannot rest on our laurels. The management of acne will change in the future, and indications of this are contained in the papers.



I will not comment on all the aspects of these papers, nor can I predict the future with any certainty. Nonetheless, I want to emphasize three points. First of all, we must now reassess antibiotic care for acne. Antibiotics have been a cornerstone of our care, as pointed out by Eady and co-authors. However, the development of *P. acnes* resistance to the macrolides, and to a lesser degree the tetracyclines, has to dictate changes in our practice. We should limit the use of antibiotics to the treatment of the acute

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John Strauss, MD
12 Brickwood Circle NE
Iowa City, IA 52240 (USA)
Tel. +1 319 351 6655, Fax +1 319 356 6366

inflammatory phase of acne, probably curb the use of sub-optimal doses of antibiotics, limit the use of oral erythromycin for acne to those in whom tetracyclines are contraindicated (such as children under 8 years of age and pregnant or nursing mothers), and combine topical antibiotics with benzoyl peroxide. The use of benzoyl peroxide should prevent the emergence of resistance strains of *P. acnes*.

My second point relates to the report by Toyoda and Morohashi, who have found immunoreactive nerve fibers containing substance P in close apposition to the sebaceous glands, and have also found the expression of neural endopeptidases in the germinative cells of the sebaceous glands of those with acne. These authors have also found an increase in the nerve fibers around the sebaceous glands in acne patients. These findings have great potential importance in understanding the control of the sebaceous gland stimulation, as well as inflammation. This may be the basis for a whole new group of therapeutic agents.

My last comment relates to future developments as mentioned throughout most of the papers. I want to emphasize in particular the concepts mentioned by Zouboulis and Piquero-Martin, as well as Thiboutot and Chen. Their concepts of the control of the sebaceous glands are leading us to consider the roles of leukotrienes, transcription factors, insulin-sensitizing agents, peroxisome proliferator-activated receptors (PPAR), 5 α -reductase, antisense oligonucleotides and Toll-like receptors, just to mention a few new substances that may be found to be the key regulating agents for the sebaceous glands. Within this group may be the future controlling mechanism for the sebaceous glands and acne.

We are in an exciting molecular biology era, both in terms of mechanisms as well as potential therapies. It is interesting to think about the topics which will be discussed at the next World Congress of Dermatology in 2007, and, in particular, to follow the development of the concepts put forth during the 2002 symposium, as described in these proceedings.

Epidemiology of Acne

Brigitte Dreno^a Florence Poli^b

^aDepartment of Dermatology, Hospital Hotel Dieu, Nantes, and ^bDepartment of Dermatology, Hospital Henri Mondor, Créteil, France

Acne vulgaris is a distressing condition related to the pilo sebaceous follicle and which is considered as an 'adolescent' disorder. It is characterized by spontaneous resolution in the late teens or early twenties in the majority of cases.

The first publication about the epidemiology of acne was in 1931 by Bloch [1]. Already at this time, the onset of acne was noted slightly earlier in girls (12.1 ± 1.5) compared to boys (12.8 ± 1.7 years), retentional lesions being the earliest lesions (13% at 6 years and 32% at 7 years of age).

Since this publication, no significant evolution has been noted concerning the age of onset of acne. According to different studies of the literature performed in different countries in the world, the mean onset of acne is 11 years in girls and 12 years in boys, remaining earlier in girls (1 or 2 years) with mainly retentional lesions (open and closed comedones). However, adult acne has also been described recently.

Adolescent Acne

Prevalence

The evaluation of the prevalence of adolescent acne is submitted to important variations directly related to the definition of 'acne' used in different studies, which is very variable. Indeed, in some studies one closed or opened

comedone is sufficient to consider the subject as a 'patient with acne' and in other studies such as the Daniel study [2], more than 20 inflammatory and retentional lesions were necessary to consider the subject as having acne. Thus, in Bloch's study [1], realized among 4,191 subjects and in which one comedone was sufficient to classify the patient as having acne, the prevalence of acne was 68.5% in boys and 59.6% in girls. On the contrary, in Daniel's study [2], performed in 914 patients, only 27.9% of the boys and 20.8% of the girls had acne lesions. Review of different studies in the literature shows a mean prevalence of between 70 and 87% without significant differences according to country.

Main Factors Influencing the Frequency of Adolescent Acne

Two main factors have to be considered:

Age

The frequency of acne in the population increases with age. Thus, among 409 patients (munroe-Ashman) only 22% of subjects had acne lesions at 13 years compared with 68% at 16 years of age.

Sex

Combined with age, gender is an important factor modulating the frequency of acne lesions. Thus, Rade-maker et al. [3] have shown that among the girls 61% had

acne lesions at 12 years and 83% at 16 years with a maximum between 15 and 17 years. Among the boys, the prevalence of acne was only 40% at 12 years but increased to 95% at 16 years with a maximum of frequency between 17 and 19 years.

Prognostic Factors in Adolescent Acne

Two main factors have to be considered:

Genetic

Previous history of acne in the family and more specifically in the father or mother increases the risk of acne in children. Thus, in an epidemiological study performed in French schools [2] among 913 adolescents between 11 and 18 years of age, in the group of acne patients, history of acne in the father was noted in 16 vs. 8% in the group without acne lesions. In a similar manner, a history of acne lesions in the mother was noted in 25% of subjects in the acne group vs. 14% in the group without acne lesions, and finally 68% of brothers or sisters had acne in the acne group vs. 57% in the group without acne lesions. Moreover, family history of acne lesions in the father and mother is more often associated with severe acne or acne that responds less to acne treatment with agents such as cyclines [4].

Early Onset of Acne Lesions

Acne lesions beginning before puberty increases the risk of severe acne and often isotretinoin is necessary to obtain control of the acne lesions. At the beginning, retentional lesions are predominant [5].

Other Factors Known to Influence Acne

Cigarette Smoking

A recent study indicates that acne is more frequent in smokers [6]. This work has been performed among 891 citizens in Hamburg (age 1–87 years; median: 42). The maximum frequency of acne lesions was noted between 14 and 29 years. 24.2% of the population were active smokers and among them 40.8% had acne lesions. 25% were ex-smokers and among them 23.5% had acne lesions, and finally among the 50.8% of non-smokers acne lesions were identified in only 23.5%. The maximum risk of acne is obtained by the association of three factors: active smoker + male + young subject.

Skin Color

An evaluation of the difference in acne according to skin color has been performed at the Skin Color Center in New York. This study has been performed among 313

patients with acne vulgaris [7]. Thus, the mean age of acne onset appears lower in Hispanic (15.9 years old) compared to Black (20.3 years old) and Asian (18.9 years old) subjects. The frequency of acne at teenage is the highest in Hispanic (79.2%) and similar in Black (59.9%) and Asian (63.2%) groups. Scarring is clearly more frequent in Hispanics (21.8%), remaining low in Blacks (5.9%) with an intermediate frequency in Asians (10.5%). The results are similar concerning severe acne with nodular and cystic lesions: Hispanic 25.5%, Black 18%, Asian 10.5%.

Oral Contraceptives

A recent study performed in Sweden [8] described the prevalence rate of acne among adolescents with allergic disease and studied the possible influence of oral contraceptives and tobacco smoking on disease prevalence. Among 186 subjects (15–22 years old) the prevalence of acne was 40.5% for males and 23.8% for females. The use of oral contraceptives was associated with a significantly lower prevalence of acne (yes 14.8%, no 32%; $p = 0.038$). However, in this study an increase of acne related to smoking is not found as in the previous study [6].

In summary, the frequency of adolescent acne in the population appears essentially dependent on age and to a minor degree on sex and skin color. An early onset of lesions and the notion of familial acne are two factors of bad prognosis.

Facial Acne in Adults

There are few studies about the prevalence and specificities of facial acne in the adult population. Several studies have been reported recently:

In England [9], 749 employees of a hospital, a university and a large manufacturing firm in Leeds, older than 25 years, were examined. Facial acne was recorded in 231 women and 130 men giving an overall prevalence of 54% in women and 40% in men. It was mainly 'physiological acne' but clinical acne (grade >0.75 on the Leeds scale) was recorded in 12% of the women and 3% of the men. Only 1% of the subjects with clinical acne had sought treatment. The majority believed that there was no effective therapy for acne.

In Australia [10], 1,457 subjects from central Victoria aged ≥ 20 years were examined. The prevalence of acne was 12.8% (13.6% for women and 11.8% for men). There was a clear decrease with age from 42% in the age group 20–29 years to 1.4% in the 60–69 age group. Acne was classified as mild in 81.2%, moderate in 17% and severe

in 1.8%. Less than 20% were using a treatment on the advice of a medical practitioner.

Two recent studies have demonstrated some specific features of acne in adult women:

– A postal survey was sent to 173 adult pre-menopausal women treated for acne between 1988 and 1996 in the USA [11]. 91 (52%) answered; all of them had received spironolactone at some point during the course of their treatment. The mean duration of acne was 20.4 years. Acne was reported to be persistent in 80% of the women and 58% of them had an ongoing need for treatment. In this selected population, acne in adult women was particularly persistent and desperately recurring.

– Another survey investigated the effect of the menstrual cycle on acne [12] in 400 women aged 12–52 years: 44% had premenstrual flare. Women older than 33 years had a 53% rate of premenstrual flare. The above-mentioned study [11] noted a premenstrual flare in 83% of the adult women with acne.

We have conducted an epidemiological study of acne in adult females in France [13]. A self-administered questionnaire was sent to 4,000 adult women aged 25–40 years representative of the French population. Three dermatologists validated the questionnaire. A definition of acne severity, according to questionnaire answers was established before the questionnaire was sent out: ‘clinical acne’ was defined as ≥ 5 pustules or papulonodules on the face at the date of the questionnaire or during the previous 3 months. ‘Physiological acne’ was defined as 1–4 papulonodules or pustules at the date of the questionnaire or during the previous 3 months.

A total of 3,394 women completed the questionnaire of which 3,305 were useable. Prevalence of acne was 41% in adult women. In 17% of the cases, it was ‘clinical acne’ – with 6.2 inflammatory lesions as a mean – and in 24% ‘physiological acne’ – with 1.3 inflammatory acne lesions as a mean. 97% and 94%, respectively, admitted that they used to scratch or squeeze their ‘pimples’. 49% of women with ‘clinical acne’ had acne sequelae, i.e. scars and/or pigmented macules. 34% of women with ‘clinical acne’ had not experienced acne during their adolescence. A premenstrual flare was recorded in 78% of women with ‘clinical acne’. The adult females with acne reported a significantly more oily or mixed type than the non-acne group, sensitive skin was slightly more prevalent in the acne (71%) and physiologic acne group (68%) than in the non-acne group (64%). The sensitivity of the skin to sun was no different among the 3 groups. Smoking, stressful lifestyle and professional occupation were not different among the three groups. Some differences were recorded

between the acne group and the non-acne group for poor sleep (35/32%), drug intake, especially benzodiazepine (10/8%), and daily skin make-up usage (16/13%). The quality of life assessed by a self-administered French translation of the DLQI was moderately impaired and more in the ‘clinical acne’ group.

Only 22% of women with ‘clinical acne’ were on medical therapy at the date of the survey versus 11% of women with ‘physiological acne’.

This study confirms that acne in the adult female is more frequent than currently accepted. A high percentage starts during adulthood without any acne during adolescence. Scars are frequent. In all studies, few adult females had sought out medical treatment. The reasons varied: they were not bothered by their acne; they thought that their acne would clear spontaneously, or they believed that there was no effective therapy. In our study, among women in the acne group who received some form of medical treatment, one third were taking oral medication. Topical treatment is often irritating. Our study shows that women with acne had sensitive skin. The management of acne in the adult female is difficult. Oral therapies are not very effective and the acne is desperately recurring. Topical therapy is not well tolerated.

Men seem to be less frequently concerned in all studies.

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Comedogenesis: Some Aetiological, Clinical and Therapeutic Strategies

W.J. Cunliffe D.B. Holland S.M. Clark G.I. Stables

Department of Dermatology, General Infirmary, Leeds, UK

Key Words

Comedogenesis · Hypercornification · Retinoids · Gentle cautery

Abstract

Hypercornification is an early feature of acne and usually precedes inflammation. It is associated with ductal hyperproliferation, and there are many controlling factors such as androgens, retinoids, sebum composition and cytokines. Cycling of normal follicles and of comedones may explain the natural resolution of comedones and, in the longer term, resolution of the disease itself. There is a need to tailor treatment according to comedonal type. Suboptimal therapy can often result from inappropriate assessments of comedones, especially microcomedones, sandpaper comedones, submarine comedones and macrocomedones. Macrocomedones can produce devastating acne flares, particularly if patients are inappropriately prescribed oral isotretinoin. Gentle cautery under topical local anaesthesia is a useful therapy in the treatment of such lesions. The newer retinoids and new formulations of all-*trans*-retinoic acid show a better benefit/risk ratio.

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The purpose of this review is to discuss comedogenesis, which is one of the four major aetiological factors of acne [1]; the other three important aetiological factors are seborrhoea [2], colonization of the duct with *Propionibacterium acnes* [3] and production of inflammation [4]. This review will discuss the aetiology of comedones, some new as well as the more commonly recognised clinical entities and their therapeutic modification.

Aetiology of Comedogenesis

Comedogenesis is due to the accumulation of corneocytes in the pilosebaceous duct [5]. This could be due to hyperproliferation of ductal keratinocytes, inadequate separation of the ductal corneocytes or a combination of both factors [6]. There is reasonable evidence to support the hyperproliferation of ductal keratinocytes [7]. This has been demonstrated immunohistochemically using a monoclonal antibody to Ki67, a nuclear marker expressed by actively cycling cells, which labels increased numbers of basal keratinocytes of the follicle wall of both comedones and microcomedones compared with normal control follicles (fig. 1) [7]. Similarly, suprabasal immunolabelling of keratin 16 (K16), a phenotypic marker of hyperproliferating and abnormally differentiating keratinocytes, is found in ductal keratinocytes of acne lesions (fig. 2) [8]. These data are further supported by the finding, using in situ hybridization, that transcripts of K6, the

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Prof. William J. Cunliffe
Department of Dermatology, General Infirmary at Leeds
Great George Street
Leeds LS1 3EX (UK)
Tel. +44 113 392 36 05, Fax +44 113 234 11 54, E-Mail Mail.Cunliffe@virgin.net.uk

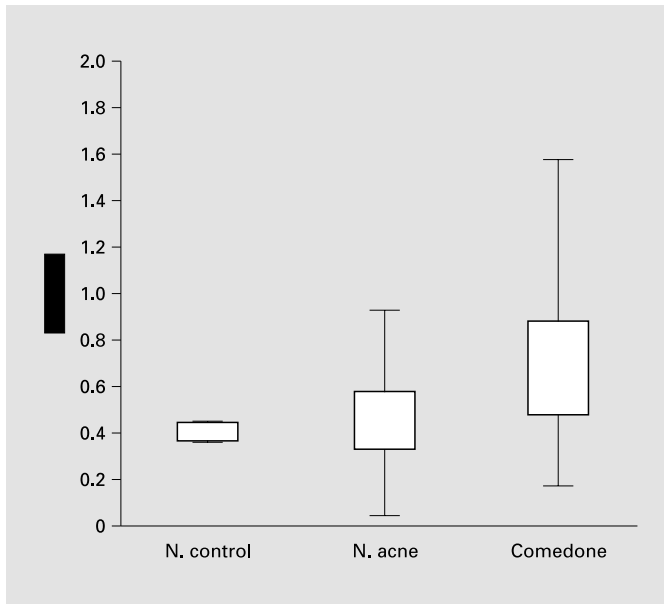


Fig. 1. Ductal keratinocytes exhibit evidence of hyperproliferation in contrast to control samples. The figure also shows that the so-called normal skin of acne patients – in an acne-prone area – evidences some ductal hyperproliferation.

expression partner of K16, are also found suprabasally in the follicle wall of microcomedones and comedones but not in control follicles [9]. In addition, our data also show that some of the so-called normal follicles of acne-prone skin may also show overexpression of Ki67 and K16. This suggests that topical therapy should be applied not just to the lesions, but also to the acne-prone areas. Limited data show no primary abnormality of ductal desmosomes [10].

Several factors may explain ductal hypercornification. There is evidence that abnormalities of the sebaceous lipids such as increased free fatty acids [11], squalene and squalene oxide [12] as well as a decrease in sebaceous linoleic acid [13] could all trigger hypercornification. The data incriminating fatty acids, squalene and squalene oxide emanate from studies on rabbits' ears. The relevance of this to humans is questionable, particularly as the rabbit ear model is overpredictive for humans [14]. Sebaceous linoleic acid has been shown to be reduced in comedones. Linoleic acid is an essential fatty acid. Animals deficient in linoleic acid become scaly. A comedo is due to the accumulation of much scale in the pilosebaceous

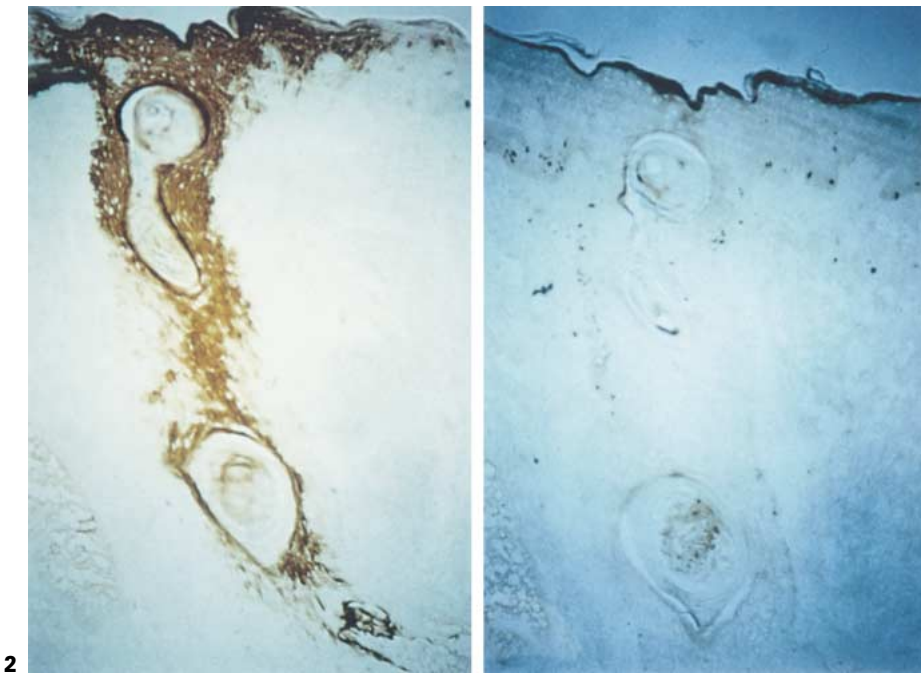


Fig. 2. The technique of in situ hybridization demonstrates (on the left) an increased expression of K16 (a marker of hyperproliferation) in contrast to normal skin (on the right) which shows virtually no such expression.

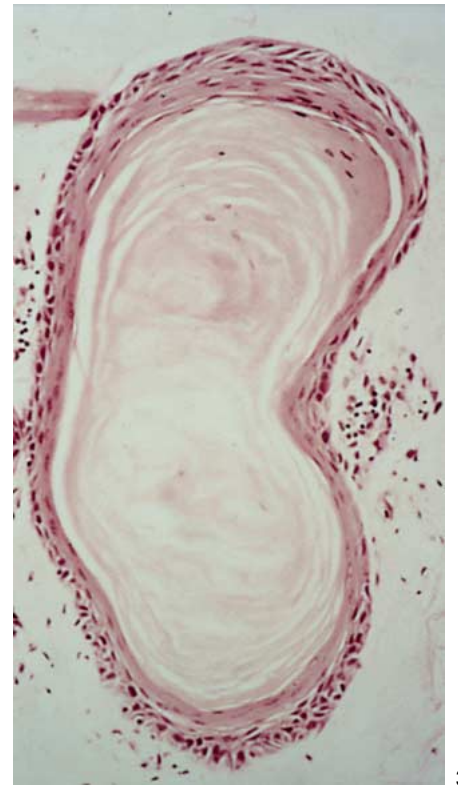


Fig. 3. Comedone formation (in vitro) as a consequence of adding IL-1 α to cultured ductal keratinocytes (with kind permission of Dr. T. Kealey).

aceous duct. Androgens may have an important part in comedogenesis. 5 α -Reductase (type 1) is present in the infrainfundibulum part of the duct as well as in the sebaceous gland [14]. The possible androgen-controlling effect is mirrored by a reduction in the number of comedones when a patient is prescribed anti-androgen therapy such as the oral contraceptive pill Dianette[®] [15].

Retinoids, both oral and topical, will suppress comedogenesis [16–18]. After 2 months of therapy, many topical retinoids will suppress comedones by 30% whereas oral isotretinoin suppresses comedones by 52% and at 4 months of therapy, the suppression is about 80%. Cytokines are likely to be important [19, 20] (fig. 3). Kealey, like others, is able to maintain the pilosebaceous duct in culture. Comedones are produced in such a system under the influence of interleukin (IL) 1 α (fig. 3), and this process can be inhibited by adding IL-1 receptor antagonist to the growth medium.

From our own laboratories we have data to suggest that the comedo cycling could be important in comedogenesis and its resolution. As part of our research we realised that similar-looking pilosebaceous follicles and comedones showed different expressions of cycling cells (using Ki67) and proliferation markers (using K16). This led us to the concept that the duct may also undergo cycling just like the hair follicles [21]. Such cycling may explain why many blackheads and whiteheads disappear without treatment. If this were not to occur, then an adolescent developing acne, especially comedonal acne, early in his/her teens would, by the late teens, have no healthy skin on the acne-affected site: it would be a mass of comedones. A cycling phenomenon is probably not an unreasonable hypothesis given the close proximity of the hair follicle and pilosebaceous duct.

Physicians are well aware that antimicrobial therapy which may also have a direct anti-inflammatory role significantly reduces comedones. One explanation for this has been its effect in reducing the ductal *P. acnes*, which in turn results in a reduction in free fatty acids – some of which may be comedogenic. More recently we have shown that biopsies of normal-looking skin from an area prone to acne exhibit, compared to control skin, a significant increase in a variety of inflammatory cells, in particular lymphocytes [Jeremy, unpubl. observations 2002] Such biopsies show no evidence of comedone formation and no evidence of hyperproliferation using Ki67 as a marker for hyperproliferation. By analogy with psoriasis, could this lymphocytic infiltrate trigger comedone formation?

Comedonal Types

The clinical type of comedo could, and perhaps should, influence the treatment prescribed.

Microcomedones

Biopsy sections of normal-looking skin in an acne-prone individual with comedonal acne will frequently (28%) show histological features of microcomedones. Biopsies of papules taken at up to 72 h of development will reveal a microcomedone in 52% of subjects, a whitehead in 22% and a blackhead in 10% [22], confirming even further the practical need to apply topical therapies to apparently non-involved skin.

Ordinary Comedones

Dermatologists recognise the typical pattern of comedones seen in clinical practice, and so this requires no further explanation.

Missed Comedones

In all patients, it is essential to stretch the skin, using a good light, at a shallow angle, otherwise even ordinary comedones will not be recognised. Stretching of the skin will demonstrate, in about 20% of patients, comedones which would otherwise not be seen, and thus prevent the prescription of inappropriate topical therapy. Our treatment protocols for ordinary, missed and microcomedones are similar. The topical treatment must be applied not just to the lesions, but also to the adjacent subclinically ‘normal’ skin. Physical methods of therapy such as blackhead removers are worthy of consideration in a small number of patients with obvious blackheads. Topical retinoids are the most effective topical therapy [16–18, 23–25].

Sandpaper Comedones

Patients with these comedones represent a difficult subgroup who present with predominantly very small, almost confluent closed comedones giving the feel of ‘sandpaper’ which may become inflamed. They are particularly seen on the forehead and are difficult to treat. On the whole, they show little or varied response to oral antibiotics and topical retinoids, and the optimum treatment is oral isotretinoin at a preferred dosage of 0.5 mg/kg/day.

Submarine Comedones

These are also easily missed (fig. 4), and therefore there is a need to stretch the skin. They infrequently present as a focus of continued inflammation. They are



Fig. 4. Submarine comedones.

Fig. 5. Macrocomedones.

surprisingly quite large and may reach a size of up to 1 cm. Treatment is difficult, and the optimum therapy is probably focal cauterization using a technique described later in this review for the treatment of macrocomedones, which allows the drainage of retained corneocytes. Such a technique is successful in about 50% of submarine comedones.

Macrocomedones

This term refers to blackheads and whiteheads which are >1 mm in size. Whiteheads are the most common. They need to be treated for two reasons. They are a cosmetic problem and may flare into inflamed lesions (fig. 5), especially in patients treated with oral isotretinoin. In such patients, they are the major reason for a severe flare of the acne and surprisingly are easily missed unless adequate lighting and examination techniques, i.e. stretching the skin, are used. The optimum therapy is gentle cauterization using an anaesthetic cream such as EMLA[®] which is applied for 60–75 min under an occlusive dressing such as Tegaderm[®]. The area is then lightly touched with a small hot-wire cauterization probe, the tip being grey in colour rather than vividly red and red-hot. The purpose is not to burn the skin significantly but to produce low-grade, localised thermal damage. This therapy is far superior to topical retinoids: at 2 weeks of treatment using light cauterization there

is typically virtually 100% clearance compared with topical retinoids which produce a reduction in the order of <10% [28]. Not all patients respond perfectly. A test area is always treated initially, and thereafter the remaining lesions are treated in further sessions. Five percent develop recurrent lesions requiring multiple treatments with gentle cauterization. Scarring and pigmentary changes are uncommon. If the patient has macrocomedones and is on oral isotretinoin and the acne flares, it is necessary to stop the oral isotretinoin, consider giving oral steroids and treat the macrocomedones. Macrocomedones are also a cause of a slow and poor response to oral isotretinoin therapy [29].

Drug-Induced Comedones

These may be due to corticosteroids [29, 30] or anabolic steroids [31, 32] and 'blue comedones' can occur, albeit very infrequently, due to minocycline-induced pigmentation. Treatment of drug-induced comedones is by removal of the cause and by treating with either topical retinoids or gentle cauterization.

Pomade Comedones

This is a clinical event seen particularly in Afro-Caribbeans who apply hair preparations to defrizz their hair. Many whiteheads (fig. 6) are frequently seen, and these may evolve into inflammatory lesions. Treatment in-

cludes stopping the hair preparations, topical retinoids and possibly oral antibiotics.

Chloracne

This is also characterised by many comedones [33–36]. Indeed, comedonal acne is a hallmark of this disease (fig. 7), and inflammatory lesions are less frequent. Inflamed lesions may be treated with oral or topical benzoyl peroxide or antibiotics. Gentle cautery is very successful; there is usually a poor response to topical and oral retinoids [27].

Naevoid Comedones

These are rare and may present before puberty but more often at and around puberty [37, 38]. The lesions may be typical confluent comedones (fig. 8) or whiteheads, usually occurring asymmetrically. They may be localised or, in some unfortunate individuals, extremely extensive. Treatment is difficult. Response to oral and topical retinoids is unsatisfactory. Physical methods are also unsatisfactory, but gentle cautery, excision of locally affected areas and carbon dioxide laser therapy can be tried; however, as yet there seems to be no satisfactory solution for the majority of patients.

Conglobate Comedones

Patients with conglobate comedones are predominantly males with extensive truncal acne characterised by severe nodular inflammation and scarring. A hallmark of the disease is grouped comedones [40, 41], particularly on the posterior neck and upper trunk. The comedones may be blackheads, whiteheads or both. This is a really difficult subgroup to treat. There are no satisfactory data to demonstrate which is the preferred way of treating such comedones.

New Topical Retinoids

New topical anti-acne therapies are required for several reasons. There is no topical anti-acne therapy which reduces lesions by over 60% in contrast to, for example, oral isotretinoin which can suppress lesions by 100%. This may simply be a measure of penetration of the drug. Most topical therapies frequently produce an irritant dermatitis, and this will reduce compliance. Many antibiotics have been shown to produce resistant *P. acnes*, and this is associated in some patients with clinical failure. New retinoid molecules such as adapalene [17, 18] have been developed, while old retinoids have been redeveloped



6



7



8

Fig. 6. Pomade acne.

Fig. 7. Chloracne.

Fig. 8. Naevoid acne.

using new vehicle delivery systems [42, 43]. It is not the intention of this review to discuss the pros and cons of such therapies, except to say that some newer drugs and new formulations of older therapies tend to show a better benefit/risk ratio.

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New Aspects in Acne Inflammation

Masahiko Toyoda Masaaki Morohashi

Department of Dermatology, Faculty of Medicine, Toyama Medical and Pharmaceutical University, Toyama, Japan

Key Words

Acne · Neuropeptides · Substance P · Neutral endopeptidase · Nerve growth factor · Sebaceous glands · Stem cell factor · Mast cells · Nerves

Abstract

There is ample clinical evidence suggesting that the nervous system such as emotional stress can influence the course of acne. We examined possible participation of cutaneous neurogenic factors including neuropeptides, neuropeptide-degrading enzymes and neurotrophic factors, in association with inflammation in the pathogenesis of acne. Immunohistochemical studies revealed that substance P (SP)-immunoreactive nerve fibers were in close apposition to the sebaceous glands, and that neutral endopeptidase (NEP) was expressed in the germinative cells of the sebaceous glands in the skin from acne patients. Nerve growth factor showed immunoreactivity only within the germinative cells. In addition, an increase in the number of mast cells and a strong expression of endothelial leukocyte adhesion molecule-1 on the post-capillary venules were observed in adjacent areas to the sebaceous glands. In vitro, the levels and the expression of stem cell factor by fibroblasts were upregulated by SP. When organ-cultured normal skin specimens were exposed to SP, we observed significant increases in the sizes of the sebaceous glands and in the number of sebum vacuoles in sebaceous cells. Furthermore, supplementation of SP to organ-cultured skin induced expression of NEP, and we demonstrated the subcellular

localization of NEP in the endoplasmic reticulum and the Golgi apparatus within the sebaceous germinative cells using preembedding immunoelectron microscopy. These findings suggest that SP may stimulate lipogenesis of the sebaceous glands which may be followed by proliferation of *Propionibacterium acnes*, and may yield a potent influence on the sebaceous glands by provocation of inflammatory reactions via mast cells. Thus, cutaneous neurogenic factors should contribute to onset and/or exacerbation of acne inflammation.

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Acne vulgaris is a skin disorder of the sebaceous follicles that commonly occurs in adolescence and young adulthood. Many lines of clinical evidence suggest that components of the nervous system, such as psychological and neurogenic factors, can influence the course of acne [1–3]. The disease has been reported to be initiated and/or exacerbated as a result of emotional or psychosocial stress. However, the nature of the association between stress and acne remains unclear, due in part to a lack of substantial evidence regarding the participation of cutaneous neurogenic factors in the pathogenesis of acne.

Cutaneous Innervation and Neuropeptides

The skin is innervated by primary afferent sensory nerves, postganglionic cholinergic parasympathetic nerves and postganglionic adrenergic and cholinergic

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M. Toyoda, MD
Department of Dermatology, Faculty of Medicine
Toyama Medical and Pharmaceutical University
2630 Sugitani, Toyama 930-0194 (Japan)
Tel. +81 76 434 7305, Fax +81 76 434 5028, E-Mail toyodam@toyama-mpu.ac.jp

sympathetic nerves. The cutaneous sensory nervous system comprises a network of fine C fibers within the skin that innervate multiple cell types and play an important role of in inflammation [4, 5]. Various stimuli may directly activate peripheral nerve endings of primary sensory neurons and impulses are conveyed centrally as well as, through antidromic axon reflexes, peripherally. Upon release of neuropeptides (NPs) from sensory terminals, important visceromotor inflammation and trophic effects occur in the peripheral tissues. This proinflammatory NPs release causes the set of changes collectively referred to as neurogenic inflammation [6–8].

Neuropeptides can manifest immunomodulatory activity, and they contribute to the cross-talk between the nervous system and the immune system in the skin [8–10]. NPs are a heterogeneous group of several hundred biologically active peptides, present in neurons of both the central and the peripheral nervous system and involved the transmission of signals not only between nerve cells, but also with the immune system where they appear to be critical mediators of different processes. Normal human skin expresses a variety of NPs that are either directly derived from sensory neurons or from skin cells such as keratinocytes. In addition, immune cells that either constitutively resides in the skin such as mast cells (MCs) or infiltrating cells into the skin under inflammatory conditions have been reported to produce NPs [8]. Clinical evidence in support of a connection between neuropeptide secretion and the development of inflammation is found in various skin diseases such as atopic dermatitis, psoriasis and alopecia areata, which are commonly exacerbated during periods of emotional stress [9–15]. Indeed, stress has been shown to elicit the release of substance P (SP) [8], a neuropeptide belonging to the tachykinin family, which can induce neurogenic inflammation. Clinical evidence in support of a connection between neuropeptide secretion and the development of inflammation is found in various skin diseases such as atopic dermatitis, psoriasis and alopecia areata which are commonly exacerbated during periods of emotional stress [10–16]. Indeed, stress has been shown to elicit the release of SP [17], a neuropeptide belonging to the tachykinins family, which can induce neurogenic inflammation. SP is associated with multiple cellular responses, including vasodilatation, increased blood flow, plasma extravasations, mast cell degranulation, the wheal and flare reaction via axon reflex, neutrophil and macrophage activation, modulation of the release of proinflammatory cytokines and chemokines, and the upregulation of adhesion molecule expression required for trafficking of leukocytes [11, 12, 18].

Nevertheless, none of those previous studies addressed the effects of SP on the sebaceous glands or on the disease process of acne.

SP-Containing Nerves in Acne

Nerve fibers showing immunoreactivity for SP were rarely observed in skin specimens from the face devoid of acne lesions in healthy subjects. On the other hand, specimens from acne patients showed a strong immunoreactivity for SP with many fine nerve fibers around the sebaceous glands. Some of them were invading into the sebaceous glands and were located in close apposition to the sebocytes [19].

Effects of SP on the Sebaceous Glands

To examine whether cutaneous neurogenic factors affect the morphology of sebaceous glands, we used electron microscopy to observe alterations of the sebaceous glands in organ culture by several kinds of NPs and nerve growth factor (NGF), the best-characterized member of the neurotrophin family [20]. The ultrastructure of the sebaceous glands with medium alone was identical to that of intact sebaceous glands. From the exterior aspect to the interior, the sebaceous glands consisted of the germinative, the undifferentiated and the differentiated sebaceous cell layers. The sebaceous glands stimulated with SP showed that most sebaceous cells contained numerous lipid droplets even in the peripheral area of the glands. These observations indicate that SP may accelerate lipogenesis. There were numerous free ribosomes and mitochondria, followed by densely packed smooth-surface membranes of the endoplasmic reticulum in sebocytes, suggesting the active phase of lipid synthesis. Morphometric analysis revealed that of all the agents tested, only SP induced significant increases in the area of the sebaceous glands as well as in the size of individual sebaceous cells. Furthermore, SP significantly increases the number of sebum vacuoles per each differentiated sebaceous cell at the electron-microscopic level. The number of sebum vacuoles induced by SP increased in a dose-dependent manner when various concentrations of SP were added to the culture medium [21]. These findings suggest that SP may stimulate the proliferation as well as the differentiation of sebaceous glands, and, further, that it upregulates lipogenesis in sebaceous cells. It has been reported that the effects of immobilization-induced stress on the plasma levels of

testosterone and lipogenesis were examined in sebaceous glands of Syrian hamsters, and demonstrated that immobilization-induced stress lowered the levels of testosterone in plasma as well as in the skin, which resulted in decreased lipogenesis in the skin [22]. Although these data suggest that psychological or physiological stress can influence sebaceous gland function by inducing changes in the neuroendocrine system, they provide no appropriate explanation for the effects of stress-induced exacerbation of acne. Taking into account that stress can elicit SP release from peripheral nerves [17], it is tempting to speculate that SP should be partially involved in stress-induced exacerbation of the disease.

Neutral Endopeptidase in the Sebaceous Glands in Acne

Tissue responsiveness to NPs depends on the presence of specific receptors and on the distribution of neuropeptide-degrading enzymes which play essential roles in the removal of NPs from the extracellular environment and are thus important regulators in neurogenic inflammation. Recent studies indicate that neutral endopeptidase (NEP; EC 3.4.24.11; enkephalinase), a zinc metallo-protease, is a cell surface enzyme and has the potential to degrade several NPs such as SP, and thereby terminates their biologic actions [5]. NEP is localized in keratinocytes, vascular endothelial cells, fibroblasts, the outer root sheath of hair follicles and mast cells in the skin [23, 24]. Administration of NEP inhibitors magnifies the proinflammatory effects of SP and other tachykinins in several tissues [25]. Thus, upregulation of NEP is a potential mechanism of limiting proinflammatory effects of NEP-degradable NPs, notably SP, by reducing the amounts of bioactive NPs.

Immunohistochemical staining for NEP in normal facial skin was negative within the sebaceous glands. On the other hand, NEP was highly expressed in the sebaceous glands of acne patients in which immunoreactivity for NEP in the sebaceous glands were restricted to the germinative cells. There was a statistically significant difference in the percentage of NEP-positive sebaceous acini to all acini between acne patients and controls [26]. We next examined effects of SP on NEP expression in the sebaceous glands using organ-cultured skin *in vitro*. Although normal facial skin specimens supplemented with medium alone showed no expression of NEP in sebaceous cells, skin specimens stimulated with SP revealed prominent NEP staining in the germinative cells of the sebaceous

acini, which appeared to be analogous to the staining pattern of the sebaceous glands in acne patients. In addition, SP induced NEP expression in sebaceous glands in a dose-dependent manner [26]. Taking into account the lack of NEP expression in tissue not stimulated with SP, sebaceous germinative cells may begin to synthesize NEP following stimulation by SP. To examine the subcellular localization of NEP in sebaceous cells more precisely, we performed ultrastructural immunocytochemistry using an indirect immunoperoxidase technique. NEP expression was restricted to the Golgi apparatus and the endoplasmic reticulum within sebaceous germinative cells [26], which indicates that NEP is synthesized through the pathway of protein synthesis in the usual fashion.

Innervation and Nerve Growth Factor in the Sebaceous Glands in Acne

It is generally accepted that sebaceous glands were not innervated and the peripheral nervous system has no effect on the sebaceous biology. Indeed, nerve fibers, as documented immunohistochemically using the general neuronal marker PGP 9.5, were rarely observed around the sebaceous glands in normal facial skin. In contrast, facial skin from acne patients shows numerous fine nerve fibers not only around but also within sebaceous acini [19]. Numerous nerve endings were also observed in close apposition to the sebaceous glands ultrastructurally. Such increase in the number of nerve fibers, some of which are even invading into sebaceous acini, may result from increased expression of NGF on the sebaceous glands of acne-prone facial skin since NGF is essential for the survival, development, differentiation and function of peripheral sympathetic and sensory neurons, and acts as a neurotrophic molecule stimulating the sprouting of nerve fibers also in the skin [20]. Immunohistochemical study revealed that the germinative cells of the sebaceous glands in acne patients highly expressed NGF, although no immunoreactivity for NGF was observed in normal sebaceous glands [19]. The precise mechanism of specific induction of NGF in the sebaceous glands of acne patients is unclear. Although we exposed normal skin specimens to SP in organ culture, the expression of NGF was not induced. There is a possibility that SP induces NGF expression in the sebaceous glands via some proinflammatory cytokines since SP is considered to modulate cytokine synthesis [4, 5, 8, 10]. Taking into account the increased number of degranulating MCs in close apposition to sebaceous glands of acne patients, we hypothesized

Fig. 1. Induction of NGF in the sebaceous glands by mast cell-derived mediators.

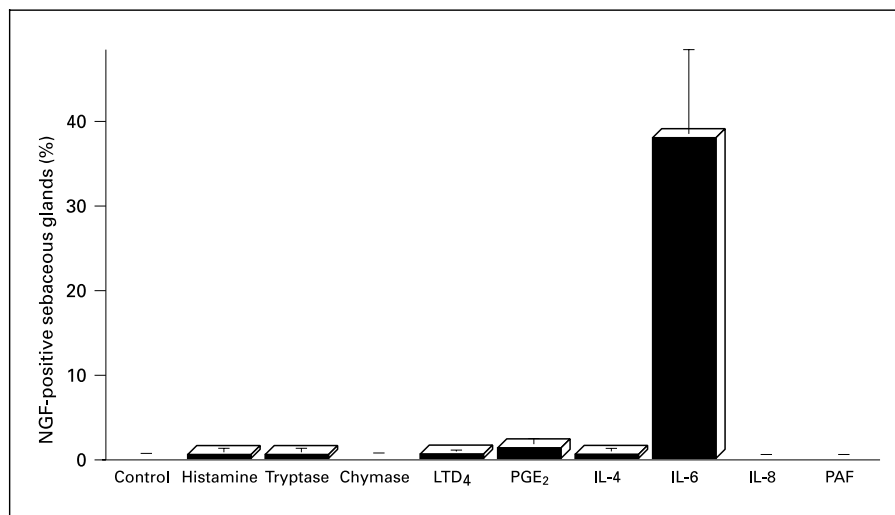
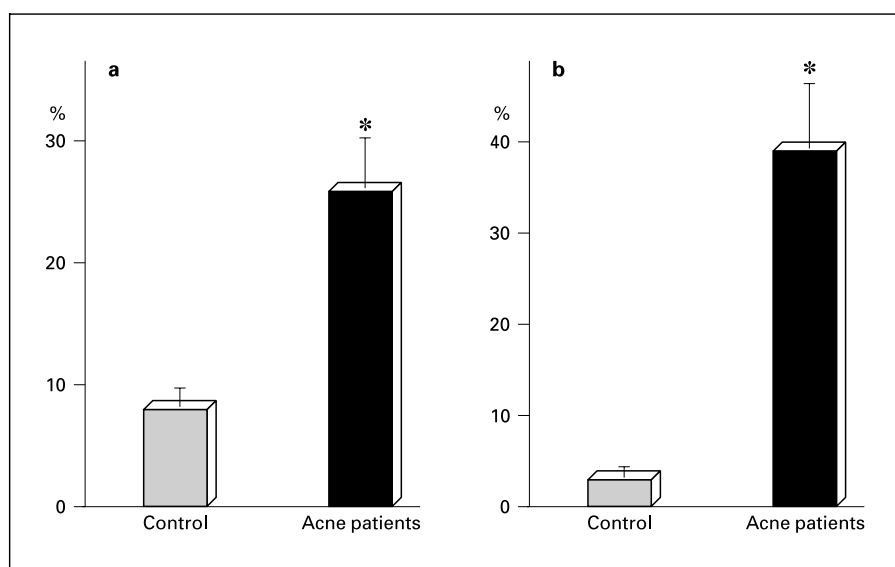


Fig. 2. IL-6 within MCs. There are statistically significant increases in the percentages of IL-6-immunoreactive MCs (a) and of IL-6-containing specific granules of MCs in facial skin of acne patients (n = 32) versus healthy volunteers (n = 35) as controls (b). * p < 0.01 compared with control (unpaired Student's t test).



that some MC-derived mediators may exert inducible activity of NGF in the sebaceous glands of acne patients. When organ-cultured normal skin was stimulated with various MC-derived mediators and cytokines including histamine, tryptase, chymase, leukotriene D₄, prostaglandin E₂, IL-4, IL-6, IL-8, TNF- α , IFN- γ and platelet-activating factor, IL-6 specifically induced expression of NGF in the sebaceous glands (fig. 1). Preincubation of explants with anti-IL-6 receptor, followed by exposure to IL-6, resulted in abrogation of NGF induction in the sebaceous glands. Immunohistochemical and immunoelectron microscopic studies revealed the presence of IL-6 within specific granules of MCs around the sebaceous glands in the skin of acne patients. The numbers of IL-

6-positive MCs and IL-6-containing MC granules were significantly increased in acne patients compared with the control (fig. 2). These findings suggest that MC-derived IL-6 has potential to induce NGF in sebaceous cells, which may result in promoting innervation within and around the sebaceous glands in acne patients.

NGF is also considered to be a primary candidate as a regulatory molecule in neuropeptidergic responses. Indeed, it has been shown that: (1) NGF is increased in nerves supplying inflamed skin; (2) injection of NGF in the skin reproduces the same neuronal peptidergic modification observed during experimental inflammation in rats, and (3) pretreatment with anti-NGF serum prevents the NP changes at a neuronal level [27]. It is therefore

tempting to speculate that NGF plays an important role in spontaneous inflammatory dermatoses, such as acne, by modulating NPs. There is increasing evidence that NGF, in addition to its actions within the nervous system, elicits a number of biologic effects on local and systemic cells of the immune-inflammatory compartment. In vivo, administration of NGF to neonatal rats increases the size and the number of mast cells in several peripheral tissues, and, in vitro, NGF induces mast cell degranulation and mediator release. NGF enhances survival, phagocytosis, and superoxide production of mature murine neutrophils, causes mediator release from basophils, stimulates T and B lymphocyte proliferation, and stimulates B-cell differentiation into immunoglobulin-secreting plasma cells [10, 20]. These data imply possible participation of NGF in the inflammatory process in the pathogenesis of acne.

Mast Cells in Acne Inflammation

Increasing attention has been directed towards interactions between components of the nervous system and multiple target cells of the immune system. Communication between nerves and MCs is a prototypic demonstration of such neuroimmune interactions. Several studies have demonstrated that MCs are often found in close contact with nerves and that there may be a functional interaction between mast cells and the nervous system [28]. In addition, recent evidence suggests that SP is an important mediator in intimate nerve-mast cell cross talk [29]. When organ-cultured normal facial skins were exposed to SP uniformly degranulated MCs adjacent the sebaceous glands were observed at the electron microscopic level. Venules around the sebaceous glands of specimens stimulated with SP showed expression of ELAM-1 on the endothelia after subsequent culture. Furthermore, preincubation of explants with the SP analogue or with cromolyn sodium, one of the MC inhibitors, abrogated the ability of SP to induce ELAM-1. These findings suggest that SP endogenously released by dermal nerve fibers may be important in the regulation of endothelial-leukocyte interaction via MCs. It has been demonstrated that the proinflammatory effect of ELAM-1 induction by MC degranulation products is inhibited by blocking antiserum to TNF- α . Thus, SP, contained within dermal nerve fibers, may represent a crucial initial mediator of a cascade of cellular events involving MC degranulation and release of proinflammatory cytokines such as TNF- α , with subsequent induction of adhesion molecules such as E-selectin on adjacent venular endothelia [30]. This would then

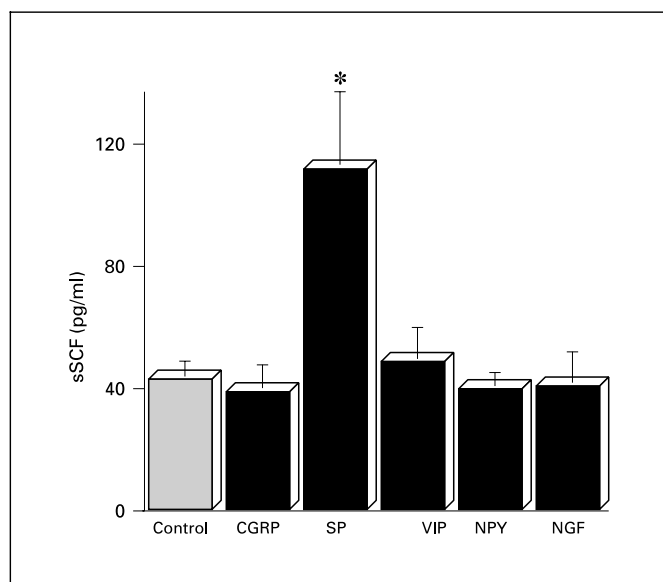


Fig. 3. Effects of neuropeptides and NGF on the levels of soluble SCF from cultured human fibroblasts. Cultured medium was collected 72 h after exposure to 100 ng/ml of each substance and then levels of soluble SCF were examined by ELISA. Means were obtained from triplicate cultures of four independent experiments. CGRP = Calcitonin gene-related peptide; VIP = vasoactive intestinal polypeptide; NPY = neuropeptides Y. * $p < 0.01$ compared with control (unpaired Student's *t* test).

facilitate the local accumulation of blood leukocytes during the inflammatory response. Immunohistochemical study demonstrated that most of venules around the sebaceous glands not in normal subjects but in acne patients expressed E-selectin (data not shown). We have recently found using immunoelectron-microscopic method that SP is localized within specific granules of human skin MCs [31]. In addition to cutaneous sensory nerves, MC-derived SP may also affect the morphologic and immunologic alterations associated with the sebaceous glands and may contribute to the development of the inflammatory events in acne.

The mechanisms of MC hyperplasia around the sebaceous glands in acne patients are unclear. The importance of stem cell factor (SCF), a potent fibroblast-derived MC growth factor, has been demonstrated using MC-deficient mutant mice [32]. SP upregulates the soluble form of SCF by human fibroblasts (fig. 3) in a dose-dependent manner (fig. 4) in monolayer culture, as measured by enzyme-linked immunosorbent assay. Expression of the membrane-bound form of SCF mRNA was detected by reverse transcriptase-PCR in cultured human fibroblasts. A pre-

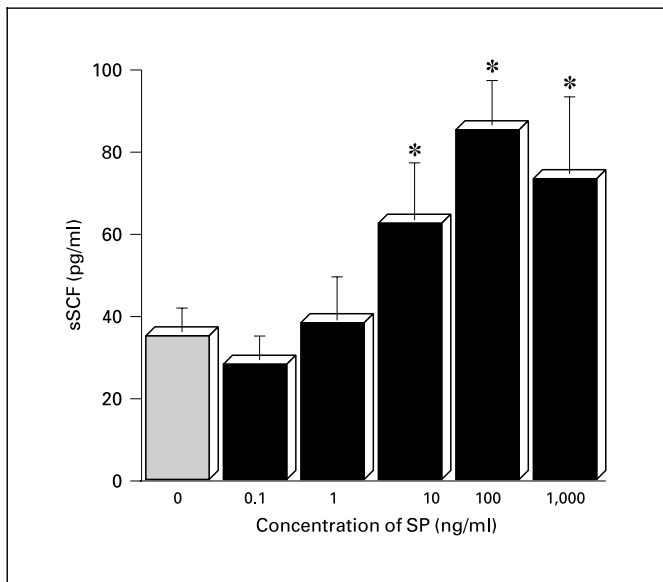


Fig. 4. A dose-dependent response of soluble SCF from cultured human fibroblasts stimulated with SP. Cultured medium were collected after 48 h exposure to a series of concentration of SP and then levels of soluble SCF were examined by ELISA. Means were obtained from triplicate cultures of four independent experiments. * $p < 0.01$ compared with medium alone (0) (unpaired Student's t test).

dicted 414-bp cDNA product was produced. When the PCR bands were quantified and the results were expressed as ratios of densitometric scores for SCF and GAPDH for each sample, SCF message after treatment with 10^2 to 10^4 ng/ml of SP was relatively more intense than that platelet-derived growth factor, a well-known SCF enhancer [32] (data not shown). These findings sug-

gest that SP may be able to enhance MC proliferation through upregulation of SCF secretion and expression by fibroblasts.

On the basis of all the data mentioned above, the following seven findings were found in association with acne inflammation from our *in vivo* and *in vitro* studies: (1) Many SP-containing nerve fibers were in close apposition to the sebaceous glands of acne patients (*in vivo*). (2) SP promoted both the proliferation and the differentiation of the sebaceous glands (*in vitro*). (3) NEP was expressed in the germinative cells of the sebaceous glands in acne patients (*in vivo*). SP-induced expression of NEP in sebaceous glands which was localized in the endoplasmic reticulum and the Golgi apparatus (*in vitro*). (4) There was an increase in the number of nerve fibers around the sebaceous glands in acne patients, which were sometimes invading into the sebaceous glands (*in vivo*). (5) Immunoreactivity of NGF was seen in the sebaceous glands only in acne patients (*in vivo*) and mast cell-derived IL-6 induced expression of sebaceous glands (*in vitro*). (6) An increase in the number of activated mast cells and a strong expression of E-selectin in postcapillary venules were observed in adjacent areas to the sebaceous glands in acne (*in vivo*). Mast cell-derived TNF- α induced expression of E-selectin on venules (*in vitro*). (7) The levels of soluble form of and the expression of membrane-bound form of SCF by fibroblasts were upregulated by SP (*in vitro*).

Taken together, these findings suggest involvement of neurogenic factors including innervation, NPs, neuropeptides-degrading enzymes and neurotrophic factors in the inflammatory process of acne and provide new insight into the possible mechanism of exacerbation of acne from the neurological point of view.

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Acne in Infancy and Acne Genetics

Maria I. Herane^a Iwao Ando^b

^aDepartment of Dermatology, West Unit Faculty of Medicine, Hospital San Juan de Dios, University of Chile, Santiago, Chile; ^bDepartment of Dermatology, Teikyo University, Mizonokuchi Hospital, Kawasaki, Japan

Key Words

Acne · Infancy · Genetics · Hereditary factors

Abstract

Acne is a disease that can be seen in the first year of age, early childhood, prepubertal age and puberty. Neonatal acne is due mainly to considerable sebum excretion rate, and infantile acne because of high androgens of adrenal origin in girls and of adrenal and testes in boys. These pathogenic mechanisms are characteristic in these ages. Important factors like early onset of comedones and high serum levels of dehydroepiandrosterone sulfate are predictors of severe or long-standing acne in prepubertal age. Hereditary factors play an important role in acne. Neonatal, nodulocystic acne and conglobate acne has proven genetic influences. Postadolescent acne is related with a first-degree relative with the condition in 50% of the cases. Chromosomal abnormalities, HLA phenotypes, polymorphism of human cytochrome P-450 1A1 and MUC1 gene are involved in the pathogenesis of acne. Several other genes are being studied.

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Neonatal Acne

Neonatal acne is present at birth or appears shortly after. It is more common than fully appreciated; if the diagnosis is based in a few comedones more than 20% of

newborns are affected [1]. The most common lesions are comedones, papules and pustules. They are few in number and usually localized on the face, more often cheeks and forehead. Involvement of the chest, back or groins has been reported. Most cases are mild and transient. Lesions appear mainly at 2–4 weeks healing spontaneously, without scarring, in 4 weeks to 3–6 months. Neonatal acne has been suggested to be more frequent in male infants [2, 3].

The pathogenetic mechanisms of neonatal acne are still unclear. A positive family history of acne supports the importance of genetic factors. Familial hyperandrogenism including acne and hirsutism give the evidence that maternal androgens may play a role through transplacental stimulation of sebaceous glands [4]. There is a considerable sebum excretion rate during the neonatal period which decreases markedly to almost not detectable levels following the significant reduction of sebaceous gland volume up to the age of 6 months [5–7]. There is a direct correlation between high maternal and neonatal sebum excretion suggesting the importance of maternal environment on the infant sebaceous glands [8]. Neonatal adrenal glands produce a certain amount of β -hydroxysteroids that prepare the sebaceous glands to be more sensitive to hormones in the future life [1]. In males from 6 to 12 months there are increasing levels of luteinizing hormone (LH) and as a consequence of testosterone; these androgens plus those of testicular origin partially explain the male predominance of neonatal and infantile acne [3, 9].

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Prof. Maria Isabel Herane
Department of Dermatology, West Unit, Hospital San Juan de Dios
Guardia Vieja 255 of. 901
Providencia, Santiago (Chile)
Tel. +56 2 331 04 49, Fax +31 2 331 04 50, E-Mail giderm@yahoo.es

The differential diagnosis include milia, miliaria, sebaceous gland hyperplasia, bilateral naevus comedonicus, acneiform eruptions due to the use of topicals, oils and ointments, to maternal medications (lithium, hydantoin, steroids), or due to virilizing luteoma in pregnancy [1, 10, 11]. Deficiency of the 21-hydroxylase and adrenal cortical hyperplasia should also be considered [12]. Neonatal acne can also be confused with cephalic pustulosis due to malassezia species (mainly *Malassezia sympodialis*). Clinically the lesions are very similar to acne and are a consequence of an overgrowth of these lipophilic yeasts (on a neonate with high sebum production) that leads to an inflammatory reaction and poral or follicular occlusion. Its response to ketoconazole cream 2% is significant [13–15].

The treatment of neonatal acne begins with reassurance of parents. Topical treatments for comedones include retinoids such as tretinoin (cream 0.025–0.05%) or azelaic acid (cream 20%) daily or in alternating days. For inflammatory lesions, topical antibiotics (erythromycin 4% pads, pledgets, cream, gel) and benzoyl peroxide (wash, gel 2.5%) are useful [16].

Infantile Acne

Infantile acne (IA) usually starts later than neonatal acne, generally between 6 and 9 months (range 6–16 months) [16]. It also presents a male predominance. Lesions are localized on the face with the cheeks being the area most affected. A large survey on IA has been recently published showing that IA was mainly moderate in 62% of cases and mild and severe in 24% and 17% of cases, respectively. In addition to open and closed comedones, there were 59% of cases with inflammatory lesions and 17% with scars [17]. Occasional cases of conglobate acne can be seen; they occur primarily on the face and the clinical picture is exactly like the adult version.

The course is variable. Some cases disappear in 1 to 2 years but others are persistent and resolve at the age of 4–5 or persist until puberty.

Infantile acne, especially conglobate infantile acne, may be related with severe forms of the disease in adolescence. A family history of severe acne can be present [18].

The exact cause of IA is not clear. There is one case described with elevated levels of LH, follicle-stimulating hormone (FSH), and free testosterone due to an abnormality of the hypothalamus [19].

In severe cases of IA or persistent neonatal acne an infantile hyperandrogenemia should be excluded [16]. Physical examination looking for precocious puberty, bone age measurements and serological examinations FSH, LH, testosterone, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) are the initial approach. Any abnormality needs an endocrinologic evaluation.

Infantile acne must be differentiated from acneiform eruptions due to topical skin care products (greasy ointments, creams, pomades, oils) applied by the parents (pomade acne); due to steroids (topical, oral, inhaled) and from skin contact, ingestion or inhalation of aromatic hydrocarbons with chlorine groups (chloracne) [1, 20]. Perioral dermatitis can mimic an IA, papules and pustules are present mainly periorally (95%) and occasionally at the periocular area (44%). It can be associated to keratoconjunctivitis and vulvar lesions in female patients and usually occurs due to steroids. A family history is present in 20% of cases [21].

The treatment of IA in mild cases is with topical tretinoin, benzoyl peroxide or erythromycin. The main difficulties are the treatment of inflammatory lesions, deep papules and nodules that can persist for weeks or months. The oral antibiotics restricted to this age are erythromycin in doses of 125–250 mg twice daily and trimethoprim 100 mg twice daily in patients with shown resistance of *Propionibacterium acnes* to erythromycin [16, 17]. Deep nodules and cysts can be treated with an injection of low concentration of triamcinolone acetonide (2.5 mg/ml). If there is no response or nodular acne develops, which can lead to scarring, oral isotretinoin can be used. The doses proportionately are similar to adult (0.5 mg/kg/day for 4–5 months). Monitoring of complete and differential blood counts, liver function tests, cholesterol, triglyceride levels and a follow-up of skeletal involvement should be performed [22, 23].

Parents have to be informed that the treatment is a long-term one with possibilities of reappearance of acne at puberty.

Mid-Childhood Acne

This type of acne occurs between 1 and 7 years of age. Acne is very rare in this group and when it occurs should be evaluated for hyperandrogenemia.

Differential diagnosis includes Cushing's syndrome, congenital adrenal hyperplasia, gonadal or adrenal tumors and a true precocious puberty. Evaluation should be

done with a bone age measurement, growth chart and laboratory tests that include serum total and free testosterone, DHEA, DHEAS, LH, FSH, prolactin and 17 α -hydroxyprogesterone. Occasional reports of acne at this age because of *D-actinomycin* are available in the literature.

Mid-childhood acne can be confused sometimes with keratosis pilaris of the cheeks and with keratin cysts (milia) particularly when they get inflamed. Both lesions are common in atopics [3, 16].

The therapy is identical to that of infantile acne.

Prepubertal Acne

Increasing number of early onset acne before obvious signs of puberty is a recognized phenomenon associated more with pubertal development than with age. There is apparently a genetic predisposition.

Pubertal development has two components, normal adrenarche related to maturation of adrenal glands and true puberty because of maturation of testis and ovary mediated by the hypothalamic-pituitary axis.

Adrenarche presents with high levels of DHEA and DHEAS that start rising at 6–7 years in girls and 7–8 years in boys and follow increasing during mid puberty. Excessive androgen production may result due to adrenal hyperandrogenism (exaggerated adrenarche, exuberant production of adrenal androgens relative to cortisol), congenital adrenal hyperplasia, Cushing's disease, 21-hydroxylase deficiency, and more rarely androgen producing tumors. Ovarian contribution to androgens can be through tumors (malignant and benign), but most commonly due to polycystic ovarian disease associated very often with obesity, persistent or resistant acne and insulin resistance [3, 12].

Acne could be the first sign of pubertal maturation and associated with increase in sebum and urinary excretion of androgenic steroids. A high frequency of acne was found in a longitudinal study of adolescent boys, where the prevalence and severity of acne correlated well with advanced pubertal maturation [24]. A similar study of the same authors in early adolescent girls concluded that acne can be the first sign of pubertal maturation; significant elevations of DHEAS correlated well in girls with comedonal and inflammatory acne. The most common locations of acne in this group were the midforehead, nose and chin [25].

In a longitudinal study of acne and hormonal analysis, Stewart et al. [26] concluded that girls with severe acne

present a statistically significantly earlier menarche (12.2 years) compared to those with moderate and mild disease (12.4 and 12.7 years). They also concluded that the number of comedones were predictive for the severity of late inflammatory acne. Mid-pubertal girls with severe comedonal acne showed more comedones even three years before menarche. This group also showed higher levels of DHEAS early in life. A correlation between DHEAS, sebum production and free testosterone was found in severe comedonal acne [26].

Lucky et al. [27] in a 5-year longitudinal cohort study of 871 girls stated clearly the predictor factors of an acne vulgaris study. They evaluated acne versus hormone levels at various ages before and after menarche. They were able to conclude that there were no ethnic differences in acne or hormone levels in the groups studied that included black and white girls. A progressive increase in number of acne lesions with age and maturation was found. The most common acne was comedonal; girls with severe acne at the end of the study had more comedones and inflammatory lesions by the age of 10 years and 2.5 years before menarche. The onset of menarche was also earlier in cases with severe acne and associated to higher levels of serum DHEAS and total and free testosterone compared to girls with mild-to-moderate disease. Early development of comedonal acne, DHEAS, free and total testosterone were good predictors for severe comedonal acne or a long-term disease [27].

The differential diagnosis is essentially similar to mid-childhood acne. Adverse effects of certain drugs (corticosteroids, anticonvulsants, etc.) and sporadic cases of prepubertal hydradenitis suppurative must be considered [28].

The therapy of acne at this age is similar to that reported before. Topical retinoids, benzoyl peroxide, antibiotics are appropriate in mild-to-moderate comedonal and inflammatory acne. In more severe cases, especially in risk of scarring, the use of oral antibiotics and oral isotretinoin may be necessary. Resistant, persistent and cases of acne appearing at unusual ages need hormonal evaluation and proper treatment. Adrenal problems may need low doses of oral corticosteroids; polycystic ovarian disease can be treated with oral contraceptives that include antiandrogens such as cyproterone acetate or the new low androgenic progestins. Spironolactone can also be considered [29].

Acne Genetics

The genetic influence on pathogenesis of acne is well documented in twins [30] and genealogic studies. In some types of acne, such as acne conglobata, hereditary factors are more apparent, and a correlation has been suggested between neonatal acne and familial hyperandrogenism [4]. Nodulocystic IA is often observed in relatives of patients with extensive steatocystoma, adolescent and postadolescent acne [31]. Fifty percent of postadolescent acne patients have at least one first-degree relative with the condition [32].

Sebum excretion also correlates with acne susceptibility, and sebum excretion rates are similar in identical twins [33]. Several chromosomal abnormalities, including 46XYY genotype [34], 46XY+ (4p+; 14q-) [35], and partial trisomy 13 [36] have been reported to be associated with nodulocystic acne.

The relationship of acne and various genes has been investigated. An HLA antigen study was negative for acne conglobata [37], but HLA phenotypes were identical in siblings affected with familial acne fulminans [38]. Polymorphism in the human cytochrome P-450 1A1 (CYP1A1) seem to be associated with acne [39], and CYP1A1 is known to be involved in the metabolism of a wide range of compounds such as vitamin A. In acne patients, a higher frequency of CYP1A1 mutation was observed on regulatory sites, and this may impair the biological efficacy of natural retinoids due to their rapid metabolism to inactive compounds. This mutation may thus be involved in the pathogenesis of acne in some patients. CYP1A1 inducibility is determined by polymorphism in the genes of the aromatic hydrocarbon (Ah) receptor. This Ah receptor mediates the toxic effects of environmental pollutants such as dioxin and polyhalogenated biphenyls. Clinical correlations between the high inducibility of CYP1A1 and some carcinomas are observed; however, no correlation was found between polymorphism of the human Ah receptor and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-induced chloracne in chemical workers accidentally exposed to this chemical [40].

An inadequate activity of steroid 21-hydroxylase, as well as CYP21 gene mutations, is the genetic basis for congenital or late-onset adrenal hyperplasia which may present with acne. Acne patients exhibit a high frequency of a CYP21 gene mutation, but a poor correlation exists between mutations and either elevated steroids or acne [41]. It has been suggested that factors other than mild impairment of CYP21 can contribute to the clinical phenotype that includes acne.

Androgen receptor polymorphisms of CAG trinucleotide repeat length has clinical implications for human disease. This polymorphism exhibits a correlation with some androgenic skin diseases but not with acne [42].

MUC1 is a glycoprotein secreted from various epithelial glands including sebaceous glands. Studies of the respiratory and digestive systems suggest that MUC1 is involved in the defense system against bacteria by inhibiting their adhesion to epithelium. The MUC1 gene and the molecule produced exhibit extensive polymorphism attributable to a variable number of tandem repeats. A higher frequency of longer repeat length of tandem repeats has been observed in severe acne patients [43].

The melanocortin 5 receptor is known to regulate sebaceous gland function in mouse. Genetic diversity is observed in human melanocortin 5 receptor coding region. Association between variation at the locus and acne is not found [44].

In conclusion, the pathogenesis of acne is multifactorial and a greater number of genes than those cited above are probably related to the condition. Genes affecting keratinization and desquamation are suspected to be involved in the pathogenesis of acne and their correlation to acne is yet to be evaluated. Advances in immunogenetic research may shed new light on the understanding of the inflammatory reaction in acne. Genes expressed in the sebaceous glands which exhibit polymorphism are of special interest, regardless of their known function. Any gene polymorphisms found to be related to acne may provide additional insights into the pathogenesis of this condition. Further research is needed to investigate the combined effects of these and other genes.

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Topical Treatment in Acne: Current Status and Future Aspects

Harald P.M. Gollnick Andrea Krautheim

Department of Dermatology and Venereology, Otto von Guericke University, Magdeburg, Germany

Key Words

Acne · Topical treatment · Retinoids · Benzoylperoxide · Antibiotics · Azelaic acid

Abstract

During the last 20 years, the number of topical and systemic drugs for the treatment of acne vulgaris has been enriched. Topical drugs on the one hand have been newly discovered or further developments of already available agents such as in the group of retinoids or galenic formulation have improved efficacy or local tolerance. Topical retinoids are a mainstay in acne treatment since 1962. All-trans retinoic acid was the first and is still in use. Its irritative potential has led to the new galenics, i.e. incorporation in microsponges and in propolyomers, which increased the tolerability significantly. The isomer of tretinoin, isotretinoin, has the same clinical efficacy, but also a lower irritancy. A real breakthrough was adapalene, a retinoid-like agent, with a different retinoid receptor-binding profile, but in addition to the same clinical efficacy on inflammatory and non-inflammatory acne lesions compared to tretinoin, a better tolerability and, therefore, compliance. Unfortunately, over the past years topical retinoids have been less used in inflammatory acne than they should be, taking the mechanisms of action into account. Topical antimicrobials, in particular topical antibiotics, should be used less often than in the past and only for short periods to avoid the

development of resistances. It seems better to combine those agents with topical retinoids, with BPO or with azelaic acid to enhance the efficacy and slow down the development of resistance. BPO is still the gold standard for papular-pustular acne of mild-to-moderate type in concentrations of 2–5%. Azelaic acid is an alternative with efficacy on the comedo and is antibacterial without development of resistances. Finally, the physical removal by electrocautery or CO₂ laser of multiple densely packed closed comedones, macrocomedones and microcysts is necessary to enhance the efficacy of topical comedolytic agents and to speed up the therapeutic results. Photodynamic therapy has not yet been proven efficacious in controlled studies. Blue and red light can probably be used in association with local agents but enhancement of the irritative potential of topical and systemic agents has to be considered.

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The combination of topical agents due to better compatibility in the galenic formulation of the vehicle has enhanced efficacy and improved patient compliance. Fortunately, improvement in the design and performance of clinical trials during the last two decades has supported the indication of new agents or new galenic formulations; however, not all of them really support the need of CONSORT and the Cochrane principles (evidence-based medicine). Meanwhile in several countries, in particular in the

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Prof. Harald P.M. Gollnick
Department of Dermatology and Venereology, Otto von Guericke University Magdeburg
Leipziger Strasse 44, D–39120 Magdeburg (Germany)
Tel. +49 391 67 15249, Fax +49 391 67 15235
E-Mail harald.gollnick@medizin.uni-magdeburg.de

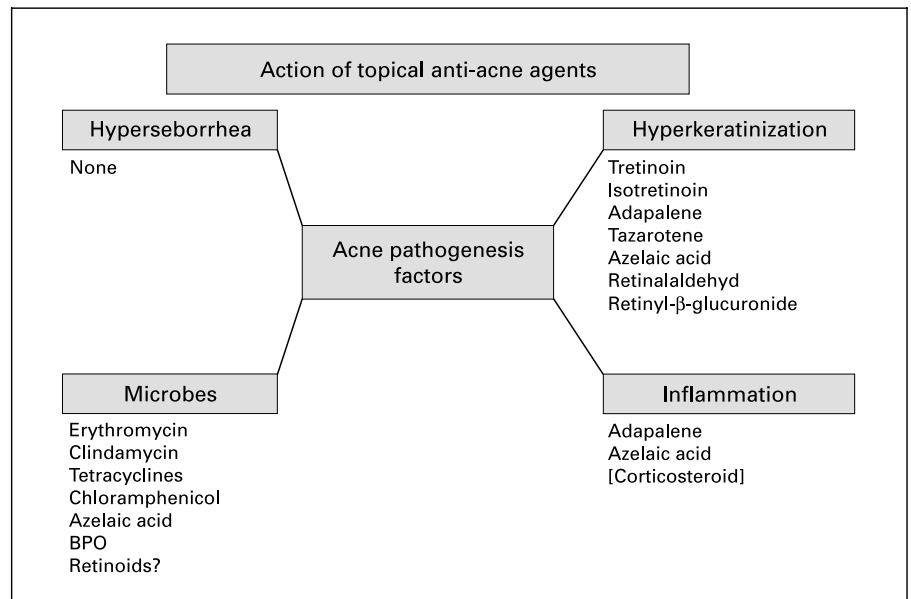


Fig. 1. Action of topical anti-acne agents.

Table 1. Topical retinoids

Substance	Indication
Tretinoin	acne + aging + cancer
Isotretinoin	acne + aging
Motretinid	acne
Adapalene	acne (+ aging + cancer)
Tazarotene	acne + psoriasis
Alitretinoin	Kaposi sarcoma, hand eczema
Retinaldehyde	aging + mild acne
Retinyl- β glucuronide	mild acne
Retinol palmitate	aging
all-trans retinyl-glucuronide	mild acne
Tamibaroten	psoriasis
Arotinoid methyl sulfate	cancer

United States, France, England, Canada and Germany, guidelines for acne treatment have been published. Because the advances in the development of therapy and new results of pathophysiological factors are continuously being published, the current therapeutic procedures and, in this manuscript, the spectrum of agents working via the topical route have to be reconsidered [1–3].

The currently available topical anti-acne drugs and the pathophysiological factors which are targeted by them are given in figure 1, as well as the adverse drug profile in tables 1–3.

Topical Retinoids

Topical retinoids have the following mechanisms of action:

- Expulsion of mature comedones (open and closed type).
- Inhibition of formation and number of microcomedones.
- Inhibition of inflammatory reactions.
- Enhancement of penetration of other anti-acne drugs
- by suppression of development of new microcomedones important for maintenance treatment.

Retinoids exert their effects on a molecular level through nuclear receptors: retinoic acid receptor (RAR) and retinoid X receptor (RXR). These ligand-dependent transcription factors bind retinoids either as homodimers (RAR/RAR, RXR/RXR) or heterodimers (RAR/RXR) [4], which then can induce subsequent target gene expression by binding to the retinoid-responsive elements (RAREs and RXREs) in the promotor region of such genes [5–7]. They also inhibit the expression of genes without retinoid-responsive elements by downregulating the action of other transcription factors such as activator protein-1 (AP-1) and nuclear factor for interleukin-6 (NF-IL6), probably through mechanisms of competition for commonly required co-activator proteins [8–10]. Retinoid receptors are members of the steroid-thyroid hormone superfamily and exist as α -, β -, and γ -subtypes with differential binding of the different synthesized com-

Table 2. Efficacy of topical acne therapeutics

Agent	Keratolytic/ anti-comedogenic	Sebo- suppressive	Anti- microbial	Anti- inflammatory
Tretinoin	++	-	(+)	(-)
Isotretinoin	++	-	(+)	(+)
Adapalene	++	-	(+)	++
Tazarotene	++	-	(+)	+
Azelaic acid	++	-	++	+
Clindamycin	-	-	++	-
Erythromycin	-	-	++	-
Tetracycline	-	-	++	(+)
Benzoyl peroxide	(+)	-	+++	(+)
Salicylic acid	+	-	(+)	-

+++ = Very strong; ++ = strong; + = moderate; (+) = weak; - = none.

pounds. The expression of the retinoid receptors is tissue-specific, with RAR γ being the predominant type of RAR expressed in human epidermis [11].

Embryotoxicity/teratogenicity is the major drawback in the therapeutic use of systemic retinoids. The exposure of the fetus during the first trimester to oral retinoids is known to produce characteristic malformations [12]. There have also been case reports about malformations associated with retinoid embryopathy after the mother had used tretinoin topically during the first trimester of pregnancy [13–15]. In a retrospective study, there were 1.9% major congenital abnormalities when mothers had used topical tretinoin during the first trimester of pregnancy versus 2.6% in women who were not exposed to tretinoin [16]. Even though the daily variation of natural retinoid plasma levels is larger than the plasma levels occurring under topical retinoid application for the treatment of skin disease [17, 18], an individual embryopathy risk under topical application cannot be fully excluded. Today, topical application of retinoids should be strictly avoided during the first trimester of pregnancy. While in Germany the administration of topical retinoids is not permitted during the entire period of pregnancy, but contraception during the topical application of retinoids is not required, in the US effective contraception during topical retinoid treatment is still recommended. The scientific and ethical discussion regarding teratogenicity of topical retinoids in pregnancy is still ongoing and will soon need a final consensus by pharmacologists and dermatologists.

Currently, the following topical retinoids are in use: tretinoin, isotretinoin and adapalene; however, they are mostly used for comedonal acne. Topical retinoids do not only have antikeratinizing effects by normalizing dis-

turbed follicular keratinization, but do have in addition some anti-inflammatory actions, in vivo and in vitro differing from retinoid to retinoid. They should therefore also be used for inflammatory types of acne, i.e. acne papulopustulosa grade I–II. In those types of acne with higher inflammatory grades (III and IV according to Plewig and Kligman), the combination of topical retinoids with oral antibiotics or topical BPO or azelaic acid is indicated.

Beside the above-mentioned retinoids, in some countries tazarotene, motretinide, retinaldehyde and β -retinoylglucuronide are also on the market. They all target the microcomedo and are comedosuppressive in different potencies; however, they vary concerning anti-inflammatory efficacy and local tolerability.

Tretinoin

Tretinoin which was the first topical retinoid described in the first reports by Stüttgen and by Beer. It significantly reduces the number of comedones but also of inflammatory acne lesions. It has been shown in several trials that at least during a 12-week course the reduction of lesion counts ranges between 32–81% for noninflammatory lesions and 17–71% for inflammatory lesions, i.e. 22–83% for the total lesion count. Comparing tretinoin 0.025% gel or 0.025% cream with its vehicle in a once daily application manner, tretinoin was significantly more effective than the vehicle in reducing both inflammatory and non-inflammatory lesions. Currently tretinoin is available in different galenic formulations: cream (0.025%, 0.1%, gel 0.01%, 0.025%) and as a solution (0.05%).

Table 3. Adverse drug reactions of topical therapeutics

Agent	Erythema	Scaling	Burning	Flare-up of acne	Bacterial resistance	Photo-sensitivity	Other
All-trans retinoic acid	+++	+++	++	++	–	++	
Isotretinoin	++	++	+	+	–	+	
Adapalene	+	+	+	+	–	–	
Azelaic acid	+	+	++	–	–	–	
Benzoyl peroxide	++	++	+	+	–	–	bleaches hair and clothes, contact allergy
Topical antibiotics	±	±	±	±	+++	tetra-cyclines	contact allergy, bacterial resistance

– = None; + = mild; ++ = considerable; +++ = extensive.

In a topical gel formulation containing polyolprepolymer-2, tretinoin penetration was shown to be significantly reduced while potentially enhancing epidermal deposition compared to a commercially available gel preparation at the same concentration. Polyolprepolymer-2 helps to retain drug molecules on the skin surface and in the upper layers of the skin [19, 20]. Another new formulation is a microsp sponge delivery system consisting of macroporous beads of 10–25 µm in diameter which are loaded with an active ingredient. After topical application this is gradually released depending on rubbing, temperature, pH and other factors [21]. Tretinoin 0.1% gel microsp sponge compared with tretinoin 0.025% gel, tazarotene 0.1% gel or adapalene 0.1% gel in a split face study showed similar facial tolerability for all retinoids [22]. A formulation of liposomally encapsulated tretinoin 0.01% was in a comparative study equipotent in clearing acne lesions as tretinoin 0.025 or 0.05% gel after once daily topical application for 10 weeks, but showed a much better cutaneous tolerability [23]. This was also reproducible on *in vitro* reconstructed epidermis [24].

With regard to systemic absorption and risk of embryotoxicity after topical application, the detected fecal and plasma tretinoin concentrations were much below the endogenous tretinoin levels [25, 26] and did not affect the endogenous levels of tretinoin or its metabolites or alter the plasma vitamin A levels [27].

Isotretinoin

Isotretinoin is available in a gel formulation having the same clinical efficacy as tretinoin leading to the reduction of comedones by between 46 and 78% and of inflammatory lesions by between 24 and 55% after 12 weeks of treatment. The relatively lower local irritancy is obviously due to the isomerization of isotretinoin over time to all-trans-retinoic acid.

In a penetration study, substantial amounts of topically applied isotretinoin were delivered via the follicular route to the sebaceous glands, resulting in comparable concentrations to those observed after oral application [28, 29]. After 42 days of excessive application of 0.1% isotretinoin cream in patients with photodamaged skin, the plasma levels of isotretinoin were compared to pretreatment levels. The results suggested systemic absorption, but to a lesser extent than that reported after the US recommended daily allowance of 5,000 IU of vitamin A supplementation. The systemic availability of topical isotretinoin is negligible and should thus not produce systemic toxicity.

Adapalene

Adapalene is a third-generation retinoid available as cream, gel or solution in 0.1% concentration. Currently, clinical studies comparing 0.1–0.3% adapalene are being performed. In a survey on nearly 1,000 patients, it could be demonstrated that adapalene 0.1% gel has the same efficacy as tretinoin gel 0.025%. The number of acne lesions was reduced by between 49 and 62%. The compar-

ison of tretinoin microsphere formulation demonstrated a similar efficacy but lower irritative potential of adapalene [30–33].

Compared to tretinoin, adapalene has additional recently discovered anti-inflammatory mechanisms of action: lowering the AP 1-dependent pathway; inhibition of polymorphonuclear granulocytes; suppression of chemotactic activity of human PMN; reduction of 5- and 15-lipoxygenase; downregulation of Toll-like receptors of type 2 with consecutive reduced release of proinflammatory cytokines IL1, IL6, TNF α and IL8.

Tazarotene

Besides psoriasis, tazarotene is currently also available for acne treatment in the US market as a 0.5 and 0.1% gel or cream. The efficacy is comparable to adapalene, but its local tolerance by daily application is quite unfavorable and similar to tretinoin. Therefore, tazarotene was recently studied for its efficacy in a so-called short contact application manner similar to dithranol short time application from 30 s up to 5 min. In this study, three arms were compared: twice daily, once daily, and vehicle. The once daily application was nearly equivalent to the twice daily and both were highly significantly better than vehicle [34–36]. The irritative potential was reduced.

Motretinide

Motretinide, available in Switzerland, is a local retinoid in an aromatic ester form with an efficacy profile similar to low-dose tretinoin concentrations but with less irritative potential.

Retinaldehyde and Retinyl- β -Glucuronide

Retinoyl- β -glucuronide is a naturally occurring, biologically active metabolite of vitamin A. A 0.16% retinoyl- β -glucuronide cream was shown to be effective against inflammatory and non-inflammatory acne lesions in Asian-Indian patients [37] as well as in patients in the US, with comparable efficacy to tretinoin, but without the irritation potential or other side effects of tretinoin [38]. The percutaneous absorption, metabolism and excretion of topically applied radioactive retinoyl- β -glucuronide and tretinoin were similar in the rat and thus not of relevance for the differences in local tolerance [39].

Retinaldehyde was shown to have a significant comedolytic activity in the rhino mouse model [40]. After topical application in acne patients of retinaldehyde 0.1% gel or its vehicle every morning and erythromycin 4% lotion every evening for 8 weeks, comedones and microcysts were significantly improved with retinaldehyde combined with erythromycin, but not with erythromycin alone. In both treatment groups, papules and pustules were reduced significantly. Local tolerance was very satisfactory [41].

To optimize the efficacy in more moderate inflammatory types of acne, it is recommended to combine topical retinoids with topical antibiotics or benzoylperoxide. It has been demonstrated that retinoids enhance penetration of its combination partner into the follicular canal. It is furthermore recommended after significant reduction of inflammatory and non-inflammatory lesions to maintain the treatment success with the topical retinoid alone to prevent the new formation of microcomedones [2, 19, 42–49].

Finally, in patients with skin types III–VI retinoids can reduce the postinflammatory hyperpigmentation. They have in addition favorable effects on skin scarring.

In summary, the following recommendations can be given for the use of topical retinoids: (a) they should be first choice for most types of acne forms including acne comedonica and acne papulopustulosa grade I–II; (b) combination of topical antimicrobials in inflammatory acne with topical retinoids is more efficacious; (c) topical retinoids are essential for maintenance treatment; (d) retinoids have a skin-repairing effect (scarring, hyperpigmentation).

Topical Antimicrobials

Topical antimicrobial agents have been in use for more than 30 years in acne. Indication is acne papulo-pustulosa grade I–II or in combination with retinoids in grade III or with oral antibiotics in grade IV (assessment score according to Plewig and Kligman). The most commonly used topical antimicrobials are benzoylperoxide, erythromycin, clindamycin and azelaic acid. Topical tetracyclines and topical chloramphenicol are less commonly used due to lower efficacy or specific side effects.

Topical Antibiotics

The most common advantage of topical antibiotics is their very low irritative profile; however, the most and increasing disadvantage is the development of bacterial

resistance for *Propionibacterium acnes* and *Staphylococcus aureus*. To overcome this problem, clindamycin and erythromycin have been increased in concentration from 1 to 4% and new formulations with zinc or combination products with BPOs or retinoids are now being marketed [1, 3, 50, 51].

The following recommendations can currently be given: (a) topical antibiotics should be used as monotherapeutics only over a short 3- to 4-week period; (b) combinations with zinc, BPO or retinoids are recommended to avoid bacterial resistance.

Benzoylperoxide

Currently, benzoylperoxide is still the gold standard for mild-to-moderate acne. Bacterial resistances have not been detected yet. Fixed combination preparations are available with erythromycin, and those with clindamycin are in preparation. They are more efficacious and better tolerated than benzoylperoxide alone. BPO is available as a solution, washing gel or cream 1–5% concentration. 10% concentrations are not significantly more efficacious but more irritative [2, 46, 51, 52].

Micromolar concentrations of benzoyl peroxide were found to inhibit the release of reactive oxygen species from human neutrophils but associated with a marked drug-induced cytotoxicity. When in cell-free assays the effects of benzoyl peroxide on protein kinase C and calmodulin as regulators of the release of reactive oxygen species were investigated, there was only a marginal inhibition of protein kinase C and no inhibition of calmodulin was detectable. Thus, the anti-inflammatory activity of benzoyl peroxide is unlikely to be mediated by protein kinase C or calmodulin [53].

In one study the sebum excretion rate was shown to increase by 22.5% after 1 or 2 months of treatment with 5% benzoyl peroxide. This was felt to be due to the comedolytic activity and thus influence the pooling of sebum in the upper parts of the pilosebaceous duct [54]. Nevertheless, today any activity on sebaceous gland activity and direct comedolytic activity can be excluded.

Benzoylperoxide does not target the comedo at the primary route and does not have significant in vivo anti-inflammatory potency.

The side effect profile of BPO depends on the galenic formulation of i.p. dryness of the skin and exsiccation eczema. It can bleach the hair and clothes. The following recommendations can be given: ideal for mild-to-moderate inflammatory acne papulo-pustulosa; optimal combi-

nation with topical retinoids; treatment for about 6–8 weeks as monotherapy; short contact benzoylperoxide washes followed by topical retinoids or azelaic acid are useful.

The common induction of an irritant dermatitis can be avoided by less frequent application making the incidence of true contact sensitivity low [55]. A water-based benzoyl peroxide preparation was found to cause significantly less skin irritation than an alcohol-based preparation [56]. In a comparison of 2.5, 5 and 10% gel formulations of benzoyl peroxide, the 2.5% formulation was equivalent to the other two concentrations in reducing inflammatory lesions and significantly reduced *P. acnes* after 2 weeks of topical application. The local adverse effects were less frequent with the 2.5% gel than with the 10% preparation, but similar to the 5% gel [57].

Azelaic Acid

Azelaic acid is a 9-dicarboxylic acid with efficacy on follicular keratinization and on *P. acnes*. It seems to have some inflammatory efficacy via effects on neutrophilic granulocytes. In clinical studies, a similar efficacy as tretinoin in comedonal acne has been demonstrated. The efficacy in papular-pustular acne in comparison to BPO is lower, but after 12–16 weeks similar results could be achieved. No bacterial resistance has yet been detected. Currently, azelaic acid is available in a 20% cream formulation. Clinical trials for a new formulation as a lotion have been performed which should be better tolerated in patients with more greasy skin [58].

Furthermore, the combination of azelaic acid with clindamycin, with BPO, with α -hydroxy acids or with retinoic acid enhances the efficacy of the monosubstance [pers. commun., Dr. Graupe, data on file, Schering Berlin].

Salicylic Acid

Salicylic acid has a mainly keratolytic effect. Additionally, it increases penetration of other substances, has a slight anti-inflammatory effect and in low concentrations is bacteriostatic and fungistatic by competitive inhibition of pantothenic acid which is important for micro-organisms. It can be supportive during maintenance therapy when used as a 1–3% alcohol solution [59].

Physical Treatments

Oftentimes, a high number of facial closed comedones do not fully respond to, for example, topical retinoids. Therefore, physical comedo extraction is necessary, in particular in those cases showing a dense distribution of closed comedones or macrocomedones or of small cysts. Physical removal by the physician or the medical cosmetician under supervision of the physician is necessary. Numerous macrocomedons are an ideal target for electrocautery or CO₂ laser treatment [60, 61].

Chemical Peeling

Chemical peeling targets the interfollicular epidermis and acroinfundibulum and seems to reduce superficial scarring and hyperpigmentation. The currently available substances are α -hydroxy acids, higher concentrations of salicylic acid, and trichloroacetic acid [1, 3].

Photodynamic Therapy

Recently, the effects of blue light have been reported which lead via porphyrines of *P. acnes* to oxidation with killing of the bacterium. Available are 415 nm or the mixed blue and red light with 415 und 660 nm [62, 63].

Photodynamic therapy with 5-aminolevulinic acid has been reported; however, controlled trials are not available yet. There is evidence that the sebaceous gland can be destroyed irreversibly with microscarring in the dermis. Therefore, this treatment procedure unless good clinically and histologically controlled trials are available is not recommended.

Topical Corticosteroids

Topical corticosteroids can be applied in certain conditions for a short time, in particular in very inflammatory acne. They play an important role in reducing the flare-up reactions in conglobate acne and for the reduction of granuloma pyogenicum-like lesions under isotretinoin treatment.

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Update and Future of Systemic Acne Treatment

Christos C. Zouboulis^a Jaime Piquero-Martin^b

^aDepartment of Dermatology, University Medical Center Benjamin Franklin, The Free University of Berlin, Berlin, Germany;

^bInstitute of Biomedicine, Hospital Vargas, Central University of Venezuela, Caracas, Venezuela

Key Words

Acne · Therapy · Update · Future · Review

Abstract

Systemic treatment is required in patients with moderate-to-severe acne, especially when acne scars start to occur. Antibiotics with anti-inflammatory properties, such as tetracyclines (oxytetracycline, tetracycline chloride, doxycycline, minocycline and limecycline) and macrolide antibiotics (erythromycin and azithromycin) are the agents of choice for papulopustular acne, even though the emerging resistant bacterial strains are minimizing their effect, especially regarding erythromycin. Systemic antibiotics should be administered during a period of 8–12 weeks. In severe papulopustular and in nodulocystic/conglobate acne, oral isotretinoin is the treatment of choice. Hormonal treatment represents an alternative regimen in female acne, whereas it is mandatory in resistant, severe pubertal or post-adolescent forms of the disease. Compounds with anti-androgenic properties include estrogens combined with progestins, such as ethinyl estradiol with cyproterone acetate, chlormadinone acetate, desogestrel, drospirenone, levonorgestrel, norethindrone acetate, norgestimate, and other anti-androgens directly blocking the androgen receptor (flutamide) or inhibiting androgen activity at various levels, corticosteroids, spironolactone, cimetidine, and ketoconazole. After 3 months of treatment control of

seborrhea and acne can be obtained. Low-dose corticosteroids (prednisone, prednisolone, or dexamethasone) are indicated in patients with adrenal hyperandrogenism or acne fulminans. New developments and future trends represent low-dose long-term isotretinoin regimens, new isotretinoin formulations (micronized isotretinoin), isotretinoin metabolites, combination treatments to reduce toxicity, insulin-sensitizing agents, 5 α -reductase type 1 inhibitors, antisense oligonucleotide molecules, and, especially, new anti-inflammatory agents, such as lipoxigenase inhibitors.

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Acne is a disorder of the pilosebaceous units located on the face, chest and back. It is an almost universal disease, occurring in all races, predominantly among adolescents [1–4]. Epidemiological studies have shown that about 70–87% of the adolescents experience acne lesions [5, 6]. The disease exhibits a peak incidence at 15–18 years of age. Spontaneous regression occurs in the majority of the patients after puberty, but in 10% of them acne persists over the age of 25 years and can last up to the 4th decade of life, and even up to the 6th decade of life in some cases.

As many as 15–30% of patients with acne need medical treatment because of the severity and/or persistence of their disease. In the years 1996–1998, more than 6 million visits per year to office-based physicians with acne as the principal reason have been registered in the USA; the

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Fax +41 61 306 12 34
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Prof. Dr. Christos C. Zouboulis
Department of Dermatology
University Medical Center Benjamin Franklin, The Free University of Berlin
Fabeckstrasse 60–62, D–14195 Berlin (Germany)
Tel. +49 30 8445 6910, Fax +49 30 8445 6908, E-Mail zouboulis@medizin.fu-berlin.de

Table 1. Simplified acne severity grading for the therapeutic decision

Severity grade	Comedones	Papules/pustules	Small nodules, cysts, fistules	Nodules	Inflammation	Scar formation
Mild	few	Ø or few	Ø	Ø	Ø	Ø
Moderate	numerous	few to many	Ø or few	Ø	marked	Ø
Severe	numerous	very numerous	many	Ø or few	strong	present
Very severe	fistule-comedones	very numerous	many	few to many, deeply located	very strong	present

patients received 6.5 million new prescriptions per year for systemic anti-acne drugs (antibiotics or isotretinoin) with a total cost likely to exceed USD 1 billion [7]. The different age ranges and the varying clinical pictures require better knowledge of the pathogenesis of the disease and clinical experience for its treatment [1–5, 8], especially since misconceptions regarding factors that exacerbate acne vulgaris not only exist in the community but have also been registered in last year medical students in an Australian study [9]. Several factors contribute to the pathogenesis of acne, among them increased sebaceous gland activity with hyperseborrhea [10], abnormal follicular differentiation and increased cornification [11], bacterial hypercolonization [12] as well as inflammation and immunological host reaction [13] are considered to be the major ones. Each of these factors provides a potential target for treatment. Genetic investigations have provided ambiguous proof for hereditary factors [14]; irregularities of the menstrual cycle, pregnancy, etc., have some influence on the acne course in females, and nutritional factors are accused to modify acne in some patients. Weather including ultraviolet light and other environmental factors may occasionally play a role. Several drugs can induce acne or acneiform lesions [3]. Psychological factors and stress have still no proven influence on the pathogenesis of acne but are often involved in its course. Recently, neuropeptides were reported to regulate the activity of the pilosebaceous unit [15, 16]. At last, acneiform eruptions can complicate the diagnosis.

Treatment of Acne: General Considerations

The exact classification and grading of acne is a fundamental requirement for the decision of the therapeutic regimen [1–4, 17–19]. In addition, acne at puberty needs subsequent prophylactic medication and care over several years after clinical healing. Infantile and pediatric acne,

androgenization signs in female patients with acne tarda [20, 21] or patients with signs of acne inversa may necessitate an alternative treatment. The compliance of the patient is an additional important parameter for the therapeutic strategy to be considered and its success. Skin type (dark skin tends to postinflammatory hyperpigmentation) and, especially, the tendency for scar formation play a role in the selection of treatment [22]. Two to 7% of the patients with acne experience a severe course associated with considerable scarring. A severe course associated with the presence of potential generators of physical and psychotic scars may require a therapeutic regimen based on systemic drugs [3, 18] (table 1).

Therapeutic Targets and Acne Drugs

Several clinical observations point to the importance of androgens in acne [23]. Androgens play an essential role in stimulating sebum production; androgen-insensitive subjects who lack functional androgen receptors do not produce sebum and do not develop acne. Moreover, systemic administration of testosterone and dehydroepiandrosterone increases the size and secretion of sebaceous glands [24–27]. Sebosuppression, i.e. suppression of sebaceous gland hyperactivity, can classically be achieved by systemic administration of anti-androgens or isotretinoin [19, 24–26, 28, 29] (table 2).

Abnormal keratinization of the infundibulum and the distal part of the sebaceous duct can be directly influenced through topical and systemic retinoids as well as through topical application of azelaic acid [30]. A number of further drugs can also secondarily induce keratolysis over their influence on other pathogenic factors [31]. Benzoyl peroxide and topical and systemic antibiotics primarily exhibit antimicrobial, but also anti-inflammatory activities [32, 33]. Various agents administered in acne treatment exhibit direct or indirect anti-inflammatory activi-

Table 2. Different action profile of systemic anti-acne drugs on the four major pathogenic factors of acne

	Follicular hyperkeratosis	Seborrhea	Bacterial hypercolonization	Inflammation
Antiandrogens(s)	-	++	-	-
Isotretinoin(s)	++	+++	(+)	++
Tetracyclines(s)	-	-	++	+

+++ = Very strong, ++ = strong, + = moderate, += indirect/weak.

ties in addition to their effects on further pathogenic factors of acne. However, solely anti-inflammatory agents have rarely been administered [13].

Bacterial hypercolonization is not involved at the onset of acne, but it plays a role in the maintenance of the disease [2, 3, 8]. *Propionibacterium acnes* (*P. acnes*), an anaerobic bacterium, is a normal constituent of the cutaneous flora; however, it is virtually absent in the skin before puberty. Sebaceous follicles turning to microcomedones provide an anaerobic, lipid-rich environment for optimum bacterial proliferation. *P. acnes* produces lipases which can split triglycerides into free fatty acids. The latter can irritate the follicular cells and may cause hyperproliferation and/or inflammation. Topical or systemic antibiotics administered successfully in acne patients exhibit a suppressive effect on *P. acnes* proliferation but also directly suppress inflammation by decreasing neutrophil chemotaxis and down-regulating the expression of pro-inflammatory mediators and the production of chemotactic factors [34]. The unique environment of the pilosebaceous follicle makes lipophilic compounds clinically more active than hydrophilic ones [35].

Inflammation in acne has been considered as secondary to bacterial hypercolonization and, consequently, neither has it been carefully investigated nor become the target of treatment. The major hypothesis was that early during development of acne lesions neutrophils accumulate around and in the follicles through chemoattractive substances which may originate from *P. acnes* [1–4]. Hydrolytic enzymes and reactive oxygen species released by neutrophils promote tissue damage, facilitating the occurrence of debris within the lumen. The latter is considered to trigger the inflammatory cascade [36]. This hypothesis has gained support because several anti-acne drugs have been shown to inhibit the generation or activity of chemotactic factors or the release of reactive oxygen species [37]. In addition, linoleic acid, which is deficient in acne comedones, inhibits neutrophil oxygen metabolism and phagocytosis.

Table 3. Indications for oral antibiotic therapy in acne

Patients with moderate to severe acne
Patients for whom topical antibiotic therapy has failed or cannot be tolerated
Patients with moderate acne with tendency for scarring or substantial post-inflammatory hyperpigmentation
Patients with involvement of the shoulders, back or chest (difficult for topical application)

Systemic Treatment

Oral Antibiotics

Oral antibiotics are indicated for several groups of patients with inflammatory acne (table 3) [33, 38]. They include tetracyclines (tetracyclines, doxycycline, minocycline), erythromycin, clindamycin, and cotrimoxazole (table 4). These agents improve inflammatory acne by inhibiting the growth of *P. acnes*; tetracyclines and erythromycin have additional anti-inflammatory properties.

Tetracyclines of the first generation (tetracycline, oxytetracycline and tetracycline chloride) are the most commonly prescribed oral antibiotics for acne. They are used as a first-line agent because of their efficacy and low cost, although they have generated high rates of bacterial resistance. A 6-week treatment decreases the number of inflammatory lesions by approximately 50%. They are usually administered at a dose of 1 g/day (500 mg twice daily) over several months and after marked clinical improvement the dose can be reduced to 500 mg/day. Because their absorption is inhibited in the presence of food and dairy products, the drug must be taken preferably on an empty stomach one hour before meals with water for an optimal absorption.

Alternatively, tetracyclines of the second generation, namely doxycycline (initial dose of 100–200 mg/day with



Fig. 1. Mild acne papulopustulosa in a 24-year-old male patient before (left) and after a 6-month treatment with doxycycline 2×100 mg/day and topical tretinoin 0.1% (right).

Table 4. Oral antibiotics used in acne treatment

Antibiotic	Usual dose	Comments
Tetracycline	250–500 mg \times 2/day	low cost decreased absorption in presence of foods and dairy products
Doxycycline	100 mg \times 2/day	may be taken with meals
Minocycline	50–100 mg \times 2/day	expensive may be taken with meals safety problems
Erythromycin	500 mg \times 2/day	common emergence of resistant <i>P. acnes</i> strains
Clindamycin	300 mg \times 3/day	safety problems after long-term use
Cotrimoxazole	160/800 mg \times 2/day	second-line therapy in acne

50 mg/day as maintenance dose) (fig. 1) and minocycline (usually 100 mg/day; 50 mg twice daily or 100 mg once daily) are more expensive but also more lipid soluble and better absorbed from the gastrointestinal tract. In contrast to tetracyclines of the first generation their absorption is not significantly limited by food, therefore, they can be taken with meals even though it is more effective when taken 30 min previously. Among tetracyclines, minocycline seems to induce more rapid clinical improvement as well as greater and more persistent reduction of inflammatory lesions and facial *P. acnes* counts, probably because it is the most lipophilic and may become highly concentrated in the pilosebaceous unit after its oral adminis-

tration [39]. Its major limitation occurs from currently observed significant safety problems (table 5) [40–43].

Erythromycin at a dosage of 1 g/day can be administered as an alternative regimen. It is equally effective with tetracycline; however, it induces higher rates of resistant *P. acnes* strains and may, therefore, be more often associated with treatment failures [12]. Its intolerable gastrointestinal side effects can be minimized by using intestine-soluble preparations.

Clindamycin is very effective but has disadvantages for long-term therapy because of the possible induction of pseudomembranous colitis. Cotrimoxazole (trimethoprim/ sulfamethoxazole, 160 mg/800 mg twice daily) is

effective in acne, however, it is recommended to reserve this drug for patients who responded inadequately to other antibiotics and for patients with gram-negative folliculitis.

Bacterial resistance is not rare after systemic administration of antibiotics over several months (table 5). Gastrointestinal upset under tetracycline and doxycycline with nausea, vomiting and diarrhea and vaginal candidosis under tetracycline are probably caused through changes in the gastrointestinal flora. Ultraviolet light sensitivity under tetracycline and doxycycline, not under minocycline, is frequent. Painful onycholysis has been occasionally observed under tetracycline treatment. Minocycline may cause allergic skin reaction, reversible vestibular disturbances (e.g. dizziness, vertigo, ataxia) and a blue-grey discoloration of the skin, particularly in inflamed areas, due to a reaction with free iron. Rarely, hepatitis and reactions resembling serum sickness and lupus erythematosus have been reported in association with oral use of tetracyclines, particularly minocycline. The teeth discoloration reported in children under 10 years can rarely also occur in adults. Tetracyclines are also accused for inducing benign intracranial hypertension which is, however, a rare adverse event. Tetracyclines must not be combined with systemic retinoids because the probability for development of intracranial hypertension increases. Since tetracyclines are contraindicated in pregnancy, erythromycin has to be administered as an alternative drug. Erythromycin causes the most frequent emergence of resistant *P. acnes* strains. It is also responsible for intolerable gastrointestinal side effects in many patients. Clindamycin treatment of acne is almost abandoned in several countries because of its association with pseudomembranous colitis due to intestinal colonization with *Clostridium difficile*. Metronidazole is then indicated in those cases. Appearance or enhancement of a vaginal candidosis can be observed in females, which frequently settles over the intestinal region.

Treatment with oral antibiotics should be administered for no less than 2 months but also generally not exceed 4–6 months [44]. Maximum clinical improvement is to be expected in the first 3–4 months; lack of improvement may indicate emergence of bacterial resistance [12]. Systemic antibiotics can be well combined with topical preparations, especially tretinoin, azelaic acid and benzoyl peroxide [45, 46].

Oral Isotretinoin

Oral isotretinoin is the most effective sebosuppressive agent and has revolutionized the treatment of severe acne

Table 5. Adverse events of systemic antibiotics

Adverse event	Compound
Bacterial resistance	tetracyclines > erythromycin > cotrimoxazole > minocyclin
Gastrointestinal discomfort	clindamycin, tetracyclines
Pseudomembranous colitis	clindamycin
Postinflam. hyperpigmentation	minocycline > tetracycline
Vestibular disturbances	minocycline
Hypersensitivity reaction	minocycline, cotrimoxazole
Lupus erythematosus-like syndrome	minocycline
Interstitial nephritis/hepatic failure/systemic eosinophilia	minocycline

[28, 47–50]. It is the only drug currently available that affects all four pathogenic factors of acne. Like other retinoids, isotretinoin reduces comedogenesis. Moreover, it reduces sebaceous gland size (up to 90%) by decreasing proliferation of basal sebocytes, it suppresses sebum production in vivo and inhibits terminal sebocyte differentiation. Its stereoisomers tretinoin and alitretinoin (9-*cis* retinoic acid) were found inferior to isotretinoin in sebum suppression or acne treatment. Although not directly affecting *P. acnes*, its inhibitory effect on sebum production leads to alteration of the follicular microclimate and indirect fall of *P. acnes* counts reducing its ability to cause inflammation [51].

There is still debate as to the choice of dose. Some authors favor isotretinoin 0.5 mg/kg/day, others advocate higher dosage of 1 mg/kg/day. Although both regimens result to the same degree of long-term clinical improvement, relapse necessitating re-treatment occurs significantly more frequently under low-doses among patients with severe acne [52–53]. A 6-month treatment course is sufficient for 99% of the patients, but it has been documented that an initial dosage of 1 mg/kg/day for 3 months, then reduced to 0.5 and, if possible, to 0.2 mg/kg/day for 3–9 additional months will optimize the therapeutic outcome. As a rule, after 2–4 weeks of treatment, a 50% reduction of the pustules can be expected. Improvement continues during the post-treatment period. Relapses may occur after a single 6-month course. A 22–30% relapse rate was noted in patients followed for 10 years after having received isotretinoin 1 mg/kg/day (or cumulative dose ≥ 120 mg/kg), as compared to 39–82% with lower dose schedules [48].

Today, a 6- to 12-month course isotretinoin 0.5–1 mg/kg/day in most cases with severe acne, to reach a



Fig. 2. Severe acne papulopustulosa in a 21-year-old male patient before (left) and after a 4-month treatment with isotretinoin 0.5 mg/kg/day (right).



Fig. 3. Acne conglobata in an 18-year-old male patient before (left) and after a 6-month treatment with isotretinoin 1 mg/kg/day (cumulative dose 144 mg/kg) (right) [from ref. 28].

≥ 150 mg/kg total cumulative dose is recommended [28] (fig. 2–4). Three to 4 weeks after administration of the drug, an apparent flare-up may occur with increased development of inflammatory lesions which usually do not require modification of the oral dose and improve spontaneously. Factors contributing to the need for longer treatment schedules include low dose regimens (0.1–

0.5 mg/kg/day), presence of severe acne, extra-facial involvement and prolonged history of the disease. Higher dosages are indicated particularly for severe involvement of the chest and back [54]. Individual risk factors must be taken into account for establishing the dosage. Indications for optimal use are shown in table 6.

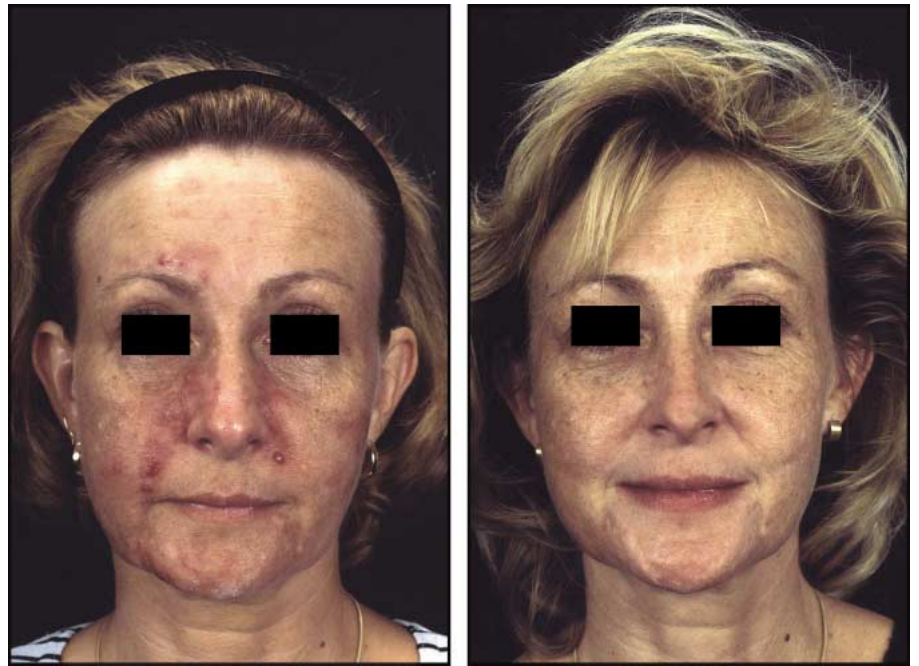


Fig. 4. Acne tarda without hormonal disturbances in a 44-year-old female patient before (left) and after a 12-month treatment with isotretinoin 0.5 mg/kg/day combined with ethinyl estradiol 35 µg/day – cyproterone acetate 2 mg/day (right).

The clinical course of isotretinoin therapy shows more rapid improvement of inflammatory lesions as compared to comedones. Pustules are cleared earlier than papules or nodules, and lesions localized on the face, upper arms and legs tend to clear more rapidly than trunk lesions [55]. Non-acne patients who have received oral isotretinoin therapy for seborrhea do not usually experience relapse for months or years. However, the duration of the sebostatic effect seems to be dose-dependent. Taking good tolerance into account, a dosage of 0.1–0.3 mg/kg/day over 4 weeks is sufficient to produce a sebostatic effect for at least 8 weeks after discontinuation of treatment. Five to 10 mg/day may be sufficient as a maintenance sebosuppressive dose over several years.

In female patients contraception is required and has to be enforced by the physician, because of the strong teratogenicity of isotretinoin [56, 57]. Isotretinoin can be well combined with a contraceptive pill which includes a hormonal anti-androgen [28, 57].

The adverse effect profile of oral isotretinoin is closely associated with hypervitaminosis A [28]. It includes a characteristic dose-dependent symptomatology with mucocutaneous side effects (table 7), elevation of serum lipids (approx. 20%), hyperostosis and extra-skeletal calcification (table 9). Arthralgia and myalgia may occur in up to 5% of individuals receiving high-dose isotretinoin. The major toxicity of isotretinoin results, however, from its

Table 6. Indications for optimal use of systemic isotretinoin

Severe acne (nodulocystica, conglobata, fulminans)
Patients with active acne and severe acne scars or potentially possible induction of physical or psychological scars
Patients with acne papulopustulosa who despite several conventional therapies, do not improve
Patients with acne papulopustulosa whose acne has responded well to conventional oral treatment on two or three occasions but has relapsed quickly after interruption of oral medication
Depressive and dysmorphic patients
In combination with oral contraceptive treatment in women with acne and signs of peripheral hyperandrogenism
Patients with excessive seborrhea
Patients with gram-negative folliculitis

teratogenic potential associated with high rate of spontaneous abortions and life-threatening congenital malformations. Therefore, the preparation can only be administered in women in combination with a secure contraceptive treatment or technique. Contraception is urgently recommended from 1 month before therapy, during the entire period of treatment and up to 3 months after discontinuation of the regimen. Oral isotretinoin treatment appears today strictly contraindicated in pregnancy, the

lactation period and in severe hepatic and renal dysfunction. Hyperlipidemia, diabetes mellitus and severe osteoporosis are relative contraindications. Co-medication with vitamin A (increased toxicity), tetracyclines (cranial hypertension) and high doses of aspirin (potentiation of mucosal damage) should be avoided. Liver and fat values in blood must be regularly controlled [58].

In long-term therapy (over 1–2 years), changes in the bone system with hyperostosis, periostosis, demineralization, thinning of the bones and premature calcification of epiphyses in adolescents have to be taken into consideration [59]. A radiograph and growth measurements are

reasonable tests before treatment of adolescents. Long-term adverse events after discontinuation of isotretinoin are rare.

Anti-Androgens

Hormonal anti-androgenic treatment can be administered in female patients to target the pilosebaceous unit and may inhibit sebum production by 12.5–65% (table 8) [25–27, 60, 61]. Once the decision has been made to initiate hormonal therapy, there are various options to choose among androgen receptor blockers and inhibitors of androgen synthesis at the levels of the ovary or the adrenal gland. Hormonal anti-androgenic treatment for acne must be continued for a sufficient period of time, at least 12 months and frequently longer. It is absolutely contraindicated in women who want to become pregnant due to the risk for sexual organ malformation in a developing fetus.

A most effective compound is cyproterone acetate, which belongs to the group of hydroxy-progesterones and blocks the binding of androgens to their receptors. There is current evidence that cyproterone acetate exhibits a dual activity by also inhibiting the synthesis of adrenal androgens because it inhibits the conversion of dehydroepiandrosterone to androstenedione by 3 β -hydroxysteroid dehydrogenase/ Δ^5 -4-isomerase, which mainly occurs in the adrenal gland, and in the skin, in the sebaceous gland. Cyproterone acetate is incorporated in a marketed hormonal contraceptive at a dose of 2 mg in combination with 35 μ g ethinyl estradiol to avoid menstrual cycle problems [62–65] (fig. 5). The preparation can be used for both contraception and treatment of acne with or without signs of hyperandrogenism, even when serum androgen levels are normal. It has been shown to decrease serum gonadotropin, testosterone and androstenedione, with control of seborrhea and acne after three months treatment. In women with abnormal androgen metabolism additional cyproterone acetate 10–20 mg/day, and in some cases up to 50 mg/day can be administered orally during the first

Table 7. Mucocutaneous adverse events of isotretinoin (% values)

Cheilitis	75–95
Dermatitis facialis	30–50
Xerosis	30–50
Dry mucosa	20–50
Conjunctivitis	30
Epistaxis	25
Itching	25
Epidermal atrophy	15–25
Skin fragility	15–20
Desquamation	10–20
Hair loss	10–20
Retinoid dermatitis	5

Table 8. Indications for optimal use of hormonal therapy in women

Acne accompanied by mild or moderate hirsutism
Inadequate response to other acne treatments
Acne that began or worsened in adulthood
Premenstrual flares of acne
Excessive facial oiliness
Inflammatory acne limited to the ‘beard area’

Table 9. Adverse events of systemic anti-acne drugs

Agent	Adverse event
Isotretinoin	teratogenicity, skin and mucosal dryness, irritation, bone changes, increase of the blood values for neutral lipids (cholesterol, triglycerides)
Hormonal contraceptives	edemas, thrombosis, increased appetite, weight gain, breast tenderness, decreased libido
Spirolactone	breast tenderness, menstrual irregularities, increased potassium blood levels



Fig. 5. Acne nodulocystica in a 20-year-old female patient before (left) and after a 6-month treatment with ethinyl estradiol 35 µg/day – cyproterone acetate 2 mg/day (right).



Fig. 6. Acne tarda with increased serum dihydroepiandrosterone in a 31-year-old female patient before (left) and after a 2-month treatment with prednisolone 5 mg/day (right).

10 days of the menstrual cycle. Alternatively, a single i.m. injection of 100–300 mg cyproterone acetate can be applied at the beginning of the cycle.

There are other hormonal blockers of androgen receptors available, such as the gestagene chlormadinone acetate (2 mg) alone or in combination with 50 µg ethinyl estradiol or 50 µg mestranol in a contraceptive pill [66].

Most oral contraceptives contain two agents, estrogen (generally ethinyl estradiol) and a progestin. In their early formulations, oral contraceptives included high estrogen concentrations of over 100 µg which could directly suppress sebum production; low estrogen levels used currently act in the liver to increase the synthesis of sex hormone-binding globulin (SHBG). Circulating free testosterone

levels are reduced by the increased SHBG levels, leading to a decrease in sebum production. Oral contraceptives inhibit the ovarian production of androgens by suppressing ovulation. This, in turn, decreases serum androgen levels and reduces sebum production. On the other hand, the progestins administered belong to the families of estranes and gonanes with a variety of drugs in each class. Some progestins can cross react with the androgen receptor or, like the progestins norgestrel and levonorgestrel, reduce SHBG increasing free testosterone, thus leading to increased androgenic effects and aggravating acne, hirsutism, or androgenic alopecia [67, 68]. They can also cause changes in lipid metabolism and can increase serum glucose, leading to glucose intolerance, as well as possibly interfering with the beneficial effect of estrogen on the SHBG. Hormonal contraceptives are associated with edema, thrombosis, increased appetite, weight gain, breast tenderness and decreased libido [61].

Spironolactone, a synthetic steroid primarily acting as aldosterone antagonist, also blocks the androgen receptor exhibiting sufficient sebosuppression at doses 50–200 mg/day, a 2 × 25 mg regimen daily or at 4–22 days of cycle being the mostly used in anti-acne therapy. It may induce, however, cycle disturbances which can be corrected by non-androgenic progestins [69]. Spironolactone may induce dose-dependent breast tenderness, menstrual irregularities and increased potassium blood levels [70].

Flutamide, a synthetic compound which has mainly been administered to hirsute females, has been also shown to be active in acne after 1–6 months of treatment at doses of 250–500 mg/day (optimum 2 × 250 mg/day over 6 months) [63]. The agent becomes active through first-pass metabolism to 2-hydroxyflutamide. It inhibits binding of 5 α -dihydrotestosterone to its receptor protein and nuclear translocation of the receptor. Also, it may accelerate conversion of active androgens to inactive metabolites. Hepatic function laboratory tests should be done periodically [71].

Among nonhormonal anti-androgens, ketoconazole (cytochrome P-450 inhibitor and steroidogenesis enzyme blocker) in a dose of >200 mg/day and cimetidine (H₂-receptor antagonist) 5 × 300 mg/day exhibit weak anti-androgenic activity [70].

Gonadotropin-releasing agonists, such as buserelin, nafarelin or leuprolide, have been used to interrupt androgen production by the adrenals and ovaries by blocking FSH and LH liberation by the pituitary gland. These drugs are efficacious in acne and hirsutism, and are available as injectable drugs or nasal spray [25, 67]. However, in addition to suppressing the production of ovarian

androgens, they also suppress the production of estrogens, thereby eliminating the function of the ovary. Thus, the patient could develop menopausal symptoms and suffer from hypoestrogenism. They have variable acceptance due to the development of headaches as well as the occurrence of bone loss, due to the reduction in estrogen. They have not been registered for the treatment of acne.

Severe Inflammatory Acne and Acne fulminans

Systemic corticosteroids can become necessary in acne fulminans to suppress the excessive immunological reaction [54], in severe inflammatory forms of acne, and in order to prevent or treat a severe flare of the disease in the first 4 weeks of isotretinoin treatment. It is preferable to administer the corticosteroids for 3–4 weeks before administration of isotretinoin [72] but a combination of isotretinoin 0.5–1 mg/kg body weight/d and prednisolone 30 mg/day for 4–6 weeks (or other doses) with gradual reduction can also accelerate the conversion of fulminate disease course to common inflammatory acne [54, 73].

In contrast, oral non-steroidal anti-inflammatory agents have rarely been administered in the treatment of severe inflammatory acne forms.

Acne tarda

Systemic corticosteroids inhibit adrenal androgen liberation and, therefore, they are indicated in acne patients with adrenal hyperandrogenism and increased dihydroepiandrosterone levels, such as female patients with acne tarda [74]. This variant of acne tarda is characterized by inflammatory lesions, since increased dihydroepiandrosterone induces inflammation [75]. They are used at low prednisone, prednisolone (2.5–7.5 mg/day prednisolone) or dexamethasone doses [20] (fig. 6).

New Developments and Future Trends

After decades of stagnation, research on systemic acne treatment has expanded markedly in the last several years. The results of numerous studies have greatly increased our understanding of both the pathophysiology of the disease and the mechanisms of action for current therapies. New developments occurred including the low-dose long-term isotretinoin regimen, new isotretinoin formulations, understanding of isotretinoin's anti-sebotropic action, new antibiotics, and combination treatments to reduce toxicity and bacterial resistance, and new oral contraceptives. Future trends represent new anti-inflammatory agents, such as 5-lipoxygenase inhibitors, insulin-sen-

sitizing agents, 5 α -reductase type 1 inhibitors, and anti-sense molecules.

Low-Dose Isotretinoin

Low-dose isotretinoin (0.1–0.3 mg/ml/day daily or intermittent use) can effectively control acne, also being cost-effective. Nevertheless, the daily dose is too low for the cumulative dose obtained to be definitively curative. Although studies have been centered on the use of low doses only in older patients with exceptionally oily skin or in patients with long duration acne [76–80], there is a trend by practicing dermatologists to use low-dose isotretinoin in adolescent acne with a tendency to become inflammatory or in moderate acne as replacement of systemic antibiotics. The suggested rationale of such use is the effective control of inflammation with the final objective of preventing inflammation and the resulting scars. The approach taken is that of control and not of absolute resolution, since this resolution will occur in the majority of patients naturally. The simultaneous use of an effective topical therapy is mandatory. Since a large percentage of patients to be treated with mini-doses are women, they should be made to understand that the teratogenesis risk is the same as with the complete dose. Adverse events with these low doses are almost absent.

New Isotretinoin Formulations

A recent study by Strauss et al. [81] using a micronized isotretinoin formulation with higher bioavailability exhibited similar efficacy results of a single daily 0.4 mg/kg dose of micronized isotretinoin and 1.0 mg/kg standard isotretinoin administered in two divided doses after 20 weeks of treatment. Micronized isotretinoin presented a safety profile similar to that of standard isotretinoin with a lower risk of mucocutaneous adverse events and hypertriglyceridemia [82].

Understanding the Unique Activity of Isotretinoin

The high anti-sebotropic activity of isotretinoin is particularly surprising because of the fact that it has low binding affinities for both cellular retinoic acid-binding proteins I and II as well as for nuclear retinoic acid receptors [83, 84]. Because retinoids are thought to exert most of their effects by modulating gene expression and/or activating nuclear retinoid receptors, it has been suggested that isotretinoin may act as a pro-drug that becomes active after isomerization to tretinoin acid or conversion to alitretinoin [84]. Indeed, current results reported by Tsukada et al. [85] have shown that isotretinoin undergoes significant isomerization to tretinoin in cultured

sebocytes, an effect being specific for these cells. In addition, administration of isotretinoin to sebocytes only led to a delayed induction of the cytochrome P450 isoenzymes responsible for tretinoin inactivation. Isotretinoin effects were found to be dependent on the extra-cellular albumin concentration [86]. On the other hand, tretinoin acted via retinoic acid receptors (RAR) to exert its anti-proliferative effect on sebocytes. Therefore, the molecular basis for this anti-sebotrophic activity is probably a selective intracellular isomerization of isotretinoin to tretinoin in human sebocytes, with isotretinoin representing a pro-drug for tretinoin in this specific tissue. Newer data indicate that isotretinoin metabolites, such as 4-oxo-isotretinoin, may also represent compounds exhibiting direct anti-acne activity.

In addition to the better understanding of isotretinoin activity, new possible adverse events have emerged. The proposed relationship between the compound and depression as well as suicide was reviewed not to be based on a putative molecular mechanism of the compound indicating that there is no evidence to support a casual connection [87]. On the other hand, 38 different signs and symptoms of ocular abnormalities were reported as 'certain' to have resulted from the use of isotretinoin, among them decreased dark adaptation may jeopardize adolescents under the drug who drive in the night [88].

New Antibiotics

Limecycline is a second-generation tetracycline linked to the amino acid lysine, with an efficacy similar to that of doxycycline and minocycline [89]. It is used at a 300 mg initial dose that is lowered to 150 mg after 2 weeks. It exhibits excellent tolerance with scarce risk of hyperpigmentation, vestibular disorders and photosensitivity, and can be administered together with food.

Roxithromycin, a macrolide antibiotic, is administered in a dose of 150 mg twice daily in the treatment of inflammatory acne. It accumulates at therapeutic levels in the pilosebaceous system [90] and exhibits an interesting spectrum of effects, namely direct anti-inflammatory and anti-androgenic activities. It significantly inhibits the production of lipase and neutrophil chemotactic factor by *P. acnes* as well as of *P. acnes*-induced NF-kB activation at concentrations much lower than the MIC at which the growth curve of *P. acnes* is not affected [34, 91]. In addition, roxithromycin was found to serve as anti-androgen only in the hypersensitive state to androgens, but not in the physiological state through modulating end-organ hypersensitive condition to androgens [92].

Azithromycin, another macrolide antibiotic, was found as effective as doxycycline (100 mg/day) administered in a dose of 500 mg once a day for 4 days per month for a total of 12 weeks on a pure protocol basis and statistically significantly better than doxycycline by intention to treat analysis [93].

In an open study, levofloxacin was found effective for inflammatory acne and achieved high levels in the lesions [94].

Combination Treatments

Combinations of a topical retinoid (adapalene, tretinoin) or azelaic acid with oral antibacterial agents are recommended to induce maximum anti-inflammatory effect in mild to moderate inflammatory acne [45, 46, 93, 95]. Such combinations can lead to a rapid dose reduction and quicker discontinuation of oral antibiotics increasing the effectiveness, improving the compliance, and reducing the development of bacterial resistance to antibiotics.

New Oral Contraceptives

When oral contraceptives are administered in the treatment of acne, it is possible that some women are more sensitive to the androgenic effects of a progestin, but it is more likely that the effect of progestin may be offset by the estrogen. Although some progestins might be more androgenic than others, all oral contraceptives, regardless of the type of progestin each contains, increase SHBG and inhibit serum androgen levels. This is also possible with the marketed combination of ethinyl estradiol (20 µg) and levonorgestrel (100 µg; one of the older and most androgenic progestins) found to produce a significant decrease in comedones, as well as in papules and pustules [66, 96, 97].

The concentrations of estrogen in oral contraceptives have decreased over the years from 150 to 35 µg, and in the most recent forms to 20 µg, in order to reduce the side effects of estrogen. On the other hand, many progestins have been developed over the years and the third-generation progestins, including desogestrel, drospirenone, gestodene, and norgestimate, are more selective for the progesterone receptor rather than the androgen receptor. The combinations of ethinyl estradiol (30–40 mg) and desogestrel (25–125 µg) [65, 98], ethinyl estradiol (20–35 µg) and norethindrone acetate (1 g) [99], ethinyl estradiol (30 mg) and drospirenone (3 mg) [64], and ethinyl estradiol and norgestimate (180–250 µg) [100, 101] have been marketed as contraceptive pills; among them those including norethindrone acetate and norgestimate have been approved for acne [27].

New Anti-Inflammatory Agents

It is widely accepted that inflammation in acne vulgaris may be mainly induced by an immunologic reaction to extracellular products of *P. acnes* [102]. However, it is by no means clear that either bacteria or their products initiate follicular inflammation. Ingham et al. [103] investigated the presence of pro-inflammatory cytokines in open acne comedones from untreated acne patients and found bioactive interleukin(IL)-1 α -like material. The majority of open comedones also contained micro-organisms, but there was no significant correlation between levels of any cytokine, in particular IL-1 α , and numbers of micro-organisms.

Additional results have shown that the sebaceous gland expresses a number of different cytokines at steady state, without the influence of any external factors. Antilla et al. [104] showed that IL-1 is present in normal sebaceous glands and Boehm et al. [105] used in situ hybridization techniques to show that messenger RNA (mRNA) for IL-1 α , IL-1 β and tumor necrosis factor- α is present at multiple sites in normal skin including the sebaceous glands. Thus, while the presence of bacteria, most notably *P. acnes*, may stimulate upregulation of cytokine expression in sebaceous glands [106], pro-inflammatory cytokines are expressed in these tissues in the absence of defined external influences.

Guy et al. [107] assessed the action of IL-1 α in the microdissected human pilosebaceous infundibulum preparations in vitro and found an IL-1 α -specific induction of hypercornification of the infundibulum similar to that seen in comedones. Follicular keratinocytes and sebocytes in vitro were also found to produce pro-inflammatory cytokines and chemokines [108]. Currently, inflammation has been suggested to occur due to enhancement of IL-8 production in human monocytes and sebocytes through a mechanism requiring transcription factor NF- κ B activation [34, 108] and involvement of Toll-like receptor 2 [109, 110]. These results provide logical support for the use of anti-inflammatory regimens in the treatment of acne [13].

The use of anti-inflammatory drugs for the treatment of acne is further supported by recent results indicating a key role for leukotriene B₄ (LTB₄) in the development of tissue inflammation [111]. LTB₄ is a pro-inflammatory mediator synthesized from arachidonic acid. Synthesis of LTB₄ is catalyzed by 5-lipoxygenase and leukotriene A₄ hydrolase and is increased by inflammatory mediators including endotoxin, complement fragments, tumor necrosis factor- α and interleukins. LTB₄ induces recruitment and activation of neutrophils, monocytes and eosin-

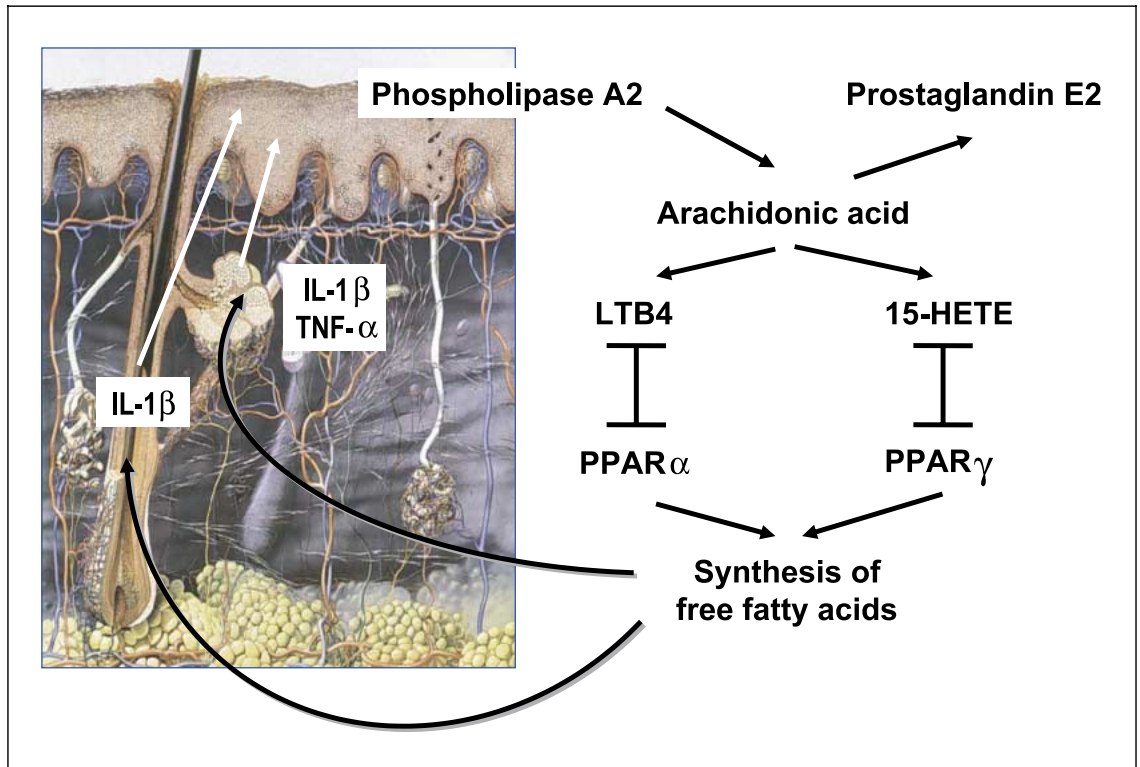


Fig. 7. The cascade of eicosanoid synthesis in the skin, as inflammatory signaling pathway possibly involved in the development of acne lesions. IL-1 β = Interleukin-1 β ; TNF- α = tumor necrosis factor- α ; LTB4 = leukotriene B4; 15-HETE = 15-hydroxyeicosatetraenoic acid; PPAR = peroxisome proliferator-activated receptor [from ref. 24].

ophils. It also stimulates the production of a number of pro-inflammatory cytokines and mediators that augment and prolong tissue inflammation (fig. 7). Limited data from pharmacological inhibition studies support a role for LTB4 in the pathogenesis of neutrophil-mediated tissue damage.

The potential importance of this inflammatory pathway for acne treatment was evaluated in a small cohort of patients [112]. A 3-month study of the effectiveness of a specific lipoxygenase inhibitor was performed by systemic administration in 10 patients with inflammatory acne. Clinical evaluation of these patients indicated an approximately 60% decrease in the acne severity index within 3 weeks of the initiation of treatment and a 70% reduction in inflammatory lesions at 3 months. Additional evaluation indicated an approximately 65% reduction in total sebum lipids as well as a substantial decrease in lipoperoxides. Free fatty acids were also decreased by almost 80%. Bivariate analysis indicated that the decrease in total sebum lipids, and especially in pro-inflammatory lipids, was directly correlated with the improvement in

inflammatory lesions. Thus, the results of this small-scale clinical trial and associated laboratory analysis strongly support the conclusion that appropriate anti-inflammatory therapy has the potential to effectively treat acne. These results also support the view that sebum lipids induce inflammation in acne, independent of the presence of bacteria or increased systemic levels of pro-inflammatory molecules.

Eleven years ago, Wozel et al. [113] assessed the ability of isotretinoin as well as a number of other agents to inhibit transdermal migration of polymorphonuclear leukocytes stimulated by LTB4. Topical treatment with isotretinoin resulted in a marked and statistically significant inhibition of the LTB4-induced migration of polymorphonuclear leukocytes. Retinoids are nowadays considered to regulate inflammation [114, 115] probably also using the Toll-like receptor 2 pathway [116].

Insulin-Sensitizing Agents

Since insulin has a direct effect on ovarian androgen production in vitro, insulin resistance may play a crucial

role in the physiopathology of peripheral hyperandrogenism, including acne [117]. Insulin-sensitizing agents have recently been investigated for their role in the short term treatment of insulin resistance in polycystic ovary syndrome. Controlled studies have shown that metformin administration, by promoting body weight loss, can decrease fasting and stimulated plasma insulin levels. However, other studies have shown metformin 500 mg 3 × daily to decrease insulin secretion and to reduce ovarian production of 17 α -hydroxyprogesterone with recovery of spontaneous or clomifene-induced ovulation, independently of weight loss. These findings suggest a new indication for metformin and present insulin-sensitizing agents as a novel approach in the treatment of ovarian hyperandrogenism.

Peroxisomes play an important role in regulating cellular proliferation and differentiation as well as in the modulation of inflammatory mediators. In addition, peroxisomes have broad effects on the metabolism of lipids, hormones, and xenobiotics [118]. On the other hand, activation of peroxisome proliferator-activated receptor (PPAR)- γ and - α by their respective specific ligands, thiazolidinedione and clofibrates, was found to induce lipid droplet formation in rat preputial gland cells (resembling sebocytes) but not epidermal cells in vitro [119]. PPAR- γ 1 mRNA was also demonstrated in rat preputial gland cells but not in epidermal cells. These findings are compatible with the concepts that PPAR- γ 1 gene expression plays a unique role in the differentiation of sebocyte-like cells. These findings have implications for the development of new modalities of treatment for acne vulgaris and explain why lipoxigenase inhibitors inhibit lipid synthesis [112]: The lipoxigenase products LTB₄ and 15-HETE are natural ligands of PPAR- α and PPAR- γ , respectively.

5 α -Reductase Type 1 Inhibitors

The inhibitors of 5 α -reductase isoenzymes (1 and 2) can be schematically divided in three groups according to their substrate specificity: Pure or preferential inhibitors of 5 α -reductase 1, pure or preferential inhibitors of 5 α -reductase 2, and dual inhibitors [26, 120]. Despite the fact that several steroidal and non-steroidal inhibitors have been synthesized and experimented in pharmacological models, only finasteride has been extensively used for clinical purposes, namely benign prostate hyperplasia and male baldness with positive results. In women, finasteride has been used in some control trials for treatment of hirsutism with an objective favorable response. On the basis of experimental observations on distribution of 1 and 2 isoenzymes in human skin, scalp and prostate, the pure 5 α -

reductase 1 inhibitors seem the ideal drugs for treatment of acne and hirsutism [121–123] and have been introduced in clinical studies [27].

Antisense Molecules

The androgen receptor is involved in the development of acne and its expression can classically be regulated by androgen receptor blockers. A more elegant way is the transient transfection of skin cells with antisense oligonucleotides against the androgen receptor [124]. The development of thioat- and ribosyl-antisense oligonucleotides against the androgen receptor led with high specificity in a transient diminished protein expression of the receptor and to a strong inhibition of the biological activity of androgens in human sebocytes and keratinocytes in vitro. Such experiments are only in an initial phase. The future clinical use of such highly specific compounds is dependent on several factors, among them being the effective administration pathway and the kind of transfection systems to be applied.

Conclusion

Despite the interest on the development of topical treatments for acne in the last decades [30], systemic treatment is still a milestone, especially in the treatment of moderate-to-severe scarring types of the disease. The establishment of new systemic drugs for acne is based on the consideration of successes and pitfalls of the past and the emerging knowledge of the future [125]. Among all pathogenetic factors of acne, inflammation seems to be rediscovered [13] and anti-inflammatory concepts seem to become the new trend of systemic and topical acne treatment.

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Propionibacterium acnes Resistance: A Worldwide Problem

E.A. Eady^a M. Gloor^b J.J. Leyden^c

^aUniversity of Leeds, Leeds, UK, ^bHautklinik Karlsruhe, Karlsruhe, Germany, and ^cUniversity of Pennsylvania, Philadelphia, Pa., USA

Key Words

Propionibacterium acnes · Antibiotic resistance ·
P. acnes mutations · Worldwide problem

Abstract

Antibiotic therapy directed against *Propionibacterium acnes* has been a mainstay of treatment for more than 40 years. Despite years of widespread use of systemic tetracyclines and erythromycin, change in *P. acnes* sensitivity to antibiotics was not seen until the early 1980s. The first clinically relevant changes in *P. acnes* antibiotic sensitivity were found in the USA shortly after the introduction of topical formulations of erythromycin and clindamycin. By the late 1980s, *P. acnes* strains with very high MIC levels for erythromycin and elevated MICs for tetracycline were increasingly found in the UK and the USA. Mutations in the genes encoding the 23S and 16S subunits of ribosomal RNA were first identified in the UK and also seen in a recent survey from clinics in Europe, Japan, Australia and the USA. In addition, strains were found in which these known mutations could not be identified, indicating that as yet unidentified resistance mechanisms have evolved. These findings indicate the need to develop strategies to minimize the use of antibiotics in acne therapy.

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The link between proliferation of *Propionibacterium acnes* in the environment of the microcomedo and the development of the inflammatory phase of acne has been well established. Over the past 25 years, antimicrobial therapy has been the major area of new drug development by the pharmaceutical industry. *P. acnes* is highly sensitive to a wide range of antibiotic classes (table 1) including the tetracycline and macrolide families. The challenge for antimicrobial therapy has been delivery into the lipid-rich environment of the microcomedo where *P. acnes* is proliferating in a cocoon of abnormally desquamated follicular corneocytes.

Widespread use of tetracyclines and erythromycin occurred for more than 25 years before less-sensitive strains and clinically relevant or 'resistant' strains were identified. In the late 1970s, a few strains of *P. acnes* that were relatively insensitive to erythromycin and clindamycin were first reported and were not viewed to be clinically significant [1]. In the early 1980s, shortly after the introduction of topical formulations of erythromycin and clindamycin, clinically relevant, less-sensitive strains were reported from a small group of patients in the USA [2]. Some of these strains were highly resistant to erythromycin. Subsequently, in the late 1980s and early 1990s in extensive studies at Leeds, more clinically significant antibiotic resistance and strains with multiple drug resistance were identified [3–5]. For example, continuous monitoring for nearly a decade in Leeds showed a steady increase in resistance with a prevalence of 65% seen in a specialized referral center by 1997 [5]. In addition, resistant *P. acnes* strains were identified in other countries [6–9].

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J.J. Leyden
Hospital University of Pennsylvania
2nd Floor Gates Bldg.
Philadelphia, PA 19104 (USA)
Tel. +1 215 662 6151, Fax +1 215 662 4131, E-Mail jleyden@mindspring.com

Table 1. *P. acnes* sensitivity to antibiotic classes

Very sensitive	Resistant
Tetracyclines, especially minocycline and doxycycline	Aminoglycoside Mupirocin
Erythromycin and other macrolides	Metronidazole
Clindamycin	
Penicillin and cephalosporins	
Quinolones	
Sulfonamides	

Table 2. *P. acnes* antibiotic resistance

Erythromycin	Mutations in the genes encoding 23S ribosomal RNA
Group I	A→G transition at <i>E. coli</i> equivalent base 2058 Highly resistant to erythromycin Variable for other macrolides and clindamycin
Group III	G→A transition at <i>E. coli</i> equivalent base 2057 Low level erythromycin resistance
Group IV	A→G transition at <i>E. coli</i> equivalent base 2059 Highly resistant to erythromycin and all macrolides Elevated but variable resistance to clindamycin
Tetracycline	Mutation in the gene encoding 16S ribosomal RNA G→C transition at <i>E. coli</i> equivalent base 1058 Variable resistance to tetracycline, doxycycline and minocycline

Molecular Basis for *P. acnes* Resistance

In general, bacteria develop antibiotic resistance by acquiring mobile genetic elements such as plasmids, which can be transferred between strains of a species and even between species in some instances. With tetracyclines and erythromycin, mobile plasmids and transposons encode for pump proteins that efflux antibiotics away from ribosomes, and less commonly resistance is due to enzymatic inactivation [10–12]. In the case of clinically relevant strains of resistant *P. acnes*, mobile elements have not been found. Rather, point mutations in the genes encoding the 23S rRNA (erythromycin) and the 16S rRNA (tetracycline) have been identified [13–16].

Three phenotypes for erythromycin-resistant *P. acnes* have been classified (table 2). Group I is associated with an A→G transition at *Escherichia coli* equivalent nucleotide base 2058 and confers resistance to erythromycin and all macrolide, lincosamide and streptogramin B (MLS)

Table 3. *P. acnes* resistance: worldwide study

	73 strains
	35 resistant to erythromycin only
	15 resistant to tetracycline only
	23 resistant to both
Erythromycin	Group I phenotype – 14 strains Group III phenotype – 3 strains Group IV phenotype – 22 strains Unidentified – 9 strains
Tetracycline	16S RNA mutations at base 1058 – 34 strains Unidentified – 4 strains

Table 4. Future strategies

Minimize antibiotic use
Withdraw antibiotics once inflammation is controlled
Use combination topical retinoids/antibiotic therapy
Maintenance therapy
Topical retinoids
Benzoyl peroxide or benzoyl peroxide-antibiotic therapy
Isotretinoin systemically for resistant cases

antibiotics with the MIC varying with both drug and strain. Phenotype III is associated with a G→A transition at base 2057 and confers low level resistance to erythromycin only. Group IV has an A→G mutation at base 2059 and confers high level resistance to all 14, 15 and 16 membered ring macrolides. In the case of tetracycline, resistance is associated with a mutation (G→C transition) in the 16S rRNA of the small ribosomal subunit at *E. coli* equivalent base 1058.

Worldwide Survey

In a recent survey, resistant strains isolated in France, Germany, Japan, Australia and the USA were compared with UK strains (table 3): a total of 73 strains of which 35 were resistant to erythromycin alone, 15 to tetracycline alone and 23 resistant to both were studied [17]. Interestingly, strains from Germany and Japan were resistant to only erythromycin and those from Australia were predominately resistant to tetracycline.

Phenotype I erythromycin resistance was found in 24 strains, type III in 3 and type IV in 22 strains and 9 strains with unidentified mutations. In the case of tetracycline, 34 of 38 strains showed the previously described mutation at base 1058. Nine erythromycin-resistant isolates

from Germany did not have base mutations for 23S rRNA but did show the resistance pattern found with phenotype I.

P. acnes was more sensitive to tetracycline than to macrolides with lowest MIC₉₀ seen with the more lipophilic tetracyclines such as doxycycline and minocycline. The highest levels of minocycline resistance was seen in strains from the USA. These strains of *P. acnes* were highly sensitive to penicillin, trimethoprim and madifloxacin (a recently approved quinolone).

Clinical Significance of 'Resistant Strains'

Classically, the clinical significance of less-sensitive strains is established by comparing the MIC or the minimum bactericidal concentration with the achievable concentration of the antibiotics in the body site in which the organism is proliferating. Unfortunately, no data exist for antibiotic levels in individual sebaceous follicles. Despite technological advances in microanalytical techniques, antibiotic levels in individual follicles have not yet been quantified. This means that no clinically relevant 'break point' has been established. Rather, we have had to resort to a much more difficult type of analysis, i.e. comparing clinical outcomes in those treated with antibiotics to which *P. acnes* is insensitive [4]. Despite the difficulties of

such studies, there are enough data to indicate that clinical outcomes are poor in those with 'resistant strains'. In clinical practice, one cannot obtain *P. acnes* antibiotic sensitivities on a routine basis. Rather, one must use clinical sense in the setting of a patient who is no longer responding to an antibiotic which was previously effective.

Implication and Strategies for the Future

It is now clear that antibiotic resistant strains of *P. acnes* are found worldwide. The level of resistance is greatest to erythromycin but tetracycline resistance including minocycline is also occurring, as is reduced sensitivity to clindamycin. The evidence points to an evolving problem. The common practice of long-term use of antibiotics, years in many instances, is now hard to defend unless one prescribes some form of benzoyl peroxide which suppresses emergence of resistant strains [18]. In this regard, the potential usefulness of benzoyl peroxide washes, which deposit benzoyl peroxide which resists rinsing off, are particularly interesting. Another strategy is the use of topical retinoids to maintain clearing once antibiotic therapy has suppressed the inflammatory phase of acne and possibly to consider systemic isotretinoin as an option for those in whom inflammation cannot be controlled without prolonged antibiotic use (table 4).

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Update and Future of Hormonal Therapy in Acne

Diane Thiboutot^a WenChieh Chen^b

^aDepartment of Dermatology, The Pennsylvania State University College of Medicine, Hershey, Penn., USA;

^bDepartment of Dermatology, College of Medicine, National Cheng Kung University, Tainan, Taiwan/ROC

Key Words

Acne · Hormone · Androgens · Steroid · Oral contraceptive

Abstract

Hormonal therapy is an important component in the treatment of women with acne who may or may not have elevated serum androgens. The mainstays of hormonal therapy include oral contraceptives and antiandrogens such as cyproterone acetate, flutamide or spironolactone. Recent research over the past several years has unraveled some of the details regarding the way that the skin and sebaceous glands synthesize and metabolize hormones. The knowledge gained from this work may provide an impetus for future drug discovery in the hormonal treatment of acne and lead to improvements in the care of our patients with acne.

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Introduction

Both clinical observation and experimental evidence confirm the importance of hormones in the pathophysiology of acne. Hormones are best known for their effects on sebum excretion. It has also been suggested that hormones may play a role in the follicular hyperkeratinization seen

in follicles affected by acne [1–3]. From a therapeutic standpoint, the importance of the role of hormones in acne is supported by the clinical efficacy of hormonal therapy in women with acne.

Although we know that hormones are important in the development of acne, many questions remain unanswered about the mechanism by which hormones exert their effects. For example, the specific hormones that are important in acne have not been definitively identified. Androgens such as dihydrotestosterone (DHT) and testosterone (T), the adrenal precursor dehydroepiandrosterone sulfate (DHEAS), estrogens such as estradiol and other hormones such as growth hormone may each be important in acne. It is not known if these hormones are taken up from the serum by the sebaceous gland or if they are made locally within the gland. Finally, the cellular and molecular mechanisms by which these hormones exert their influence on the sebaceous gland have not been fully elucidated. The goal of this chapter is to present the clinical and experimental evidence for the role of hormones in acne while pointing out gaps in our current understanding. As future research fills in these gaps, we will be able to design improved therapies that target the hormonal causes of acne.

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Diane Thiboutot
Division of Dermatology, Milton Hershey Medical Center
Pennsylvania State University, P.O. Box 850
Hershey, PA 17033 (USA)
Tel. +1 717 531 7437/8307, Fax +1 717 531 4821, E-Mail dthiboutot@psu.edu

Androgens and Sebum Production

The majority of potent androgens are produced by peripheral target tissues. For example, in postmenopausal women, 100% of active sex steroids are synthesized in peripheral target tissues from inactive steroid precursors while in adult men approximately 50% of androgens are locally made in intracrine target tissues [4]. The major androgens that interact with the androgen receptor are testosterone and dihydrotestosterone. Androgen receptors have been localized to the basal layer of the sebaceous gland and the outer root sheath keratinocytes of the hair follicle [5, 6]. Dihydrotestosterone is approximately 5–10 times more potent than testosterone in its interaction with the androgen receptor.

An essential role for androgens in stimulating sebum production is supported by the following clinical evidence: (1) androgen-insensitive subjects who lack functional androgen receptors do not produce sebum and do not develop acne [7], and (2) systemic administration of testosterone and dehydroepiandrosterone increases the size and secretion of sebaceous glands [8].

Several clinical observations point to the importance of androgens in acne. The development of early acne in the prepubertal period has been associated with elevated serum levels of dehydroepiandrosterone sulfate (DHEAS), a precursor of testosterone [9, 10]. For example, acne occurs near the time of puberty. In fact, investigators have demonstrated that acne begins to develop at the time of adrenarche when the adrenal gland begins to produce large quantities of DHEAS [9, 10]. This hormone can serve as a precursor to the production of more potent androgens within the sebaceous gland. The rise in serum DHEAS in prepubescent children is associated with an increase in sebum production and the development of comedonal acne.

Severe acne is often associated with elevated serum androgens [11]. Conditions of androgen excess or hyperandrogenism are associated with increased sebum production and the development of acne. Hyperplasia or carcinomas that produce excess androgens (e.g. of the ovary or the adrenal) are often associated with the development of acne. Sudden onset of acne or treatment-resistant acne may be associated with hyperandrogenism from causes such as an adrenal or ovarian tumor or from conditions such as congenital adrenal hyperplasia or polycystic ovary disease. Conversely, it has been observed that men with androgen insensitivity (nonfunctional androgen receptors) do not produce adult levels of sebum and they do not develop acne [7]. This clinical observation implies that a

functional androgen receptor is required for sebum production. Since both testosterone and dihydrotestosterone act at this receptor, either one or both of these androgens is required to produce adult levels of sebum.

Several early experiments have demonstrated that androgens act to stimulate sebum secretion. For example, prepubertal boys given injections of testosterone were shown to have increased sebum production [12]. Histologically, increase in the size of their sebaceous glands was demonstrated. In addition, systemic administration of DHEAS, androstenedione and testosterone were shown to exert similar effects on the sebaceous gland [8]. It has been hypothesized that DHT is the effector androgen that mediates sebum production and the development of acne. Since testosterone also acts at the androgen receptor, a role for this androgen in mediating sebum production cannot be excluded [13].

Serum androgens are elevated in cases of acne associated with hyperandrogenism and in cases of severe cystic acne. Serum androgens are however within normal limits in the majority of females with acne. For this reason, it has been hypothesized that there may be increased local production of androgens within the sebaceous glands of subjects with acne [14, 15]. Alternatively, the sebaceous glands from subjects with acne may be more sensitive to the effects of androgens. It is unclear as to whether acne is mediated by serum androgens, locally-produced androgens or a combination of both. Recently, insights have been gained regarding the local metabolism of androgens within sebaceous glands. Such insights may be of benefit in the design of new acne therapies.

Androgen Metabolism within the Skin

Dehydroepiandrosterone sulfate (DHEAS) is produced in large quantities by the zona reticularis of the adrenal gland. It circulates in the bloodstream in high levels in relatively high levels compared to other hormones with the exception of cortisol. The enzyme 3 β -hydroxysteroid dehydrogenase (3 β -HSD) acts on DHEA to convert it to androstenedione (fig. 1). This conversion may take place in the adrenal gland and tissues such as the sebaceous gland where activity of the 3 β -HSD enzyme has been identified by several investigators [16–18]. There are two known forms or isozymes of 3 β -HSD. The type I isozyme is active in skin, placenta and mammary tissue, whereas the type II isozyme is active in the adrenal gland and the gonads [19]. The major isozymes of steroid-metabolizing enzymes that are active in human sebaceous glands are listed in table 1.

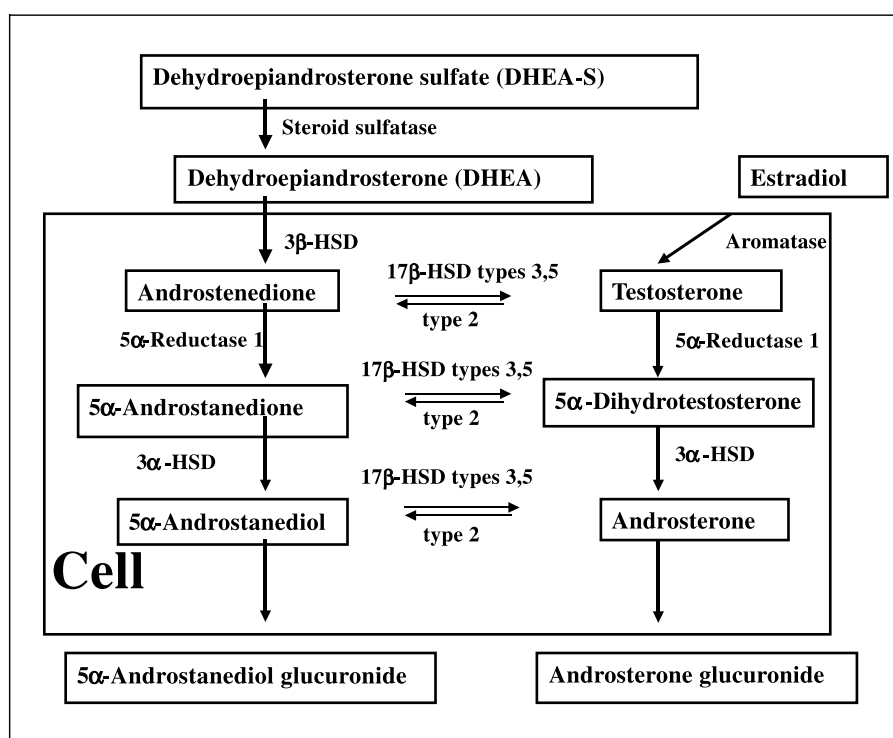


Fig. 1. Biochemical pathway of sex steroid hormone metabolism. HSD = Hydroxysteroid dehydrogenase; 5 α -R = 5 α -reductase.

Another important enzyme that is found within the skin is 17 β -hydroxysteroid dehydrogenase (17 β -HSD). This is a reversible enzyme that can oxidize and reduce both androgens and estrogens. It is responsible for converting the weak androgen androstenedione into the more potent androgen testosterone. It can also interconvert weak and potent estrogens such as estrone and estradiol. Testosterone in turn can be produced from androstenedione. To date, seven types of human 17 β -HSDs have been cloned, sequenced, and characterized, designated types 1–7 in the chronological order of their isolation [20–23]. Recently, the type 8 17 β -HSD also known as Ke6 gene was shown to efficiently transform estradiol to estrogen in transfected HEK-293 cells [24]. The type 2 isozyme of 17 β -HSD appears to be the most active within the sebaceous gland where it prefers to oxidize testosterone back to androstenedione [25–27]. In this regard, the 17 β -HSD enzyme may play a protective role in the skin by metabolizing testosterone back to the less potent precursor, androstenedione. It may also represent a regulatory point in androgen and estrogen metabolism within the skin.

Dihydrotestosterone is produced from testosterone within peripheral tissues such as the skin by the action of the 5 α -reductase enzyme. Recently, two isozymes of 5 α -reductase have been identified [28]. The type 1 isozyme is

Table 1. Predominant isozymes of steroid metabolizing enzymes expressed in sebaceous glands

3 β -Hydroxysteroid dehydrogenase	type 1
17 β -Hydroxysteroid dehydrogenase	type 2
5 α -Reductase	type 1

active within the sebaceous gland and in keratinocytes derived from the infrainfundibular region of pilosebaceous follicle (from the base of the epidermis to the point of insertion of the sebaceous duct) [3, 29]. The type 2 isozyme is most active in the prostate gland where it can be inhibited by drugs such as finasteride. While the type 1 5 α -reductase has a broad alkaline pH optima of 6.0–8.5 and demonstrates relatively moderate affinity for steroid substrates ($K_m = 1\text{--}5\ \mu\text{M}$), the type 2 5 α -reductase has a narrow acidic pH optimum of 5.0–6.0 and demonstrates high affinity for substrates ($K_m = 4\text{--}50\ \text{nM}$) [30, 31]

Activity of 5 α -reductase and 17 β -HSD exhibits regional differences depending upon the source of the sebaceous glands [25, 29] (fig. 2). In skin that is prone to acne, such as facial skin, activity of the type 1 5 α -reductase in sebaceous glands is greater than in sebaceous glands obtained

from nonacne-prone skin. This implies that more DHT is being produced in sebaceous glands from facial skin compared to other areas of the body that are not prone to develop acne. In contrast, the oxidative activity of the type 2 17 β -HSD enzyme is greater in sebaceous glands from nonacne-prone areas compared to sebaceous glands obtained from facial skin. Since the predominant activity of this isozyme is to transform testosterone back to its less active precursor, it may be inferred that facial skin is less able to metabolize testosterone to its less potent precursor. The net effect of the activity of these two enzymes is the greater production of potent androgens such as T and DHT within sebaceous glands of facial areas that may in part account for the development of acne in these areas.

Site of Androgen Action in Acne

The sebaceous gland is known to be a site of androgen action within the pilosebaceous unit. It has also been hypothesized that androgens may play a role in follicular hyperkeratinization in acne in addition to their effects on stimulating sebum secretion [1, 2]. Indirect evidence in support of this hypothesis includes the finding of androgen receptors in the outer root sheath of sebaceous follicles, the clinical observation that antiandrogens may reduce follicular casts and the finding of activity of androgen-metabolizing enzymes such as 3 β -HSD, 17 β -HSD and 5 α -reductase in follicles. Furthermore, the activity of 17 β -HSD and 5 α -reductase is significantly greater in infrainfundibular keratinocytes compared to keratinocytes obtained from the interfollicular epidermis, suggesting that follicular keratinocytes have a greater propensity to produce potent androgens [32]. Direct evidence in support of the effects of androgens on follicular keratinization is needed.

Mechanism of Androgen Action in Acne

Androgens are thought to stimulate the growth and differentiation (sebum production) of sebaceous glands. The exact mechanism by which this is accomplished has not been defined. Androgens such as testosterone and DHT form complexes with nuclear androgen receptors. The androgen/receptor complex then interacts with DNA in the nuclei of sebaceous cells to regulate genes involved in cell growth and lipid production. The exact target genes have not been identified, but likely candidates would include genes for various growth factors or enzymes involved in lipid production (lipogenic enzymes) (table 2).

It is not known if androgens act directly, indirectly or both on epithelial cells within the pilosebaceous unit by

Table 2. Enzymes involved in lipogenesis in human sebaceous glands

Enzymes involved in cholesterol synthesis	Enzymes involved in fatty acid synthesis
Acetoacetyl CoA thiolase	Acetyl CoA carboxylase
HMG CoA synthetase	Fatty acid synthetase
HMG CoA reductase	
Mevalonic acid kinase	
Mevalonate decarboxylase	
Isopentenyl pyrophosphate isomerase	
Geranyl transferase	
Squalene synthetase	
Squalene oxidocyclase	

regulating the production of growth factors by dermal fibroblasts. The stromal/epithelial interaction of sex steroid hormones and growth factors is an important phenomenon in the local regulation of other endocrine-responsive tissues such as the prostate, breast, endometrium and ovary. Evidence exists for the importance of these autocrine and paracrine effects of androgens and growth factors in the regulation of sebaceous glands. In addition to androgen receptors, sebocytes also possess receptors for growth factors such as epidermal growth factor (EGF) and insulin-like growth factor I (IGF-I) [33]. Evidence exists for the role of EGF, IGF-I and keratinocyte growth factor (KGF) in modulating sebaceous gland growth. For example, growth of sebocytes is enhanced by supplementation of cell culture medium with EGF and insulin. Treatment of experimental animals with KGF stimulates growth of hair and sebaceous glands [34, 35]. The action of androgens in the sebaceous gland may thus be mediated by growth factors.

Several important enzymes involved in lipid metabolism have been identified in sebaceous glands. These include 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase which is the rate-limiting enzyme in the synthesis of cholesterol and acetyl CoA carboxylase which is the key in the synthesis of fatty acids [36]. Whether or not androgens act by stimulating these enzymes remains to be determined.

In summary, there is strong clinical and experimental evidence that androgens stimulate the proliferation of sebaceous glands and sebum secretion. Acne is associated with systemic circulating hyperandrogenism. In acne subjects with normal circulating levels of androgens there may be a local or in situ excess production of androgens or imbalance of androgen metabolism. Acne subjects with



Fig. 2. Acne secondary to an adrenal tumor. This 10-year-old female patient developed acne and hirsutism as a result of an androgen-producing tumor of the adrenal gland.



Fig. 3. Acne associated with polycystic ovarian disease. This 28-year-old patient had recalcitrant acne and an elevated serum testosterone level.

normal circulating or local levels of androgens may be 'hypersensitive' to androgens either due to an increased number of androgen receptors or abnormal postbinding response [37, 38].

Estrogens and Sebum Production

Very little is known about the role of estrogens in modulating sebum production. Any estrogen given systemically in sufficient amounts will decrease sebum production. The dose of estrogen required to suppress sebum production however is greater than the dose required to suppress ovulation. Although some patients acne will respond well to lower-dose agents containing 0.035–0.050 mg of ethinyl estradiol or its esters, higher doses of estrogen are often required to demonstrate a reduction in sebum secretion [39]. The major active estrogen is estradiol which is produced from testosterone by the action of the enzyme aromatase. Aromatase is active in the ovary, adipose tissue and other peripheral tissues. Estradiol can be converted to the less potent estrogen, estrone by the action of the 17 β -HSD enzyme. Both aromatase and 17 β -

HSD are present in the skin [26, 40]. As in the case of androgens, it is not known if circulating estrogens or locally-produced estrogens are important in modulating sebum secretion. Estrogens may act by several mechanisms, they may: (1) directly oppose the effects of androgens locally within the sebaceous gland; (2) inhibit the production of androgens by gonadal tissue via a negative feedback loop on pituitary gonadotrophin release; (3) regulate genes that negatively influence sebaceous gland growth or lipid production. It is important to note, however, that the expression of estrogen receptors in the sebaceous gland is not well defined [41–43]. Furthermore, if high circulating levels of estrogen antagonized androgen effects, it would become difficult to explain the exacerbation of acne that some women experience during pregnancy.

Growth Hormone, Prolactin and Acne

Growth hormone is secreted by the pituitary gland. It acts on the liver and peripheral tissues to stimulate the production of insulin-like growth factors (IGFs) formerly known as somatomedins. There are two forms of IGF,

termed IGF-1 and IGF-2. IGF-1 is the more prevalent growth factor. It has been hypothesized that growth hormone may be involved in the development of acne [44]. Acne is most prevalent in adolescents during a time when growth hormone is maximally secreted and serum levels of IGF-1 are at their highest. In addition, IGF-1 can be locally produced within the skin where it can interact with receptors on the sebaceous gland to stimulate its growth. Furthermore, conditions of growth hormone excess, such as acromegaly are associated with seborrhea and the development of acne. In some tissues, the actions of IGF-1 can be mediated by androgens. It is possible that androgens may influence IGF-1 action in the sebaceous gland as well. Acne can also be exacerbated by hyperprolactinemia [45, 46].

When to Suspect an Endocrine Disorder in Acne Patients

Although hormones influence acne, it is clear that the majority of acne patients do not have an endocrine disorder. Hyperandrogenism should be considered in female patients whose acne is severe, sudden in its onset or is associated with hirsutism, or irregular menstrual periods. Additional clinical signs of hyperandrogenism include Cushingoid features, increased libido, acanthosis nigricans or a deepening of the voice. Women with hyperandrogenism may also have insulin resistance. They are at risk for the development of diabetes and cardiovascular disease. It is therefore important for the long-term health of these patients to identify hyperandrogenism so that they can receive appropriate therapy from an endocrinologist or gynecologist.

Screening for an Endocrine Disorder

A medical history and physical examination directed towards eliciting any symptoms or signs of hyperandrogenism should be performed. Screening tests for hyperandrogenism include serum DHEAS, total testosterone, free testosterone, and luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio. In some cases additional information can be gained from a serum level of 17-hydroxyprogesterone. These tests should be obtained in the luteal phase of the menstrual cycle (within 2 weeks prior to the onset of menses). If a patient is taking oral contraceptives, any underlying hyperandrogenism would be masked. Therefore, it is required that the patients dis-

continue oral contraceptives 4–6 weeks prior to the endocrine evaluation.

In women there are three possible sources of androgen production:

(1) The ovary, where androgens are produced under the influence of follicle stimulating hormone (FSH) and luteinizing hormone (LH), which are secreted by the pituitary gland. LH causes the theca cells of the ovary to make androstenedione, which can be converted into testosterone. Testosterone in turn can then be released into the circulation or converted into estrogens by the aromatase enzyme present in the follicular cells of the ovary.

(2) The adrenal gland, which is acted upon by adrenocorticotrophic hormone (ACTH), also secreted by the pituitary, to produce dehydroepiandrosterone (DHEA) that can then be metabolized into more potent androgens such as androstenedione and testosterone.

(3) Within the skin itself, where all the necessary enzymes exist to convert compounds such as DHEA into more potent androgens such as DHT [47].

An elevated level of DHEAS would indicate that the source of androgens is the adrenal gland. Patients with a serum DHEAS greater than 800 µg/dl may have an adrenal tumor and should be referred to an endocrinologist for further evaluation. Values of DHEAS in the range of 400–800 µg/dl may be associated with congenital adrenal hyperplasia which is most commonly a partial deficiency in the 21-hydroxylase or 11-hydroxylase enzyme in the adrenal gland. Such an enzyme deficiency results in the shunting of steroids into the pathway resulting in increased androgen production.

If the ovary is the source of androgens, this is most commonly indicated by an elevation in testosterone. Serum total testosterone in the range of 150–200 ng/dl or an increased LH/FSH ratio (greater than 2–3) can be found in cases of polycystic ovary disease which can be characterized by irregular menstrual periods, reduced fertility, obesity, insulin resistance and hirsutism (fig. 4). Greater elevations in serum testosterone may indicate an ovarian tumor and appropriate referral should be made. However, an elevated testosterone level does not necessarily preclude an adrenal abnormality. In this case, an additional test, the LH/FSH ratio, can be performed, and an elevated serum level of 17-hydroxyprogesterone would also be indicative of a congenital adrenal hyperplasia, thus enabling an identification of an adrenal source of androgens. There is a significant amount of variation in an individual's serum androgen levels. In cases where abnormal results are obtained, it is recommended to repeat the test before proceeding with therapy or a more extensive work-up.

In the majority of cases of women with acne, serum androgens are completely normal, yet it may nonetheless seem clear that there is a hormonal component to the acne. That is, the acne becomes worse prior to menstruation, for example, and it does in fact respond if treated with hormonal therapy. This dilemma has led to studies that have found that, as a group, women with acne will have higher levels of serum DHEAS, testosterone, and DHT, than those without acne [11, 47]. However, the laboratory values may still be within the normal range. Worth noting is that these values are at the high end of the normal range and that clinical and laboratory data support the use of hormonal therapy in this group in that their acne does respond to the therapy [47].

Options for Hormonal Therapy

Once the decision has been made to initiate hormonal therapy, there are various options to choose from: (1) androgen receptor blockers, or antiandrogens (this class of drugs block the effect of androgens on the sebaceous gland and on the infundibulum of the follicle); (2) inhibition of androgen production by the ovary or adrenal gland, or (3) in the future, inhibition of androgen metabolizing enzymes in the skin may be possible (see 'Enzyme inhibitors' section below). It is important to note that hormonal therapy is absolutely contraindicated in women who want to become pregnant due to the risk for sexual organ malformation in a developing fetus.

Androgen Receptor Blockers

Spironolactone

Within the class of androgen receptor blockers, the drug options are spironolactone, cyproterone acetate, and flutamide. In the United States, spironolactone is the drug most commonly used. Oral spironolactone decreases sebum excretion rate and inhibits the type 2 17β -HSD [48, 49]. Recommended doses for the treatment of acne are 50–100 mg, taken with meals [50]. However, many women respond well to 25 mg twice daily, and some even respond to just 25 mg a day. These low doses in healthy young women are well tolerated. However, if this drug is used in older women with other possible medical problems, or if higher doses are used for conditions such as hirsutism or androgenic alopecia, serum electrolytes should be monitored. Side effects to be aware of include breast tenderness and menstrual irregularities.

Cyproterone Acetate

Through dual activity, cyproterone acetate inhibits ovulation and blocks the androgen receptor. There are two ways to use cyproterone acetate: low dosage at 2 mg per day in combination with ethinyl estradiol in an oral contraceptive (Diane, Dianette) or high dosage at 50–100 mg from days 5 to 14 of the menstrual cycle [51]. There can be improvement in 75–90% of patients who are treated with the high-dose regimen.

Flutamide

Flutamide, a very potent antiandrogen that is also used to treat prostate cancer, can be used in the treatment of acne, hirsutism, and androgenic alopecia [52]. It can be given in doses of 250 mg twice daily, in combination with an OC. Fatal hepatitis is a concern with this drug, and liver function tests should be followed [53]. The hepatotoxicity associated with flutamide seems to be dose- and age-dependent [54]. Low dose (62.5–125 mg) has been reported to be safe and effective [55].

Adrenal Androgen Production Blockers

Glucocorticoids

Another option in hormone therapy is to block the production of androgens, which can be accomplished through the use of oral contraceptives and low-dose glucocorticoids. This is most commonly used to treat the patient with late-onset congenital adrenal hyperplasia, which is an inherent defect in the 21-hydroxylase or the 11-hydroxylase enzyme. This defect causes a block in the cortisol biosynthetic pathway, which results in a buildup of precursors for potent androgens. Low-dose prednisone (2.5–5 mg a day, at bedtime) is one option. Dexamethasone can also be used, but the risk of adrenal suppression is higher. To ascertain if the therapy is having the desired effect, the serum DHEAS can be monitored. A decrease or normalization of the blood levels indicates that treatment is successful. To check for adrenal suppression, an ACTH-simulation test can be performed. This consists of injecting ACTH and assessing the plasma cortisol 30 min later. If plasma cortisol has risen by an appropriate amount, the adrenal gland is not suppressed.

Ovarian Androgen Blockers

Gonadotropin-Releasing Agonists

In addition to blocking the adrenal production of androgens, production in the ovary can also be blocked through the use of gonadotropin-releasing hormone agonists, such as buserelin, nafarelin or leuprolide. These gonadotropin-releasing agonists block ovulation by inter-

rupting the cyclic release of FSH and LH from the pituitary. These drugs are efficacious in acne and hirsutism, and are available as injectable drugs or nasal spray. However, in addition to suppressing the production of ovarian androgens, these drugs also suppress the production of estrogens, thereby eliminating the function of the ovary. Thus, the patient could develop menopausal symptoms and suffer from hypoestrogenism. Headaches can also develop, as well as the occurrence of bone loss, due to the reduction in estrogen.

Oral Contraceptives

Oral contraceptives contain two agents, an estrogen (generally ethinyl estradiol) and a progestin. In their early formulations, oral contraceptives had high concentrations of over 100 µg of estrogen. In doses higher than 100 µg, estrogens can suppress sebum production. Estrogens also act hepatically to increase the synthesis of sex-hormone-binding globulin. Circulating testosterone levels are reduced by the increased sex-hormone-binding globulin production, leading to a decrease in sebum production. Oral contraceptives inhibit the ovarian production of androgens by suppressing ovulation. This, in turn, decreases serum androgen levels and reduces sebum production.

Oral contraceptives containing cyproterone acetate such as Diane[®] and Dianette[®] are highly effective for the treatment of acne and have often served as the 'gold standard' for efficacy evaluation in clinical trials. It is available in Europe, Canada and Asia, but not in the United States. It is of use in patients with acne resistant to other therapies and reduces sebum production. In addition, it may have a direct effect on comedogenesis, which is known to be androgen mediated. Dianette[®] may represent a treatment of choice in patients who need oral therapy and who are sexually active and need a contraceptive pill or in those patients who need hormonal therapy to regulate irregular periods.

Two families, the estranes and the gonanes, comprise the progestin components of other oral contraceptives, with a variety of drugs in each class. Progestins can cross-react with the androgen receptor, which can lead to increased androgenic effects and thus aggravate acne, hirsutism, or androgenic alopecia [56]. They can also cause changes in lipid metabolism and can increase serum glucose, leading to glucose intolerance, as well as possibly interfering with the beneficial effect of estrogen on the sex-hormone-binding globulin.

However, as with the estrogens, many progestins have been developed over the years and the third-generation

progestins, including norgestimate, desogestrel, and gestodene, are more selective for the progesterone receptor rather than the androgen receptor. In the United States, the only two oral contraceptives approved for use in acne treatment are Ortho Tri-Cyclen[®] (Ortho-McNeil Pharmaceutical, Raritan, N.J., USA), which is composed of ethinyl estradiol and norgestimate and Estrostep (Parke Davis, Detroit, Mich., USA) which contains doses of 20–35 µg of ethinyl estradiol in combination with 1,000 mg norethindrone acetate. Four large placebo-controlled studies, involving a total of approximately 1,093 women with moderate acne, found improvement in inflammatory lesions, total lesions and global assessment with the estrogen-norgestimate combination (500 patients) [57, 58] and with the estrogen-norethindrone acetate combination (593 patients) [59].

The biological relevance of the different progestins is also of interest. For years it has been known that oral contraceptives are beneficial in the treatment of acne [60], and it is possible that some women are more sensitive to the androgenic effects of a progestin, but it is more likely that the effect of progestin may be offset by estrogen. All oral contraceptives, regardless of the type of progestin each contains, will inhibit serum androgen levels. Moreover, although some progestins might be more androgenic than others, there is an increase in sex-hormone-binding globulin with the use of any OC and an improvement of the acne in women who are treated with them. One OC, Triphasil[™] (Wyeth-Ayerst Pharmaceuticals, Philadelphia, Pa., USA), which contains ethinyl estradiol and levonorgestrel (one of the older progestins), was studied in acne and found to produce a 75% decrease in comedones, as well as a greater than 50% decrease in papules and pustules [61].

Oral Contraceptives with Low-Dose Estrogen

The concentrations of estrogen in oral contraceptives have decreased over the years from 150 to 35 µg, and in the most recent forms, to 20 µg, in order to reduce the side effects of estrogen. Three preparations of low-dose (20 µg) estrogens are available: Alesse[™] (Wyeth-Ayerst Pharmaceuticals), which contains ethinyl estradiol and 100 µg levonorgestrel; Mircette[™] (Organon, Inc., West Orange, N.J., USA), which contains ethinyl estradiol and desogestrel, and Estrostep (Parke Davis) which contains ethinyl estradiol and norethindrone acetate. These formulations offer the advantage of fewer estrogenic side effects, and their role in the treatment of acne is currently being evaluated [59, 62–64].

Oral Contraceptives and Antibiotics

The concern regarding oral contraceptives and antibiotics is essentially theoretical, owing to the action of broad-spectrum antibiotics, which reduce the gut flora bacteria and thus may result in decreased absorption of estrogen. This could lead to a possible reduction in the efficacy of oral contraceptives. Nevertheless, there have been very few reports in the literature of pregnancies associated with the use of antibiotics in conjunction with oral contraceptives [65, 66]. Existing reports have focused on tetracycline, and the incidence was 1.2–1.4 pregnancies/100 woman-years of use of the OC. Unfortunately, these data cannot be compared to the background failure rate of oral contraceptives [65].

Enzyme Inhibitors

As previously mentioned, certain enzymes in the skin can produce androgens locally. It is possible that these local enzymes may be mediating sebum production in individuals with acne whose serum levels are at the high end of the normal range. If so, therapies that block the activity of this enzyme may be useful in the treatment of acne [47]. Since dihydrotestosterone (DHT) is the most potent androgen that directly influences acne, in theory, either the enzymes that synthesize DHT from DHEAS (steroid sulfatase, 3 α -HSD, 17 β -HSD or 5 α -reductase) or that 'detoxify' DHT (aromatase or 3 β -HSD) can be targeted or modified as a potential means of treating acne. However, since the proximal portion of the pathway of androgen metabolism (steroid sulfatase, 3 α -HSD) is also a key to the synthesis of other steroid hormones, it would be safer to target the downstream enzymes such as 5 α -reductase. Of note is that testosterone binds to the type 1 5 α -reductase at micromolar concentrations whereas the affinity of testosterone for the type 2 isozyme is in the nano-

molar range. This implies that much higher doses of a type 1 inhibitor may be required to inhibit this isozyme, as is the case with dutasteride, a dual inhibitor of the types 1 and 2 5 α -reductase [67]. Studies also suggest that the type 1 5 α -reductase may also be inhibited by green tea extract catechins, phytoestrogens/isoflavonoids and lignans, suramin, zinc and azelaic acid [31, 68, 69]. It remains possible that specific, locally acting enzyme inhibitors may be of future use in males with acne in addition to females.

Conclusions

Hormonal therapy is an option for treatment when acne is not responding to conventional therapy. If there are signs of hyperandrogenism, an endocrine evaluation is indicated, consisting of an assessment of DHEAS, total and free-testosterone levels and an LH/FSH ratio. Although an indication for hormonal therapy is hyperandrogenism, women with normal serum androgen levels also respond well to treatment. Hormonal therapy choices consist of androgen-receptor blockers, androgen-production blockers, and, potentially in the future, androgen-metabolizing enzyme inhibitors. The mainstays of hormonal therapy include oral contraceptives and spironolactone. Other agents to choose from are cyproterone, flutamide, and glucocorticoids.

As more is learned about the hormones involved in acne, their source of production and the mechanisms by which they influence sebaceous gland growth and sebum production, new opportunities will arise for the development of novel therapies aimed at the hormonal aspects of acne.

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Less Common Methods to Treat Acne

Ana Kaminsky

Department of Dermatology, Durand Hospital, School of Medicine, University of Buenos Aires, Argentina

Key Words

Acne · Sulfur · Hydroxy acids · Corticosteroids · Dapsone · Zinc sulfate · Ibuprofen · Clofazimine · Physical modalities

Abstract

Effective medications to treat acne sometimes become unavailable in certain countries, either for economic reasons or for shortage of them in the pharmaceutical market. The purpose of this report is to review a series of drugs of topical and systemic use; some old and some new. The topical group includes agents such as sulfur, salicylic acid and the alpha-hydroxy acids, while the systemic group includes diaminodiphenylsulfone, clofazimine, ibuprofen and others. Some presumably useful physical methodologies and the recent findings in phototherapy, particularly the properties of blue light and blue-red light, are also reviewed. Finally, we report on the results obtained from the combined use of isotretinoin and methylprednisone in severe inflammatory acne, to prevent a possible triggering of the 'pseudo' acne fulminans.

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Recent advances in the etiology and pathogenesis of acne have led to the development of new treatment modalities which have significantly expanded the spectrum of medications available to treat this condition predominantly affecting adolescents.

At present, topical and systemic antibiotics and retinoids, the recent release of adapalene or tazarotene, both with retinoid properties, and the use of a bacteriostatic such as benzoyl peroxide, have been shown effectively to change the progression of the disease.

This presentation will attempt to briefly review some of the less common treatments, namely the topical, systemic and physical varieties, as well as those inexpensive methods to be used by underprivileged sectors of the population, both in emerging and industrialized countries. New uses of ultraviolet radiation will also be reviewed.

Topical Treatment

Sulfur

Sulfur used to be the most common ingredient in antiacne formulations. In spite of its comedogenic and presumably comedolytic properties, it has now come into disuse, particularly because of its odor. Sulfur-containing formulations have been reported to be comedogenic in the rabbit ear model and also in humans, when applied under occlusions for 6 weeks [1]. However, other studies have failed to reproduce this experience on the potential comedogenicity of sulfur-containing preparations [2]. Although its use has been discontinued, it may eventually be found in some preparations in combination with benzoyl peroxide, resorcinol and other compounds. Recommended concentrations are 1–5%.

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Prof. Dr. Ana Kaminsky
Catedra de Dermatología, Facultad de Medicina
Universidad de Buenos Aires, Ayacucho 1570
1112 Buenos Aires (Argentina)
Tel. +54 11 4803 3607, Fax +54 11 4806 5798, E-Mail anakaminsky@fibertel.com.ar

Two sulfur-containing formulations are of interest: Vlemminckx solution and Ress solution. Both still have their advocates.

Vlemminckx's solution [3]:	
Sublimed sulfur	250 g
Calcium oxide	165 g
Water to	1,000 ml

A spoonful of this solution is dissolved in 250 ml of hot water and stipes impregnated with it are applied for 20 min. The solution may also be applied pure at night. Both the amount of time the application requires, and particularly its unpleasant odor put it at a disadvantage in comparison with other treatments. This solution has been shown to be highly effective in the treatment of moderate and severe inflammatory acne.

Ress' solution [4]:	
Precipitated sulfur/zinc sulfate (equal parts)	3.6
Sodium borate/zinc oxide (equal parts)	6.0
Acetone	30.0
Camphorated water/rose water (equal parts)	120.0
It is applied locally on inflammatory lesions.	

Hydrogen Peroxide

Lately, hydrogen peroxide cream was compared with fusidic acid in the treatment of impetigo. It has been noted that the new cream formulation stabilizes hydrogen peroxide avoiding fast degradation and producing a direct and prolonged antimicrobial effect. The formulation is based on crystalline lipids and it is effective against gram-positive as well as gram-negative bacteria. It may therefore be an additional topical treatment for patients with gram-negative folliculitis in particular [5].

Hydroxy Acids

β -Hydroxy Acid

Salicylic acid: This is the best known of the keratolytic agents in dermatologic therapy. This desquamative agent acts on the stratum corneum producing a dissolution of the intercellular cement and, sometimes, a moderate peeling [6]. It acts on the interfollicular epidermis and on the acroinfundibulum. In acne, it is the active ingredient in a variety of cleansers and astringent lotions and has a mild comedolytic and anti-inflammatory effect. It is used in concentrations of 1–3%. As well, 5% salicylic acid in propylene glycol may be useful [7].

In comparison with tretinoin and isotretinoin, it is a mild comedolytic agent. In concentrations of 2% it is well tolerated probably due to its anti-inflammatory effects [8].

At present, it is used in peeling lotions in concentrations of 15–35%, complementary to the treatment of non-inflammatory acne.

α -Hydroxy Acids

The α -hydroxy acid family is made up of different compounds with application for the treatment of several dermatoses. They are weak organic acids and, structurally, all of them have one hydroxyl group attached to the alpha position of the acid. Although found in nature, the α -hydroxy acids used in dermatologic and cosmetic products are usually produced synthetically. The mechanism of action is unknown. However, it has been shown that, at low concentrations, α -hydroxy acids decrease corneocyte cohesion at the lower levels of the stratum corneum and it has been suggested that this occurs by interference with the formation of ionic bonds [9]. Essentially, by dissolving adhesions between cells in the upper layers of the skin, these acids induce shedding of dry scales from the skin surface in an exfoliative-like fashion. In lower concentrations, α -hydroxy acids reduce follicular corneocyte adhesion, enabling comedone elimination and preventing its formation. In higher concentrations they cause unroofing of pustules and loosening of the corneocytes that line the follicular epithelium [10, 11].

Glycolic acid is the most frequently used therapy in superficial peeling. It is used for brief exposures, in concentrations of 30, 50 and 70% but it is considered a complement rather than a first-line treatment.

Corticosteroids

A few topical preparations contain weak corticosteroids, but proof of their efficacy is lacking. Clobetasol propionate is a potent corticosteroid that may help to reduce inflammation in nodular acne when applied twice a day for 5 days [12].

Dapsone

Dapsone in a gel formulation, at concentrations of 3 and 5% has been experimentally used for the last 3 years. It appears to be a new and promising therapeutic modality for moderate to moderately severe acne. It has not been available in the past as it is highly insoluble in the aqueous solvents traditionally used in dermatological preparations. New technologies provide a formulation based on the solvent ethoxydiglycol, which will eventually solve the problem. The delivery is through the skin in two stages; with preferential uptake of the drug immediately in the skin oil in and near the pilosebaceous follicle, followed by slower release from a suspension of microparticles in the

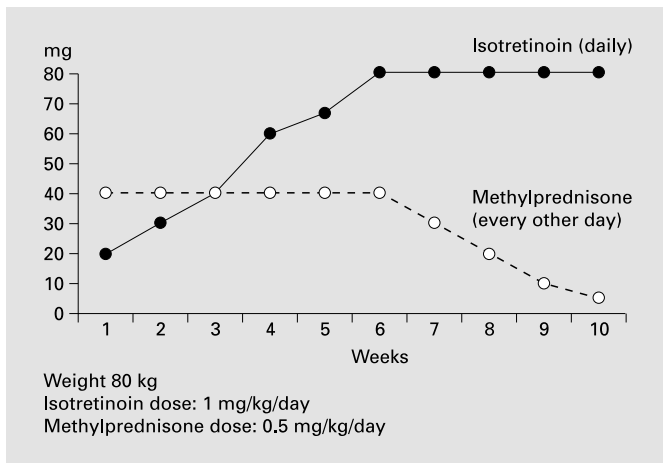


Fig. 1. Simultaneous utilization of isotretinoin and methylprednisone in very severe inflammatory acne.

surrounding region (Dr. D. Osborne, 2001, 59th Annual Meeting of the American Academy of Dermatology, Washington, D.C.). Clinical studies conducted have demonstrated that numbers of both inflammatory and non-inflammatory lesions were reduced by 50% at the end of a 28-day treatment period.

Systemic Treatment

The use of antibiotics, isotretinoin or hormonal regimens, according to the case, are the most relevant systemic treatments. Other treatment modalities are discussed below.

Corticosteroids

Oral prednisone 0.5–1.0 mg/kg daily should be prescribed to patients with severe inflammatory acne vulgaris, acne fulminans and pyoderma faciale. Prednisone must be administered for 4–6 weeks and then reduced gradually. In acne fulminans and pyoderma faciale it is preferable to prescribe the steroids for 3–4 weeks before prescribing the isotretinoin. Similar oral doses are also indicated in patients whose acne flares badly while taking isotretinoin [13]. Many times the worsening of acne observed between the third and the sixth week may be very severe and even trigger genuine manifestations of acne fulminans, although they should, more appropriately, be called ‘pseudo’ acne fulminans, since systemic features are minimal or almost absent and no pyrexia is noted. Baseline hematology and biochemistry parameters

are within normal ranges. As this was observed in our department in 18 of 590 patients between 1983 and 1990, we decided to use isotretinoin and corticosteroids simultaneously and from the beginning in the very inflammatory and severe acne. An example of dosage according to body weight (i.e. 80 kg) is as follows:

We started with an initial isotretinoin dose of 20 mg/day for a week, with slow dosage increases until the desirable dose of 1 mg/kg/day was reached in the 6th week, amounting to a total accumulated dose of 150 mg/kg/day. We preferred methylprednisone at a starting dose of 40 mg every other day for 6 weeks and progressively decreased the dose until total withdrawal of the corticosteroid in the 10th week, leaving isotretinoin as sole course of therapy (fig. 1). The aim behind this therapeutic scheme, over the period of isotretinoin pharmacologic impregnation, is to avoid the early exacerbation phenomenon that would be triggered by an antigen-antibody reaction. There is altered immunological reaction to *Propionibacterium acnes* in some patients, with previous demonstration of both type III and IV hypersensitivity to this organism. Another theory is that altered neutrophil function may result in severe acne flares. *P. acnes* destruction is thought to result in mediator, inducing neutrophil chemotaxis, which may be responsible for flares seen on treatment with isotretinoin. Patients developing severe flares of the disease may be showing an exaggeration of this response [14]. It has also been suggested that increased fragility of the pilosebaceous duct is induced by isotretinoin, leading to a massive contact with *P. acnes* antigens [15]. Since we routinely implemented the simultaneous use of isotretinoin and corticosteroids for the most severe inflammatory acne (nodules, abscesses, cysts), we have no longer observed this horrendous manifestation. Therefore, we conclude that this combination prevents the development of ‘pseudo’ acne fulminans as a complication derived from the use of isotretinoin.

Zinc Sulfate

Zinc sulfate appears to have little treatment efficacy. Some authors have demonstrated in a double-blind trial that zinc sulfate capsules, 220 mg/day, corresponding to 50 mg of elemental zinc three times daily with food, may be beneficial to selected patients with mild-to-moderate pustular acne. However, these authors are reluctant to recommend oral zinc sulfate as treatment for acne vulgaris because of the high incidence of gastrointestinal side effects. They consider that the incidence of nausea would have been lower had they used gluconate zinc 200 mg/day rather than zinc sulfate [16].

Ibuprofen

As inflammatory acne lesions are infiltrated with neutrophils, the use of anti-inflammatory drugs (NSAIDs) was suggested and ibuprofen was selected for its properties. Effectively, ibuprofen decreases inflammation by inhibiting cyclooxygenase, a pivotal enzyme in the arachidonic acid cascade leading to the formation of the pro-inflammatory prostaglandin products. Thus, ibuprofen may inhibit human leukocyte chemotaxis and the formation of the inflammatory lesions in acne. A study demonstrated that tetracycline hydrochloride capsules (1,000 mg/day) associated with ibuprofen tablets (2,400 mg/day) is effective when administered for 2 months to patients with moderately severe acne [17]. Other authors combine minocycline capsules (150 mg/day) and ibuprofen tablets (1,200 mg/day) with excellent clinical response and the additional benefit of fewer side effects at low ibuprofen doses.

Dapsone

Dapsone (diaminodiphenylsulfone or DDS), effectively tested on lepra, was shown to possess anti-inflammatory activity for various dermatological diseases, primarily dermatitis herpetiformis in the early 1950s and subcorneal pustular dermatosis in 1956. The sulfones have been widely used to treat other dermatological conditions including bullous diseases, vasculitis, neutrophilic dermatoses, pilosebaceous diseases, infectious diseases, as well as pustular psoriasis and relapsing polychondritis. Dapsone has been reported to be effective in the management of nodulocystic acne, but the few studies available are based on a limited number of cases [18, 19]. In 1974, we examined 484 patients treated with oral DDS. Patients with acne characterized by papules, pustules and occasional cysts accompanied by inflammatory lesions, did not respond to the medication, although, in some, there was a slight improvement not comparable with the one obtained with tetracycline, in view of which DDS was discontinued. The cystic, tuberous and phlegmonous acne cases, as well as the very severe manifestations thereof, improved markedly when treated with DDS at a dosage of 50–100 mg daily for 3 months. The condition gradually subsided until remission, with only a few low-intensity relapses [20]. At present, DDS has undoubtedly been replaced by isotretinoin. However, due to its affordable cost, DDS is more advisable to be used in emerging countries. Dapsone use must be concomitant with the knowledge of its side effects. Some of them are pharmacological and predictable, but there are allergic and idiosyncratic reactions as well. Most patients with a deficiency of glu-

cose-6 phosphate dehydrogenase (G6PD) tolerate this drug well, except when very high dosages are used. Follow-up examinations and laboratory testing should be performed according to the monitoring guidelines. A complete blood count, a chemistry profile, a urinalysis and analysis of the G6PD levels should be included [21].

Clofazimine

This drug has both antimicrobial and anti-inflammatory activity. The exact mechanism of clofazimine action is unknown, but the primary sites of action appear to be the neutrophil and the monocyte. As both cystic acne and acne fulminans may present granulomatous components, clofazimine was found to be effective in cases of recurrence after several courses of isotretinoin [22]. At a dosage of 200 mg three times weekly, it has been used successfully in the treatment of acne fulminans [23]. Finally, clofazimine has been shown to be of value in the treatment of solid facial edema, which is an exceptionally rare complication of acne [24].

Physical Treatment

Many abrasive materials, usually based on polyethylene and aluminum oxide, are of little value.

Comedone Extraction

Mechanical extraction of open comedones, by applying light pressure over individual lesions with a comedone extractor, may be useful. There is a great variety of specially shaped tools, particularly for blackhead removal.

Electrocauterization

Light cautery after the application of a local anesthetic with EMLA cream (0.025% lidocaine and 0.025% prilocaine) for 60–90 min beneath an occlusive dressing, has been shown to help patients with multiple macro-whiteheads and blackheads greater than 1.5 mm in diameter [25]. The electrocautery is used at a very low setting so as to produce little or no pain. The aim is to produce very low-grade thermal damage so as to stimulate the body's own defence mechanisms to eliminate the comedones.

Cryotherapy

The beneficial effects derived from the use of low temperatures in the treatment of different dermatological conditions have long been known. In that respect, cold compresses, to relieve inflammatory acne, as well as car-

bonic snow, alone or combined with sulfur and acetone, are used to treat sequels of superficial scars.

Cryoslush Therapy

Solid carbon dioxide is mixed with acetone to produce a slush-like mixture that is brushed lightly over the skin. It produces erythema and desquamation. The degree of erythema and peeling is determined by the amount of time the slush is in contact with the skin.

Liquid Nitrogen

The superficial freezing with liquid nitrogen will hasten the resolution of chronic fluctuant nodular lesions and is comparatively painless. Two freeze/thaw cycles of 15 s each are recommended. This therapy works by producing cold damage to the fibrotic cyst wall, resulting in chemotaxis of neutrophils, whose proteases will subsequently, hopefully, destroy the wall and allow healing [26].

Radiation Therapy

The introduction of isotretinoin and a better management of its usage successfully solve nearly all cases of acne. Radiation therapy is being reserved at present for the most recalcitrant cases and should be administered only by highly skilled people who are fully aware of its risks.

Intralesional Corticosteroids

In nodular lesions, an intralesional injection with corticosteroids (triamcinolone 2.5 mg/ml) may be used. It may be administered using a syringe with a 30-gauge needle. If placed too superficially or too deeply, it may cause atrophy.

Phototherapy

Ultraviolet light is scarcely used. Yet, it is well known that acne often improves clinically after exposure to sunlight or artificially produced solar radiation and more than 70% of patients report definite improvement after exposure to the sun during the summer.

Reddening, as well as ultraviolet light-induced tan, produce a camouflage effect. Its therapeutic action might be linked to a biologic effect of the sunlight on the pilosebaceous system. It may have an anti-inflammatory action in acne, possibly by its effect on follicular Langerhans cells. *P. acnes* produce porphyrins which absorb light energy at the near ultraviolet and blue light spectrum. Irradiation of *P. acnes* colonies in vitro with blue visible light leads to photoexcitation of bacterial porphyrins, singlet oxygen production and eventually bacterial destruc-

tion [27]. As well, they have comedogenic potential because squalene is oxidized to squalene peroxide, which, in turn, may irritate the follicular keratinocytes. The use of visible light alone is perhaps the most practical, common and free treatment existing. However, it is carcinogenic and the photoaging effects render its use unwise. Blue light is theoretically the most effective visible wavelength for photoactivation of the major endogenous porphyrin component of *P. acnes*, but has poor depth of skin penetration. The red light is less effective at photoactivating porphyrins, but penetrates more deeply into tissue. Red light may also have anti-inflammatory properties by influence of cytokines released from macrophages [28]. Light in the violet-blue range (407–420 nm) has been shown to exhibit a phototoxic effect on *P. acnes* when irradiated in vitro. This effect is most likely due to the destruction of porphyrins necessary in heme biosynthesis. Stillman et al. [29] conducted a study to determine if the levels of *P. acnes* decreased when irradiated in vivo with this radiation. This study examined two groups of patients simultaneously irradiated twice a week with a high-intensity fiber optic lamp emitting visible light in the violet-blue range for a total of 4 weeks. Different parts of the face were treated either on the forehead or the cheek for a 20-min session with the lamp placed 5 cm from the skin. After 6 sessions, both the treated and the untreated symmetric area demonstrated a significant reduction in the levels of *P. acnes*. They also observed that 7 of 10 patients with mild-to-moderate acne showed significant improvement in reducing the number of non-inflammatory, inflammatory and total facial lesions. The authors conclude that the use of visible light may inhibit heme production in *P. acnes*. Papageorgiou et al. [30] conducted a study to evaluate the use of blue light (peak 415 nm) and a mixed blue and red light (peaks at 415 and 660 nm) in the treatment of acne vulgaris. They examined 107 patients with mild-to-moderate acne vulgaris that were randomized into four treatment groups: blue light, mixed blue and red light, cool white light and 5% benzoyl peroxide cream. Patients in the phototherapy group used portable light sources and irradiation was carried out daily for 15 min. Assessments were performed every 4 weeks. After 12 weeks of active treatment, a mean improvement of 76% in inflammatory lesions was achieved by the combined blue-red light phototherapy and the result was significantly superior to that obtained with the other treatments. Regarding comedones treated with the blue-red light combination, a 58% of improvement again indicates better results than those achieved by the other treatments. Considering all the groups under study, the authors concluded

that phototherapy with mixed blue-red light, probably by combining antibacterial and anti-inflammatory action, is an effective means of treating acne vulgaris of mild-to-moderate severity, with no significant short-term adverse effects. Further studies are required to elucidate the exact mechanism of action [31].

Conclusion

We have made reference to less common therapies used in clinical forms of acne. Even though some of them may be rather infrequent nowadays, they are worth considering on the following grounds: (a) cases of hypersensitivity reactions or allergy to drugs; (b) high cost of the

drugs which render them unaffordable to large sectors of the population not covered by health insurance plans, even in industrialized countries, or to poor people in emerging countries; (c) unavailability of the drug in the local pharmaceutical market.

We have also mentioned new methods using high cost equipment for which, in our opinion, more clinical studies are still needed. Finally, in our experience, the satisfactory results obtained with the combined use of isotretinoin and methylprednisone allow us to conclude that this should be the therapy of choice in the very severe inflammatory acne, to prevent the appearance of a dreadful complication such as the one posed by 'pseudo' acne fulminans.

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