PUBLICATION OF THIS SUPPLEMENT WAS MADE POSSIBLE BY AN EDUCATIONAL GRANT FROM GALDERMA

Management of Acne

A Report From a Global Alliance to Improve Outcomes in Acne

Authors and Guest Editors

Harald Gollnick, MD, and William Cunliffe, MD, FRCP

Co-Authors

Diane Berson, MD, Brigitte Dreno, MD, PhD, Andrew Finlay, MD, James J. Leyden, MD, Alan R. Shalita, MD, Diane Thiboutot, MD

INTRODUCTION

In the past 25 years, numerous topical and systemic drugs have been developed for the treatment of acne vulgaris. The voluminous amount of clinical trial information has become increasingly difficult for individual physicians to monitor. Clinical trials are a science no different than any other aspect of medicine. There has been improvement in the design and performance of clinical trials in the past several years. Currently, most authoritative opinions fully support the need for studies to be performed under the CONSORT and Cochrane principles. We accept that many studies have not been as rigorously performed in the past as trials done in 2002. But to discard such studies is inappropriate, because they were done well according to the standards of the time.

Thus, for the time being, clinical opinion, based in part on formal discussion among expert colleagues with an interest in acne and a logical analysis of the literature, is not unreasonable as the basis for a Consensus Recommendation. Such recommendations highlight the indications for use of medications and the optimal approach to the management of specific clinical problems. Overall, the goal is to provide a comprehensive overview of rational therapy, which can form the basis for more uniform therapeutic strategies throughout the world, enhanced patient compliance, and more effective use of healthcare resources.

Several sets of guidelines have been developed for the treatment of acne during the past decade, including a practice guideline for the Oral Treatment of Acne in France (1999), Canadian Acne Treatment Guidelines (1995), German Guidelines for Acne Treatment (2001), Treatment of Acne Vulgaris: Guidelines for Primary Care Physicians (1991), and Guidelines of Care for Acne Vulgaris from the American Academy of Dermatology (1990). However, advances in medicine occur relatively rapidly, and practice guidelines may be out of date shortly after they are issued. Thus, there is a continuing need to update existing recommendations so that recent advances in therapy can be brought to the attention of physicians in a timely manner.

In recognition of this need, this supplement to the *Journal of the American Academy of Dermatology* has been developed by a panel of physicians and researchers in the field of acne, working together as a Global Alliance to Improve Outcomes in Acne. The mission of this group is to develop consensus recommendations for the treatment of acne, which are evidence-based when possible, and which include input from numerous countries. The members of the group represent a broad list of international dermatologists with a special interest in acne and reflect a wide range of experiences and opinions. The activities of the group have been coordinated by Dimensional Healthcare, Inc, and funded by an educational grant from Galderma. As might be expected, some of the physicians involved in the development of this document have past or current, direct or indirect financial

From the American Academy of Dermatology, Inc.
Reprint requests: Ted Schwarz, Laboratoires Galderma S. A., Tour Europlaza-La Defense 4, 20, avenue Andre Prothin, 92927 La Defense, Cedex, France. +33(1)5886 4591.

Copyright © by the American Academy of Dermatology, Inc.
J Am Acad Dermatol 2003;49:S1-38.
0190-9622/2003/$30.00 + 0
doi:10.1067/mjd.2003.618

associations with pharmaceutical companies whose products are discussed in this document. These financial associations include (but are not limited to) research grants, payment for travel to meetings, honoraria for speaking engagements, participation on scientific advisory boards, consulting agreements, and ownership of stock. This document has been created with the advice and feedback of the entire group, and every effort has been made to achieve fair balance and reach consensus on difficult and controversial issues. As a result, although it is understood that potential conflicts of interest exist—indeed they are commonplace and difficult to avoid in projects of this kind—each of the 20 physicians listed on the preceding pages has reviewed the publication and believes that it appropriately reflects current thinking concerning the optimal approach to the management of acne.

PATHOGENESIS OF ACNE

Consensus: Knowledge of Pathophysiology Should Influence Treatment

Primary pathophysiologic factors in acne
Sebaceous hyperplasia with seborrhea
Ductal hypercornification
Propionibacterium acnes colonization of the duct
Inflammation and immune response
Treatment should target as many factors as possible

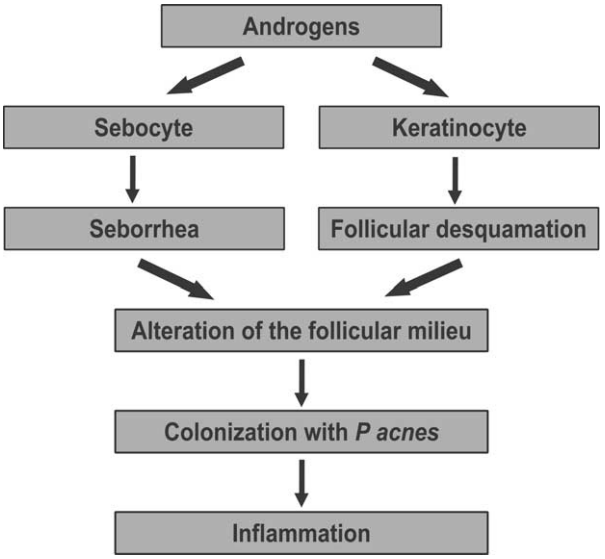

Fig 1. Pathogenesis of acne. Adapted from Plewig G, Kligman AM. Acne and rosacea. 3rd ed. New York: Springer-Verlag; 2000, with permission from Professor Gerd Plewig.

Acne is an extremely common condition, affecting almost 80% of adolescents and young adults aged 11 to 30.[1-3] In recent years, research has led to a greater understanding of the pathogenesis of this widespread disease. The pilosebaceous unit is the target organ in acne, explaining the distribution of acne primarily on the face, chest, and back—areas with the greatest concentration of pilosebaceous glands.[2,4-6]

The most notable pathophysiologic factors that influence the development of acne are (Fig 1).[4,7-11]

- Sebaceous gland hyperplasia with seborrhea
- Altered follicular growth and differentiation
- *Propionibacterium acnes* colonization of the follicle
- Inflammation and immune response

Of these, altered follicular growth and differentiation and sebaceous hyperplasia are the most important, because they combine to induce the microcomedo—the primary lesion of acne (Fig 2). The microcomedo can evolve into either a noninflammatory comedo or become inflamed and present as a papule, pustule, or nodule.

Increase in sebum production

The sebaceous follicle is associated with large and multilobular sebaceous glands.[2,6] In patients with acne, the overall size of the sebaceous follicle increases and the number of lobules per gland increases.[4] The sebaceous glands start to enlarge with androgenic stimulus at approximately 7 to 8 years of age (adrenarche), with a resultant increase in sebum excretion.[12,13] Androgens drive changes in both sebocytes and follicular keratinocytes that lead to the microcomedo and subsequent development of inflammatory lesions and comedones.

In addition, sebum production increases with the influence of androgens, the major sebotropic hormones.[8] There is evidence that sebocytes and the follicular keratinocytes have the cellular mechanisms needed to metabolize androgens, in particular 5-α-reductase (type 1) and 3β and 17β hydroxysteroid dehydrogenase.[14-18] Enzymes are present in the undifferentiated basal sebocyte; with time, the sebocyte differentiates and finally ruptures, releasing lipids into the sebaceous duct and the follicular cast.[2] The differentiation of the sebocyte is initiated by androgen uptake into the cell and its coupling

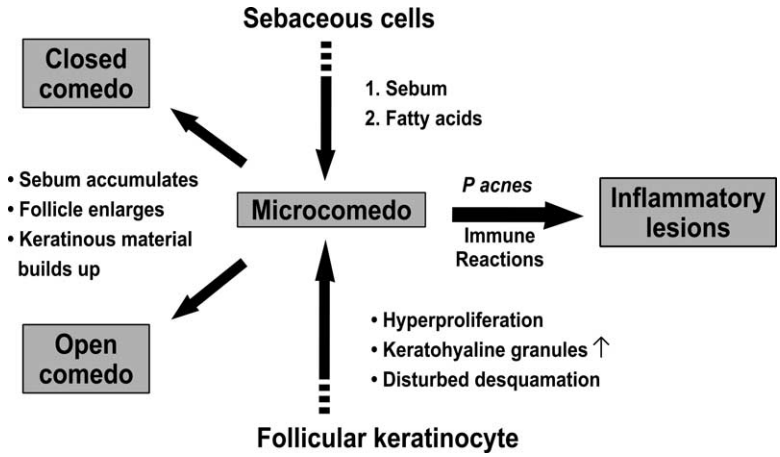

Fig 2. Lesion progression in acne.

with the androgen receptor, which, in turn, stimulates gene transcription and differentiation.[4,14,19]

In acne patients, excess sebum production is mainly due to a difference in the response of the target organ (the pilosebaceous unit), increased circulating androgens, or both. Several lines of evidence suggest that end-organ hyper-responsiveness is quite likely in acne, because not all sebaceous gland follicles are affected—as demonstrated by the nonsymmetrical distribution of acne lesions (primarily on the face, chest, and back)—despite a constant level of androgen in the blood.[8,20] In addition, sebocytes from various areas of the body have different responses to dihydrotestosterone (DHT) and testosterone.[21] Sebocytes from the leg have a lower response or do not respond, whereas those from the face show a dose-dependent increase in proliferation.[21] Further, some females with high androgen levels (including those with adrenal tumors) have a high degree of virilization but no acne.[8]

In summary, androgens are a causative factor in acne, yet most acne patients do not typically have significant endocrine abnormalities. A few acne patients do have excessive androgen production (as may be indicated by hirsutism or significant menstrual dysfunction) and should receive an endocrinologic evaluation. (See the section titled "Hormonal Therapy" for a more complete discussion of when hormonal therapy is indicated and screening tests for endocrinologic dysfunction.) However, it is known that hormonal and nonhormonal therapies that reduce sebum production may be beneficial in treating acne, as discussed below.

Abnormal follicular desquamation

In the normal follicle, the keratinocytes are shed as single cells to the lumen and then excreted.[4,5] In acne, keratinocytes hyperproliferate and are not shed as normal. They also become densely packed along with monofilaments and lipid droplets.[4,6,22-25] Comedogenesis occurs when abnormally desquamated corneocytes accumulate in the sebaceous follicle.[7]

Acne lesions begin with the microcomedo, a microscopic lesion not visible to the naked eye. With time, the follicle fills with lipids, bacteria, and cell fragments. Ultimately, a clinically apparent lesion occurs, either a noninflammatory lesion (open or closed comedo) or an inflammatory lesion, if *P acnes* proliferate and generate inflammatory mediators (Fig 2).[23,24]

Several theories have been proposed to explain the abnormal desquamation that occurs in patients with acne. Immunohistochemical studies have shown an increase in the proliferation rate of the basal keratinocyte and abnormal differentiation of the follicular keratinocytes in the follicle wall of microcomedones and comedones.[7,26-27] These abnormalities may be due to a relative decrease in sebaceous linoleic acid.[28] An androgen-controlled defect may also contribute to proliferation via the 5-α reductase enzyme (type 1) in the infundibulum.[16] Follicular hyperproliferation is also associated with abnormal lipid inclusions (a measure of abnormal differentiation).[24,25,29-30] This may be due to abnormal cellular differentiation or passive diffusion of lipids from the sebaceous follicle lumen.[2] Finally, retinoid control, local cytokine modulation, and ductal bacteria may also have an effect.[8,31-32]

Accumulating evidence is demonstrating the importance of cytokines in mediating comedogenesis. Ingham et al showed that high levels of biologically active interleukin-1α (IL-1α) occur in comedones; it is thought that the IL-1α is expressed by follicular keratinocytes.[33] In a model of comedo formation involving infundibular segments from the human sebaceous follicle, Guy and Kealey showed that addition of IL-1α stimulated abnormal desquamation

and led to disruption of the integrity of the follicular wall in organ culture in vitro.[32] They suggested that changes in sebum composition or secretion may irritate infundibular keratinocytes, resulting in release of IL-1α and initiation of comedogenesis. In addition, IL-1α in comedones may induce inflammation after compromise of the follicular barrier.[32]

In summary, abnormal desquamation occurs early in the formation of acne lesions and is linked to keratinocyte hyperproliferation and abnormal differentiation. The mechanisms that control this process have not yet been fully elucidated; however, lipid composition, androgens, and local cytokines are all thought to have an important role. Also, comedones can resolve naturally, suggesting that study of this phenomenon may contribute to increased understanding of the pathogenesis of acne.

Bacterial proliferation

P acnes is not thought to be infectious, but it does play a role in acne. However, skin surface *P acnes'* counts and the severity of acne often do not correlate.[10] What is likely to be important is the microenvironment of the follicle, which encourages colonization of this non-motile bacterium into the follicular duct and the subsequent production of inflammation. Just how *P acnes* colonizes the duct is uncertain. There is a correlation between the reduction of *P acnes* and the clinical improvement of acne. This reduction in *P acnes* is associated with a reduction in pro-inflammatory mediators.[2,34-35] The host response to inflammatory stimuli most likely explains the variations in the intensity of inflammation.

Inflammation

Patients often seek treatment for acne once inflammatory lesions occur. These lesions may be macules, papules, pustules, or nodules; in addition, an inflamed area may progress from one type of lesion to another. In severe cases, scarring may result.[36] In addition, clinicians should be aware that scarring may occur not infrequently in patients with less severe disease.[37]

In the early events of papule formation, a microcomedo is present in 80% of such lesions.[38] Thereafter, CD4 lymphocytes invade the follicular wall, usually leading to disruption.[38] Later, neutrophils migrate to the scene.[4,38,39] Although disruption of the duct is not the primary event in the development of papules, rupture is associated with extravasation of lipids, corneocytes, and bacteria into the dermis.[36] Certain cytokines may be inflammatory triggers, and whether neuroinflammatory mediators play an additional role is currently under debate. Recently, it has been shown that sebocytes express neuropeptides, particularly substance P. This peptide consistently and significantly affects the individual size of the gland and the number of sebum vacuoles, contributing to abnormalities in differentiation and proliferation as well as lipid synthesis.[40]

Targeting pathophysiologic processes in acne treatment

The improved understanding of the pathophysiologic features of acne has brought about changes in acne management. The pathophysiologic features of acne suggest that combination therapy should be utilized as early as possible (except in patients requiring oral isotretinoin)—preferably at the initiation of therapy—to simultaneously attack two or three pathogenic factors. In mild acne, particularly comedonal acne with a few inflammatory lesions, topical retinoids are thought to be the treatment of choice. All topical retinoids affect the microcomedo and lead to a decrease in comedones and inflammatory lesions, as seen in all clinical trials. Furthermore, clinical studies have demonstrated significantly greater reductions in both inflammatory lesions and comedones when topical retinoids are added to antimicrobial therapy. For acne with a predominantly inflammatory component, benzoyl peroxide and/or topical antibiotics, along with the topical retinoid, speed the clearing of inflammatory acne lesions. For moderate and severe acne, oral antibiotics combined with topical retinoids are appropriate. Females may also be candidates for anti-androgenic hormonal therapy, especially if they require oral contraception for other purposes. In the most severe and refractory cases of acne, such as severe nodular acne or conglobate acne, oral isotretinoin is the treatment of choice. For patients unresponsive to conventional therapies, the options include hormonal therapy (primarily for women) and oral isotretinoin.

REFERENCES

1. Kraning KK, Odland GF, eds. Prevalence, morbidity, and cost of dermatologic diseases. J Invest Dermatol 1979;73:395-513.
2. Leyden JJ. New understandings of the pathogenesis of acne. J Am Acad Dermatol 1995;32:S15-S25.
3. Cunliffe WJ, Gould DJ. Prevalence of facial acne vulgaris in late adolescence and in adults. BMJ 1979;1:1109-10.
4. Gollnick HPM, Zouboulis CC, Akamatsu H, Kurokawa I, Schulte A. Pathogenesis and pathogenesis-related treatment of acne. J Dermatol 1991;18:489-99.
5. Cunliffe WJ, Gollnick H. Acne: diagnosis and management. London: Martin Dunitz, Ltd; 2001.
6. Plewig G, Kligman AM. Acne and Rosacea. 3rd ed. New York: Springer-Verlag; 2000.
7. Cunliffe WJ, Holland DB, Clark SM, Stables GI. Comedogenesis: some new aetiological, clinical and therapeutic strategies. Br J Dermatol 2000;142:1084-91.
8. Cunliffe WJ, Simpson NB. Disorders of the sebaceous gland. In: Textbook of dermatology. Champion RH, Burton JL, Burns DA, et al, eds. 6th ed. Oxford: Blackwell Science; 1998. p. 1927-84.
9. Burton JL, Shuster S. The relationship between seborrhoea and acne vulgaris. Br J Dermatol 1971;84:600-1.
10. Leyden JJ, McGinley KJ, Mills OH, Kligman AM. Propionibacte-

rium levels in patients with and without acne. J Invest Dermatol 1975;65:382-4.
11. Webster GF. Inflammation in acne vulgaris. J Am Acad Dermatol 1995;33:247-53.
12. Pochi PE, Strauss JS, Downing DT. Age related changes in sebaceous gland activity. J Invest Dermatol 1979;73:108-11.
13. Pochi PE, Strauss JS. Endocrinologic control of the development and activity of the human sebaceous gland. J Invest Dermatol 1974;62:191-201.
14. Thiboutot D, Harris G, Iles V, Cimis G, Gilliland K, Hagari S. Activity of the type 1 5-alpha-reductase exhibits regional differences in isolated sebaceous glands and whole skin. J Invest Dermatol 1995;105:209-14.
15. Thiboutot D, Knaggs H, Gilliland H, Lin G. Activity of 5-α-reductase and 17-β-hydroxysteroid dehydrogenase in the infraindibulum of subjects with and without acne vulgaris. Dermatology 1998;196:38-42.
16. Thiboutot DM, Knaggs H, Gilliland K, Hagari S. Activity of type 1 5a-reductase is greater in the follicular infrainfundibulum compared with the epidermis. Br J Dermatol 1997;136:166-71.
17. Chen W, Zouboulis CC, Fritsch M, Kodelja V, Orfanos CE. Heterogeneity and quantitative differences of type 1 5α-reductase expression in cultured skin epithelial cells. Dermatology 1998;196:51-2.
18. Fritsch M, Orfanos CE, Zouboulis CC. Sebocytes are the key regulators of androgen homeostasis in human skin. J Invest Dermatol 2001;116:793-800.
19. Schmidt JB, Spona J, Huber J. Androgen receptor in hirsutism and acne. Gynecol Obstet Invest 1986;22:206-11.
20. Deplewski D, Rosenfield RL. Role of hormones in pilosebaceous unit development. Endocrine Rev 2000;21:363-92.
21. Akamatsu H, Zouboulis CC, Orfanos CE. Control of human sebocyte proliferation in vitro by testosterone and 5-α-dihydrotestosterone is dependent on the localization of the sebaceous glands. J Invest Dermatol 1992;99:509-11.
22. Holmes RL, Williams M, Cunliffe WJ. Pilosebaceous duct obstruction and acne. Br J Dermatol 1972;87:327-32.
23. Plewig G, Fulton JE, Kligman AM. Cellular dynamics of comedo formation in acne vulgaris. Arch Dermatol Forsch 1971;242:12-29.
24. Kurokawa I, Mayer-da-Silva A, Gollnick H, Orfanos CF. Occurrence and distribution of cytokeratins and filaggrin in the human pilosebaceous unit: an immunocytochemical study. In: Marks R, Plewig G, eds. Acne and related disorders. London: Martin Dunitz; 1989. p. 19-22.
25. Thielitz A, Helmdach M, Roepke EM, Gollnick H. Lipid analysis of follicular casts from cyanoacrylate strips as a new method for studying therapeutic effects of antiacne agents. Br J Dermatol 2001;145:19-27.
26. Knaggs HE, Holland DB, Morris C, Wood EJ, Cunliffe WJ. Quantification of cellular proliferation in acne using the monoclonal antibody Ki-67. J Soc Invest Dermatol 1994;102:89-92.
27. Hughes BR, Morris C, Cunliffe WJ, Leigh IM. Keratin expression in pilosebaceous epithelia in truncal skin of acne patients. Br J Dermatol 1996;134:247-56.
28. Downing DT, Stewart ME, Wertz PW, Strauss JS. Essential fatty acids and acne. J Am Acad Dermatol 1986;14:221-225.
29. Lavker RM, Leyden JJ. Lamellar inclusions in follicular horny cells: a new aspect of abnormal keratinization. J Ultrastruct Res 1979;69:362-70.
30. Kluznik AR, Wood EJ, Cunliffe WJ. Keratin characterization in the pilosebaceous ducts of acne patients. In: Marks R, Plewig G, eds. Acne and related disorders. London: Martin Dunitz; 1989. p. 113-5.
31. Guy R, Green MR, Kealey T. Modeling acne in vitro. J Invest Dermatol 1996;106:176-82.
32. Guy R, Kealey T. Modelling the infundibulum in acne. Dermatology 1998;196:32-7.
33. Ingham E, Eady EA, Goodwin CE. Pro-inflammatory levels of interleukin-1 α like bioactivity are present in the majority of open comedones in acne vulgaris. J Invest Dermatol 1992;98:895-901.
34. Webster GF, Tsai C-C, Leyden JJ. Neutrophil lysosomal release in response to Propionibacterium acnes [abstract]. J Invest Dermatol 1979;72:209.
35. Webster GF, Kligman AM. A method for the assay of inflammatory mediators in follicular casts. J Invest Dermatol 1979;73:266-8.
36. Cunliffe WJ. The sebaceous gland and acne—40 years on. Dermatology 1998;196:9-15.
37. Layton AM, Henderson CA, Cunliffe WJ. A clinical evaluation of acne scarring and its incidence. Clin Exp Dermatol 1994;19:303-8.
38. Norris JF, Cunliffe WJ. A histological and immunocytochemical study of early acne lesions. Br J Dermatol 1988;118:651-9.
39. Puhvel SM, Sakamoto M. The chemoattractant properties of comedonal components. J Invest Dermatol 1978;71:324-9.
40. Toyoda M, Morohashi M. Pathogenesis of acne. Med Electron Microsc 2001;34:29-40.

TOPICAL RETINOIDS

Consensus: Topical Retinoids Have Multiple Anti-Acne Actions

- Inhibit the formation of and reduce the number of microcomedones (precursor lesions)
- Reduce mature comedones
- Reduce inflammatory lesions
- Promote normal desquamation of follicular epithelium
- Some may be anti-inflammatory
- Likely to enhance penetration of other drugs
- Likely to maintain remission of acne by inhibiting microcomedo formation, thus preventing new lesions

Indications

Most patients with acne benefit from the use of a retinoid, whether a topical agent as part of conventional therapy or oral isotretinoin for treatment-resistant cases. Topical retinoids target the microcomedo—the precursor of almost all other acne lesions. The group strongly recommends that topical retinoids should be included in the management of most patients with acne. There is now consensus that topical retinoids (alone or in combination) should be used as first-line therapy for mild to moderate inflammatory acne in addition to comedonal acne in most cases, excluding very severe disease. Topical retinoids are also preferred agents for maintenance therapy. The goal is to minimize antibiotic use in acne.

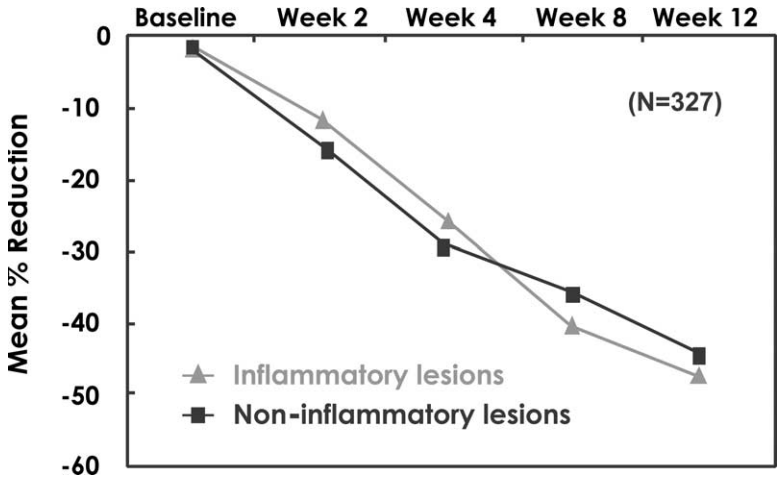

Fig 3. The effect of topical retinoid therapy on inflammatory and noninflammatory lesions. Reprinted with permission from Shalita AR, et al. The effect of topical retinoid therapy on inflammatory and noninflammatory lesions. J Am Acad Dermatol 1996;34:482-5.

Mechanism of action

Topical retinoids reverse the abnormal desquamation by affecting follicular epithelial turnover and maturation of cells.[1-3] In addition, some topical retinoids have an effect on inflammation by modulating the immune response, inflammatory mediators, and the migration of inflammatory cells.[4,5] Because retinoids inhibit the formation of the microcomedo, they prevent the formation of both mature comedones and inflammatory lesions and may produce equal reductions in inflammatory lesions and comedones (Fig 3).[6,7] Finally, retinoids alter the follicular microclimate and are likely to enhance the penetration of other compounds, including antibacterial compounds like benzoyl peroxide or topical antibiotics.[2,8] As a result, the topical retinoids effectively control microcomedo development, reduce existing comedones and inflammatory lesions, and minimize the formation of new acne lesions.

Recently, chromatographic studies have shown that topical retinoids, adapalene, and tretinoin decrease the free fatty acids in the microcomedo, as do antibiotics. This observation may indicate normalization of the functional barrier in the infundibulum and also explain the anti-inflammatory role of adapalene.[3] In the infundibulum, *P acnes* lipase metabolizes triglycerides to free fatty acids, producing irritation. During treatment, microcomedones are dramatically reduced; however, they increase again after cessation of therapy.[3] This supports a recommendation for maintenance therapy with a topical retinoid to prevent recurrence.

Clinical experience

The currently available topical retinoids for acne include tretinoin, adapalene, tazarotene and, in some countries, topical isotretinoin, motretinide, retinaldehyde, and β-retinoyl glucuronide.[2] Although these agents have differing chemical structures, they all target the microcomedo (the originator of all acne lesions) and are comedosuppressive in different strengths. They differ somewhat in anti-inflammatory effects and tolerability.

Tretinoin, the first retinoid to be studied, significantly reduces both comedones and inflammatory lesions.[6] In 12-week studies, reductions in lesion counts have been reported in the range of 33% to 81% for noninflammatory lesions, 17% to 71% for inflammatory lesions, and 22% to 83% for total lesions. In vehicle-controlled studies, once-daily tretinoin therapy (0.025% gel and 0.025% cream) reduced all types of acne lesions by 40% to 50%.[9,10] In these studies, tretinoin was significantly more effective than vehicle in reducing both inflammatory and noninflammatory lesions by week 12.

Tretinoin is available in six strengths and three formulations: cream (0.025%, 0.05%, and 0.1%), gel (0.01% and 0.025%), and liquid (0.05%). Formulations and concentrations may vary from country to country. The original tretinoin formulations were associated with cutaneous irritation, including erythema, desquamation, burning, and pruritus. Persons with sensitive skin, rosacea, and eczema may be most prone to skin irritation with tretinoin. To counter these problems, tretinoin therapy is often initiated at a low dose.

Tretinoin has also been reformulated to overcome tolerability problems; two of the newer formulations include tretinoin microsphere and polymerized tretinoin. Retin-A Micro (0.1% gel) contains tretinoin trapped within porous copolymer microspheres.

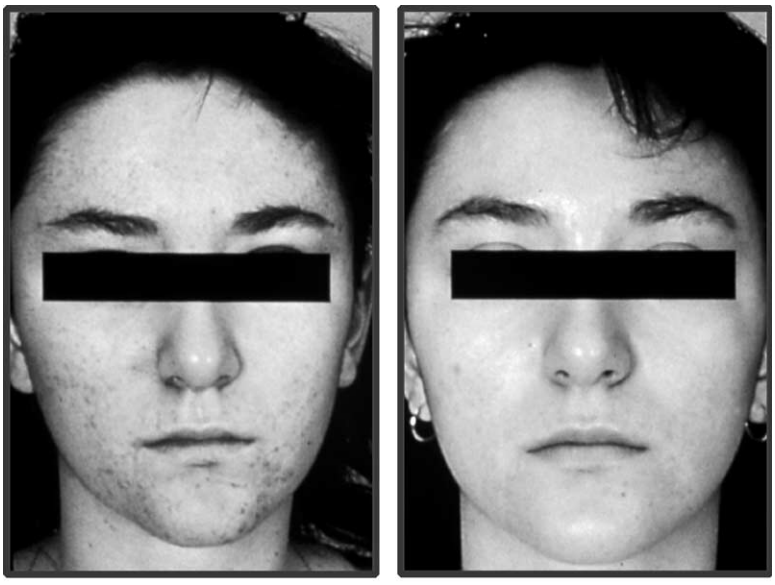

Fig 4. Topical retinoid monotherapy.

These particles selectively localize to the follicle, where tretinoin is released over time, reducing the concentration of tretinoin on the skin and, thus, irritation. Retin-A Micro was not compared to Retin-A in acne clinical trials; however, clinical safety and efficacy results in vehicle-controlled studies appear consistent with results observed with other forms of Retin-A.[11] Avita (0.025% cream and 0.025% gel) utilizes a novel vehicle—polyolprepolymer-2—designed to release tretinoin in a slow, controlled manner. The efficacy and safety of Avita are comparable to tretinoin 0.025% cream and tretinoin 0.025% gel.[9,10]

Adapalene is a third generation retinoid available as cream, gel, solution, and pledgets in 0.1% concentration. The safety and efficacy of adapalene has been demonstrated in numerous controlled clinical trials.[7,12-21] Recently, a meta-analysis of five large, well-controlled studies involving more than 900 patients showed that adapalene gel 0.1% was as effective as tretinoin gel 0.025% (Fig 4).[22] Overall, there was a 49% to 63% mean reduction in lesions among patients receiving adapalene during 12 weeks of treatment, and the majority of patients (80-89%) were considered to have achieved a favorable clinical response.

In addition, adapalene was better tolerated than tretinoin at all evaluation periods.[22] These results have been consistently duplicated in other studies, regardless of the adapalene and tretinoin formulations utilized. More recently, adapalene has demonstrated equivalent efficacy to tretinoin microsphere gel 0.1% and tretinoin cream 0.05%, as well as greater tolerability than tretinoin cream 0.025%.[21] However, in a double-blind 12-week study, Nyirady et al reported that tretinoin microsphere gel may have a faster onset of action than adapalene. These authors reported a greater reduction in comedone counts at week 4 with tretinoin versus adapalene; reductions in acne lesions at 12 weeks were similar with the two drugs. In this study, tretinoin microsphere gel was associated with an increased incidence of dryness and peeling when compared with adapalene gel.[23]

The improved tolerability and anti-inflammatory activity of adapalene and some of the newer formulations of retinoic acid allows the early use of these agents, even in mild acne. When retinoids are used in combination with a topical or oral antimicrobial agent, the combination produces faster results and significantly greater reductions in acne lesions versus antimicrobials alone. Thus, it is no longer necessary to initiate a course of antibiotic therapy and wait for a subsequent visit to initiate topical retinoid therapy.

Isotretinoin is available in a gel formulation; it should be noted, however, that topical isotretinoin has very different effects from oral isotretinoin.[1,2] In the topical formulation, isotretinoin does not reduce sebum secretion. Rather, it is similar to topical tretinoin but causes less skin irritation.[24,25] The effectiveness of topical isotretinoin demonstrated in controlled studies is within the range reported for tretinoin and adapalene; reductions in noninflammatory lesions range from 46% to 78%, and reduc-

tions in inflammatory lesions from 24% to 55% after 12 to 14 weeks of treatment.

Tazarotene, available as a gel or cream in 0.05% or 0.1% concentrations (the 0.1% concentration is approved for treatment of acne) has also been shown effective in controlled clinical trials.[26-28] In a 12-week, vehicle-controlled, double-blind, randomized, multicenter study, tazarotene 0.1% and 0.05% gels applied once daily were associated with treatment success rates (excellent or good rating by investigator, >50% improvement) in 68% and 51% of patients, respectively. The treatment success rate in the vehicle arm was 40%.[28] Both concentrations had acceptable tolerability profiles, with no serious adverse events. The adverse events that did occur were primarily mild to moderate local skin irritation, consistent with other topical retinoids.[28] Preliminary results from comparative studies of tazarotene versus tretinoin or adapalene suggest that once-daily tazarotene is more effective than once-daily tretinoin in reducing papules and open comedones, with equal efficacy against closed comedones.[29, 30] Tazarotene administered every other day achieved comparable reductions in noninflammatory and inflammatory lesion counts versus adapalene administered daily.[29]

Retinaldehyde is transformed into all-trans-retinoic acid and induces biologic effects similar to topical retinoic acid when administered at lower concentrations versus retinoic acid. In animal models, topical retinaldehyde has been shown to induce differentiation and proliferation and to have comedolytic activity.[31] Retinaldehyde has also been studied in acne patients. Morel et al evaluated the efficacy and safety of topically applied retinaldehyde 0.1% gel in combination with topical erythromycin 4% in 74 patients.[32] Over the 8-week treatment period, the combination significantly improved acne lesions; no statistical differences were observed between the groups. In this study, retinaldehyde was well tolerated.[32]

Both retinol and retinoic acid are metabolized to retinyl β-glucuronide and retinoyl β-glucuronide, and the effects of these agents in acne have been studied. The glucuronides of retinol and retinoic acid possess some unique properties. Besides being water-soluble, these glucuronide conjugates show biologic activity similar to the fat-soluble forms, but are much less toxic. Retinoyl β-glucuronide has shown promise as a nontoxic drug for the treatment of acne and other skin disorders. Goswami et al found that 18 weeks of treatment with topical retinoyl β-glucuronide 0.16% cream resulted in a significant reduction in acne lesions versus vehicle among 39 acne patients in India.[32] Retinoyl β-glucuronide was also well tolerated.

Optimizing therapy with topical retinoids

Topical retinoids should no longer be reserved for patients with predominantly comedonal acne. Studies have shown that topical retinoid therapy significantly improves inflammatory acne. The current best practice is thought to add topical retinoids at the onset of therapy even in patients presenting with predominantly inflammatory acne. In these patients, topical or oral antibiotics should be added to provide a significantly greater and more rapid effect.

The efficacy of retinoids against inflammatory lesions is not fully appreciated, perhaps because they act more slowly than oral antibiotics. However, some retinoids have a direct anti-inflammatory action and are very useful when combined with oral or topical antimicrobials for treating papular pustular acne grades 1, 2, and 3, according to the grading system of Plewig and Kligman (Fig 5). Retinoids have demonstrated similar reductions in inflammatory lesions and in open/closed comedones.[7,34] This is not surprising, because retinoids target the precursor lesion—the microcomedo—and the newer agents have demonstrated specific anti-inflammatory activity and modulate neutrophil chemotaxis to reduce some aspects of the inflammatory response.[3-5] This mechanism is similar to that observed with antibiotics.

Therefore, it seems reasonable to initiate topical retinoid therapy as a first-line management approach in acne. Alternatives could possibly include combination of antibiotic with zinc, benzoyl peroxide, or even topical antibiotics alone. In 1980, Melski and Arndt commented that benzoyl peroxide is antimicrobial and comedolytic and was considered a cornerstone of early acne treatment.[35] Some studies have shown benzoyl peroxide to have a significant effect against comedones as well as it having a potent antimicrobial affect. There is a need to perform very well controlled clinical trials comparing benzoyl peroxide with the newer retinoids.

In addition, long-term use of antibiotics has the potential for bacterial resistance, especially if used as monotherapy. Topical retinoids should be started at the patient's first visit, and should be a part of therapy for virtually all patients receiving antimicrobial agents. As will be discussed in detail later, combination therapy achieves greater results for mild and moderate acne with an inflammatory aspect. An effective strategy is to initiate topical retinoid therapy at the same time as oral or topical antibiotics and continue until reasonable clearing of inflammatory lesions occurs. Then stop the antibiotic and continue therapy, with topical retinoids to maintain remission of comedones and inflammatory lesions by inhibit-

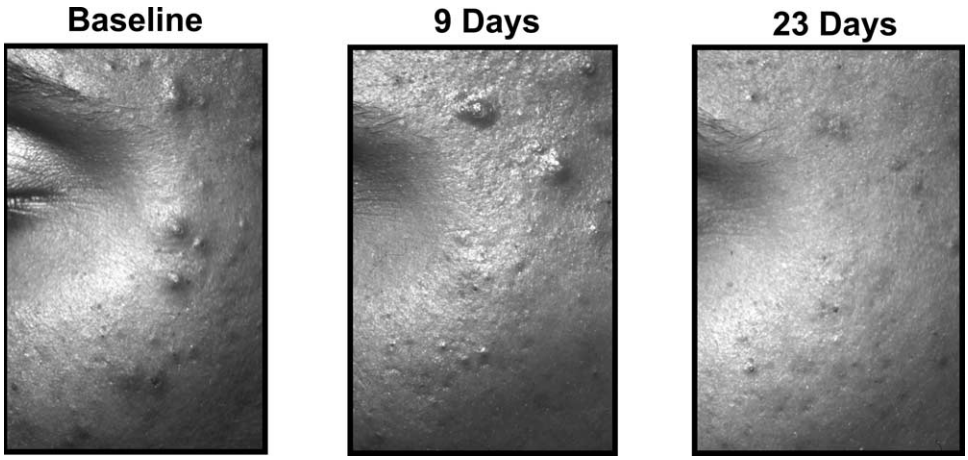

Fig 5. Effect of topical retinoid monotherapy on inflammatory lesions (parallel-polarized photography). Adapalene monotherapy demonstrated faster clearing of inflammatory acne lesions compared with the pretreatment period. After the skin was cleared of existing lesions, the retinoid maintained remission of both comedones and inflammatory lesions. Reprinted with permission from Rizova E. New photographic techniques for clinical evaluation of acne. J Eur Acad Derm Venereol 2001;15(Suppl 3):13-8.

ing microcomedo formation. Maintenance therapy should be supervised by the physicians. This minimizes long-term use of antibiotics and the potential for bacterial resistance.

Topical retinoid therapy may also be a particularly good therapeutic choice for patients with dark skin, as these agents help improve and avoid the hyperpigmentation that occurs with inflammatory acne lesions in this population.[36] Dark pigmented skin may be sensitive, discolors quickly, and scars easily because of the active melanin and hyperpigmentation. Jacyk et al recently conducted an open-label, noncomparative study of adapalene gel 0.1% in the treatment of facial acne vulgaris in patients (n = 44) with dark-pigmented skin.[38] Adapalene gel 0.1% significantly improved acne, reducing total lesion counts and improving the global facial acne score. At the start of the study, several patients had marked postinflammatory hyperpigmentation on the face. In this group, most had a reduction in their postinflammatory hyperpigmentation with treatment, and some patients had a marked decrease in hyperpigmentation. These results suggest that adapalene is well suited for the treatment of acne in patients with dark skin.[38] Similarly, Rafal et al reported significant lightening of hyperpigmented lesions among 58 patients treated with tretinoin 0.1% for 10 months.[39] Differences in lesions were apparent after one month of treatment with tretinoin.

Last, patients should be informed about the time to response with acne therapy and ways to minimize irritation, such as using a gentle cleanser and a moisturizer along with the retinoid.

In summary, normalizing follicular desquamation is the key to achieving and maintaining control of mild to moderate acne. Retinoids are an integral part of acne therapy, both alone and in combination with other topical and/or oral antimicrobial agents. Retinoids from our current knowledge are recommended at the initiation of therapy in inflammatory acne. Some retinoids possess anti-inflammatory properties and, when added to antibiotic therapy, the combination provides greater and faster results compared with antimicrobials alone. Tables I and II present an overview of the efficacy and safety of commonly used topical therapeutic agents.

Consensus Recommendations: Topical Retinoids

- Should be primary treatment for most forms of acne vulgaris
- Use early for best results
- Should be applied to entire affected area
- Combine with antimicrobial therapy when inflammatory lesions are present
- Essential part of maintenance therapy

Maintenance therapy

In a study evaluating the number of closed comedones and microcomedones in acne patients, topical tretinoin 0.025% had a marked effect in reducing both microcomedones and comedones (Fig 6).[3] Visual assessment and full-face comedonal counts

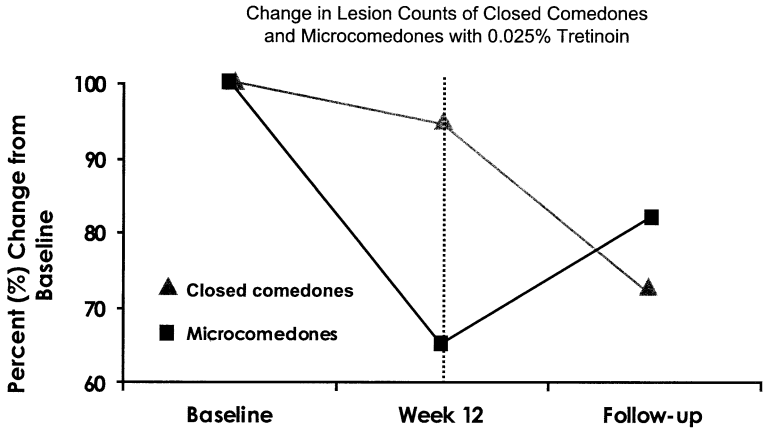

Fig 6. Importance of maintenance therapy. Data from Thielitz A, et al. Br J Dermatol 2001;145:19-27 and Gollnick H, unpublished data.

Table I. Spectrum of efficacy of topical agents in acne treatment

	Reduction in Comedones	Sebosuppressive	Antimicrobial	Anti-inflammatory*
Tretinoin	++	----	----	----
Isotretinoin (topical)	++	----	----	(+)
Adapalene	++	----	----	+
Tazarotene	++	----	----	(+)
Azelaic acid	+	----	+	(+)
Erythromycin	(+)	----	++	+
Clindamycin	(+)	----	++	+
Benzoyl peroxide	+	----	+++	(+)
Salicylic acid	(+)	----	----	----

+++ very strong; ++ strong; + moderate; (+) weak; ---- none.
*Only direct *in vivo* anti-inflammatory effects are mentioned. The spectrum of *in vitro* activity is different from this scoring.
Adapted with permission from Gollnick H, Schramm M. Topical therapy in acne. J Eur Acad Dermatol Venereol 1998;11(suppl 1):S8-12, S28-29.

Table II. Adverse drug reactions* of topical therapeutics in acne treatment

	Erythema	Scaling	Burning	Flare	Resistance	Other
Tretinoin**	+++	+++	++	++	----	----
Isotretinoin	++	++	+	+	----	----
Adapalene	+	+	+	+	----	----
Tazarotene	++	+	+	+	----	----
Azelaic acid	+	+	++	----	----	----
Benzoyl peroxide	++	++	+	+	----	Bleaches hair/clothes
Topical antibiotic	(+)	(+)	(+)	(+)	+++	

*Adverse reactions may vary due to skin type and sensitivity.
**Depends on formulation.
+++ most often; ++ often; + occasional; (+) very occasional; ---- none.
Only direct *in vivo* anti-inflammatory effects are mentioned. The spectrum of *in vitro* activity is different from this scoring.
Adapted with permission from Gollnick H, Schramm M. Topical therapy in acne. J Eur Acad Dermatol Venereol 1998;11(suppl 1):S8-12, S28-29.

were used to assess comedones, and skin surface biopsies were used to assess microcomedones. However, as shown, the number of microcomedones increased immediately after cessation of the tretinoin treatment.[3] This emphasizes the importance of maintenance therapy in sustaining acne remission.

REFERENCES

1. Plewig G, Kligman AM. Acne and rosacea. 3rd ed. New York: Springer-Verlag; 2000.
2. Gollnick H, Schramm M. Topical drug treatment in acne. Dermatology 1998;196:119-25.
3. Thielitz A, Helmdach M, Ropke EM, Gollnick H. Lipid analysis of follicular casts from cyanoacrylate strips as a new method for studying therapeutic effects of antiacne agents. Br J Dermatol 2001;145:19-27.
4. Verschoore M, Bouclier M, Czernielewski J, Hensby C. Topical retinoids: their use in dermatology. Dermatol Ther 1993;11:107-15.
5. Hensby C, Cavey D, Bouclier M, Chatelus A, Algate D, Eustache J, et al. The in vivo and in vitro anti-inflammatory activity of CD271: a new retinoid-like modulator of cell differentiation. Agents Action 1990;29:56-8.
6. Kligman AM, Fulton JE, Plewig G. Topical vitamin A acid in acne vulgaris. Arch Dermatol 1969;99:469.
7. Shalita AR, Weiss JS, Chalker DK, Ellis CN, Greenspan A, Katz HI, et al. A comparison of the efficacy and safety of adapalene gel 0.1% and tretinoin gel 0.025% in the treatment of acne vulgaris: a multicenter trial. J Am Acad Dermatol 1996;34:482-5.
8. Mills OH Jr, Marples RR, Kligman AM. Acne vulgaris. Oral therapy with tetracycline and topical therapy with vitamin A. Arch Dermatol 1972;106:200-3.
9. Lucky A, Cullen S, Funicella T, Jarrat MT, Jones T, Reddick ME. Double-blind, vehicle-controlled multicenter comparison of two 0.025% tretinoin creams in patients with acne vulgaris. J Am Acad Dermatol 1998;38:S24-S30.
10. Lucky A, Cullen S, Jarratt M, Quigley JW. Comparative efficacy and safety of two 0.025% tretinoin gels: results from a multicenter, double-blind, parallel study. J Am Acad Dermatol 1998; 38:S17-S23.
11. Retin A Full Prescribing Information.
12. Dunlap FE, Mills OH, Turley MR, Bauer MD, Plott RT. Adapalene 0.1% gel for the treatment of acne vulgaris: its superiority compared to tretinoin 0.025% cream in skin tolerance and patient preference. Br J Dermatol 1998;139(Suppl 2):17-22.
13. Weiss JS, Shavin JS. Adapalene for the treatment of acne vulgaris. J Am Acad Dermatol 1998;39:S50-S54.
14. Caron D, Sorba V, Kerrouche N, Clucas A. Split-face comparison of adapalene 0.1% gel and tretinoin 0.025% gel in acne patients. J Am Acad Dermatol 1997;36:S110-S112.
15. Millikan LE. Adapalene: an update on newer comparative studies between the various retinoids. Int J Dermatol 2000;39:784-8.
16. Clucas A, Verschoore M, Sorba V, Poncet M, Baker M, Czernielewski J. Adapalene 0.1% gel is better tolerated than tretinoin 0.025% gel in acne patients. J Am Acad Dermatol 1997;26:116-8.
17. Cunliffe WJ, Caputo R, Dreno B, Forstrom L, Heenen M, Orfanos CE, et al. Clinical efficacy and safety comparison of adapalene gel and tretinoin gel in the treatment of acne vulgaris: Europe and US multicenter trials. J Am Acad Dermatol 1997;36:S126-S134.
18. Pierard-Franchimont C, Henry F, Fraiture AL, Fumal I, Pierard GE. Split-face clinical and bio-instrumental comparison of 0.1% adapalene and 0.05% tretinoin in facial acne. Dermatology 1999; 198:218-22.
19. Galvin SA, Gilbert R, Baker M, Guibal F, Tuley MR. Comparative tolerance of adapalene 0.1% gel and six different tretinoin formulations. Br J Dermatol 1998;139(suppl 2):34-40.
20. Grosshans E, Marks R, Mascaro JM, Torras H, Meynadier J, Alirezai M, et al. Evaluation of clinical efficacy and safety of adapalene 0.1% gel versus tretinoin 0.025% gel in the treatment of acne vulgaris, with particular reference to the onset of action and impact on quality of life. Br J Dermatol 1998;139(suppl 2)26-33.
21. Wolf JE. An update of recent clinical trials examining adapalene and acne. J Eur Acad Venereol 2001;15(suppl 3):23-9.
22. Cunliffe WJ, Pncet M, Loesche C, Verschoore M. A comparison of the efficacy and tolerability of adapalene 0.1% gel versus tretinoin 0.025% gel in patients with acne vulgaris: a meta-analysis of five randomized trials. Br J Dermatol 1998;139(Suppl 52):48-56.
23. Nyirady J, Grossman RM, Nighland M, Berger RS, Jorizzo JL, Kim YH, et al. A comparative trial of two retinoids commonly used in the treatment of acne vulgaris. J Dermatol Treat 2001;12:149-57.
24. Chalker D, Lesher J, Smith J. Efficacy of topical isotretinoin 0.05% gel in acne vulgaris: results of a multicenter, double-blind investigation. J Am Acad Dermatol 1987;17:251-4.
25. Hughes B, Norris J, Cunliffe W. A double-blind evaluation of topical isotretinoin 0.05%, benzoyl peroxide gel 5% and placebo in patients with acne. Clin Exp Dermatol 1992;17:165-8.
26. Russell JJ. Topical therapy for acne. Am Fam Physician 2000;61: 357-65.
27. Foster RH, Brogden RN, Benfield P. Tazarotene. Drugs 1998;55: 705-11.
28. Shalita AR, Chalker DK, Griffith RF, Herbert AA, Hickman JG, Maloney JM, et al. Tazarotene gel is safe and effective in the treatment of acne vulgaris: a multicenter, double-blind, vehicle-controlled study. Cutis 1999;63:349-54.
29. Bershad S. Topical retinoids in the treatment of acne vulgaris. Cutis 1999;64(suppl 2):8-23.
30. Kakita L. Tazarotene versus tretinoin or adapalene in the treatment of acne vulgaris. J Am Acad Dermatol 2000;43:S51-S54.
31. Morel P, Vienne MP, Beylot C, Bonerandi JJ, Dreno B, Lehucher-Ceyrac D, et al. Clinical efficacy and safety of a topical combination of retinaldehyde 0.1% with erythromycin 4% in acne vulgaris. Clin Exp Dermatol 1999;24:354-7.
32. Goswami BC, Baishya B, Barua AB, Olson JA. Topical retinoyl β-glucuronide is an effective treatment of mild to moderate acne vulgaris in Asian-Indian patients. Skin Pharmacol Appl Skin Physiol 1999;12:167-73.
33. Mills OH Jr, Kligman AM. Treatment of acne vulgaris with topically applied erythromycin and tretinoin. Acta Dermatovener (Stockholm) 1978;58:555-7.
34. White GM. Acne therapy. Adv Dermatol 1999;14:29-57.
35. Melski JW, Arndt K. Current concepts: topical therapy for acne. N Engl J Med 1980;302:503-6.
36. Lyons RE. Comparative effectiveness of benzoyl peroxide and tretinoin in acne vulgaris. Int J Dermatol 1978;17:246-51.
37. Dunlop KJ, Barnetson RS. A comparative study of isolutrol versus benzoyl peroxide in the treatment of acne. Australas J Dermatol 1995;36:13-5.
38. Jacyk WK, Mpofu P. Adapalene gel 0.1% for topical treatment of acne vulgaris in African patients. Cutis 2001;68(4 Suppl):48-54.
39. Rafal ES, Griffiths CE, Ditre CM, Finkel LJ, Hamilton TA, Ellis CN, et al. Topical tretinoin (retinoic acid) treatment for liver spots associated with photodamage. N Engl J Med 1992;326:368-74.

COMBINATION THERAPY

Consensus: Antimicrobial Therapy + Topical Retinoid Therapy Is Signficantly Better Than Antimicrobials Alone

- Clearing of both inflammatory lesions and comedones is faster and significantly greater with combination therapy versus antibiotic therapy alone
- Combination therapy allows targeting of different pathophysiologic factors
- Topical retinoid therapy is likely to enhance penetration of antimicrobial agents
- Add topical retinoids early—at the onset of therapy—for greatest and fastest results
- Maintain success by continuing with topical retinoid

One approach to treating patients with inflammatory acne has included both topical and systemic broad-spectrum antibiotics. Treatment typically lasts a minimum of 3 to 6 weeks via the topical route and 3 to 6 months via the oral route. A duration of several years of overall treatment is not uncommon. Often, agents are changed periodically, exposing the patient with acne to multiple antibiotics. As will be discussed, the antibiotics used in acne include tetracyclines, macrolides, and, in some countries, trimethoprim. Given that acne is an exceedingly common condition, use of antibiotics as first-line therapy significantly increases the risk of two problems: resistance of *P acnes* in acne patients, and an increase in the pool of resistant organisms, including *Staphylococcus aureus*. One strategy to limit the increase in resistance is the use of treatment regimens that combine agents with complementary but different mechanisms of action.

Topical retinoids plus antimicrobial agents

In patients with inflammatory and comedonal lesions, best results may occur when topical retinoids are used in combination with antimicrobial therapies. Topical retinoids in combination with topical or oral antimicrobials have been proven to reduce acne lesions faster and to a greater degree than antimicrobial therapy alone. This is true for both comedones as well as inflammatory lesions.[1-16]

Furthermore, combination therapy with antimicrobials and retinoids targets three major areas of acne pathophysiology (ductal hypercornification, *P acnes* proliferation, and inflammation).[3] These mechanisms are additive and, to some extent, independent processes; therefore, it is logical to expect enhanced therapeutic benefits from the combination (Fig 7). In addition, topical retinoids may affect skin permeability by weakening the horny layer barrier, enhancing the penetration of topical antibiotic. During topical retinoid therapy, skin surface corneocytes loosen and the number of cell layers is reduced by approximately 50%.[17] Furthermore, the increased cell turnover of the follicular epithelium allows more oral antibiotic to be transported into the canal where *P acnes* resides.[2] There is indirect evidence that by increasing the tissue concentration of the antibiotic, the topical retinoid potentiates the antimicrobial activity of the agent and lowers the potential for low-concentration-induced antibiotic resistance.[3]

This strategy may minimize the potential for microbial resistance by working faster and limiting the duration of antimicrobial therapy. Also, the

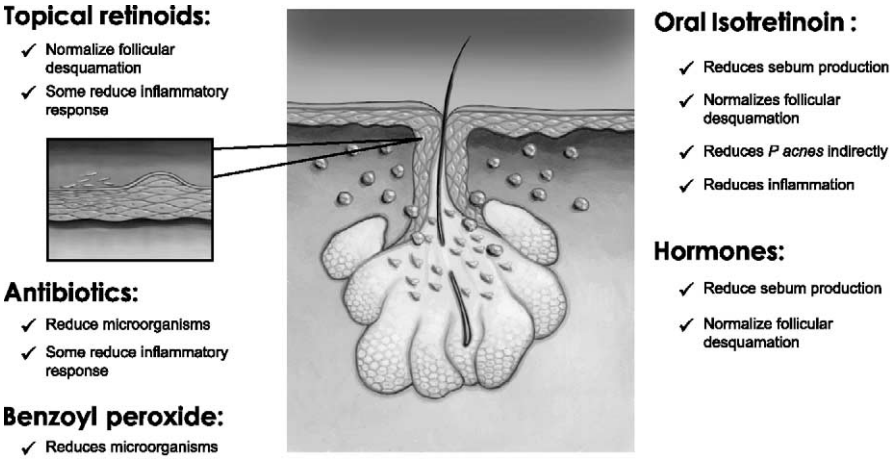

Fig 7. Overview of acne medications' mechanisms of action.

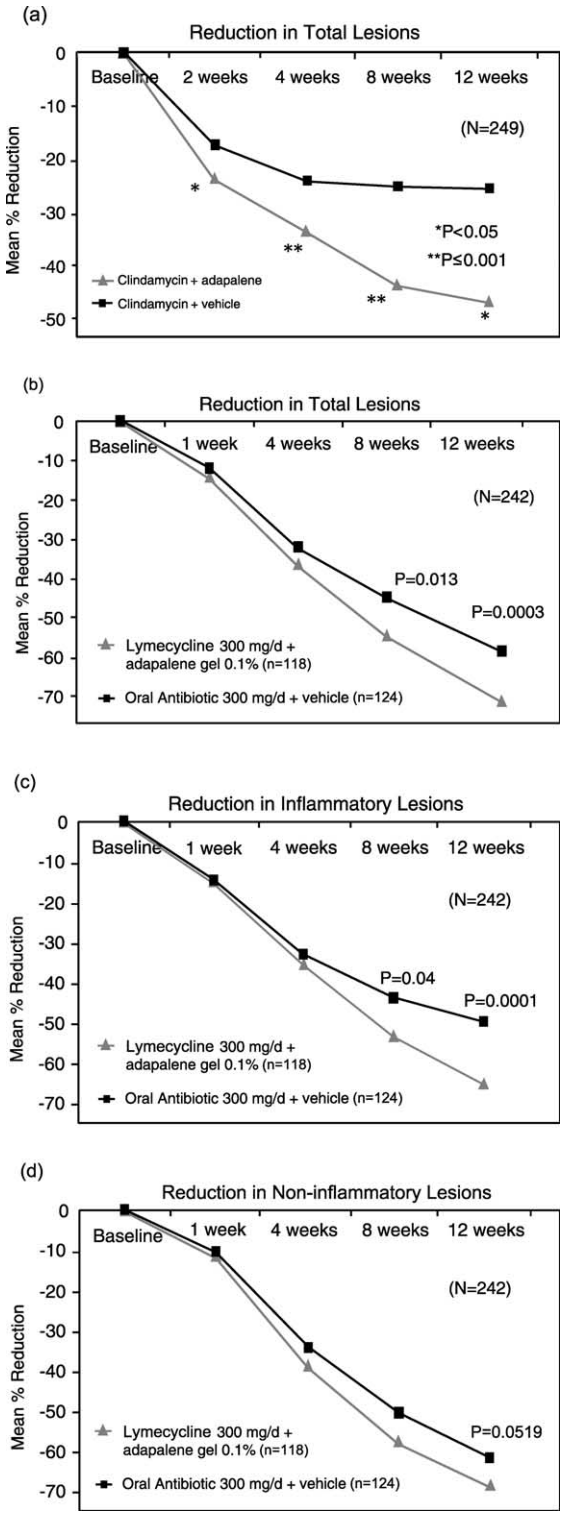

Fig 8. Effect of combination therapy on lesion counts. **A**, Reduction in total lesions with topical antibiotic plus topical retinoid[1]; **B**, Reduction in total lesions with oral antibiotic plus topical retinoid[2]; **C**, Reduction in inflammatory lesions with oral antibiotic plus topical retinoid[2]; **D**, Reduction in noninflammatory lesions with oral antibiotic plus topical retinoid[2]. *P* values are calculated based on lesion counts.

combination of a topical retinoid and antibiotic suppresses the *P acnes* population faster and to a greater extent than the antibiotic is capable of alone.[2,4,14-15]

Clinical experience

In an early study evaluating combination therapy, Mills and Kligman compared the efficacy of topical tretinoin 0.05% solution plus erythromycin 2% solution twice a day versus tretinoin or erythromycin alone in patients with moderately severe acne.[3] An inert vehicle was used as a control. Subjects were randomized to one of four treatment groups: tretinoin 0.05% solution once daily at bedtime; 2% erythromycin solution applied in the morning and at bedtime; the combination of 2% erythromycin twice a day plus tretinoin 0.05% in the night; or vehicle twice a day. Clinical effectiveness was judged by the investigators to be excellent (≥75% reduction in lesion count), good (50-74% reduction), fair (25-49% reduction), or poor (<25% reduction). The percentage of patients with an outcome rated excellent or good was markedly higher in the combination group than either monotherapy or vehicle (75% combination, 50% tretinoin, 45% erythromycin, 10% vehicle).[3] In addition, none of the patients in the combination therapy group had a poor clinical outcome, whereas 20% of the patients in both monotherapy groups received a rating of poor.[3]

Korting et al conducted a community-based large-scale, open, multicenter study of a gel formulation combining tretinoin 0.025% plus erythromycin 4%.[5] A total of 1337 patients participated; of these, 499 patients had previously received acne treatment, which was described as ineffective or poorly effective in the majority (90%). Efficacy was evaluated by acne lesion counts at baseline and every 2 weeks during the 14-week treatment period. As in the previous study, combination therapy was more effective in reducing acne lesions, with clearing or reduction of comedones in 84% of patients and inflammatory lesions in 91% of patients at the end of treatment. Furthermore, a visible response was apparent after 2 weeks in 35% of patients. Side effects were reported in 15.3% of patients, and included erythema, burning, pruritus, scaling, and dryness of the skin. However, only 1.9% of subjects discontinued therapy due to tolerability problems.[5] These figures compare favorably with the side effect and discontinuation rates with tretinoin therapy alone.

Significant results have also been achieved with a fixed combination of clindamycin phosphate 0.1% and tretinoin 0.025% gel.[9,12] In one study, the fixed combination was associated with a significantly greater reduction in noninflammatory lesions (P =

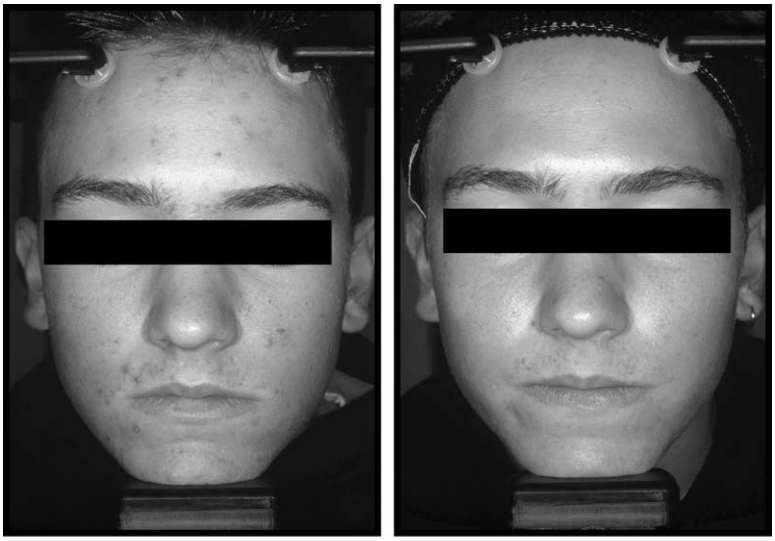

Fig 9. Combination therapy with topical retinoid and topical antibiotic.

.05) and inflammatory lesions ($P = .018$) after 12 weeks of therapy. In addition, combination therapy resulted in a faster onset of improvement compared with clindamycin alone.[9]

Most recently, the combination of adapalene gel 0.1% plus clindamycin 1% was studied in a 12-week randomized, multicenter trial involving 249 patients with mild to moderate acne (Fig 8A).[16] Subjects were randomized to receive clindamycin topical lotion plus adapalene gel (n = 125) or clindamycin topical lotion plus adapalene gel vehicle (n = 124). Clindamycin lotion was applied twice daily and adapalene gel or vehicle once daily. Both treatments reduced total lesion counts; however, the combination group (adapalene and clindamycin) cleared acne lesions faster and was significantly greater compared to clindamycin monotherapy at all time points ($P < .05$ at week 2 and $P < .001$ at all other visits). Similarly, combination therapy had a significantly greater effect on both inflammatory lesion counts and noninflammatory lesion counts than clindamycin alone. The low irritation profile of adapalene was demonstrated by the finding that adverse events were similar in the combination group and the clindamycin alone group.[16] Figure 9 shows one subject at baseline and after 12 weeks of therapy.

In a similar study evaluating adapalene gel 0.1% plus oral lymecycline in 118 patients with moderate inflammatory acne, combination therapy with an oral antibiotic plus a topical retinoid was again faster and significantly more effective than oral lymecycline alone in clearing both inflammatory lesions and comedones (Fig 8B-D).[18] Subjects were randomized to receive either lymecycline 300 mg/day plus adapalene gel 0.1% or lymecycline 300 mg/day plus adapalene vehicle. The mean percent reduction in total facial lesion counts at week 12 was 70.5% in the combination therapy group and 58.0% in the lymecycline monotherapy group ($P = .0019$). Notably, combination therapy was associated with a significantly greater reduction in noninflammatory lesions ($P = .0519$) and inflammatory lesions ($P = .0001$) versus lymecycline alone. Mean scores for local tolerance were comparable between the two groups at baseline and endpoint, although skin irritation was slightly more common in the adapalene group.[18]

Consensus Recommendations: Combination Therapy

- Should be used when inflammatory lesions are present
- Speeds clearing and provides greater resolution of both inflammatory lesions and comedones
- Topical retinoid should be started at the initiation of antimicrobial therapy
- Antibiotic should be discontinued when inflammatory lesions resolve adequately
- If this is not possible, then switch to a combination agent with benzoyl peroxide plus an antibiotic
- Continue use of topical retinoid to maintain remission of new acne lesions when antibiotic therapy is discontinued

REFERENCES

1. Kligman AM, Mills OH Jr, Leyden JJ. Acne vulgaris. A treatable disease. Postgrad Med 1974;55:99-105.
2. Kligman AM, Mills OH, McGinley KJ, Leyden JJ. Acne therapy with tretinoin in combination with antibiotics. Acta Dermatovener (Stockholm) 1975;74(Suppl):111-5.
3. Mills OH Jr, Kligman AM. Treatment of acne vulgaris with topically applied erythromycin and tretinoin. Acta Dermatovener (Stockholm) 1978;58:555-7.
4. Mills OH Jr, Marples RR, Kligman AM. Acne vulgaris. Oral therapy with tetracycline and topical therapy with vitamin A. Arch Dermatol 1972;106:200-3.
5. Korting HC, Braun-Falco O. Efficacy and tolerability of combined topical treatment of acne vulgaris with tretinoin and erythromycin in general practice. Drugs Exp Clin Res 1989;15:447-51.
6. Amblard P, Bazex A, Beylot C, Civatte J, Garrel J, Grupper C, et al. The association tretinoin-erythromycin base: a new topical treatment for acne. Results of a multicentric trial on 347 cases. Semin Hop 1980;56:911-5.
7. Rietschel RL, Duncan SH. Clindamycin phosphate used in combination with tretinoin in the treatment of acne. Int J Dermatol 1983;22:41-3.
8. Gould DJ, Ead R, Cunliffe WJ. Oral tetracycline and retinoid acid gel in acne. Practitioner 1978;221:268-271.
9. Zouboulis CHC, Derumeaux L, Decroix J, Maciejewska-Udziela B, Cambazards F, Stuhlert A. A multicentre, single-blind, randomized comparison of a fixed clindamycin phosphate/tretinoin gel formulation (Velac) applied once daily and a clindamycin lotion formulation (Dalacin T) applied twice daily in the topical treatment of acne vulgaris. Br J Dermatol 2000;143:498-505.
10. Glass D, Boorman GC, Stables GI, Cunliffe WJ, Goode K. A placebo-controlled clinical trial to compare a gel containing a combination of isotretinoin (0.05%) and erythromycin (2%) with gels containing isotretinoin (0.05%) or erythromycin (2%) alone in the topical treatment of acne vulgaris. Dermatology 1999;199:242-7.
11. Morel P, Vienne MP, Beylot C, Bonerandi JJ, Dreno B, Lehucher-Ceyrac D, et al. Clinical efficacy and safety of a topical combination of retinaldehyde 0.1% with erythromycin 4% in acne vulgaris. Clin Exp Dermatol 1999;24:354-7.
12. Richter JR, Forstrom LR, Kiistala UO, Jung EG. Efficacy of the fixed 1.2% clindamycin phosphate, 0.025% tretinoin gel formulation (Velac) and a proprietary 0.025% tretinoin gel formulation (Aberela) in the topical control of facial acne. J Eur Acad Dermatol Venereol 1998;11:227-33.
13. Thielitz A, Helmdach M, Ropke EM, Gollnick H. Lipid analysis of follicular casts from cyanoacrylate strips as a new method for studying therapeutic effects of antiacne agents. Br J Dermatol 2001;145:19-27.
14. Leyden JJ, Marples RR, Mills OH, Kligman AM. Tretinoin and antibiotic therapy in acne vulgaris. South Med J 1974;67:20-5.
15. Hurwitz S. The combined effect of vitamin A acid and benzoyl peroxide in the treatment of acne. Cutis 1976;17:585-90.
16. Wolf JE, Kaplan D, Kraus S, Loven K, Rist T, Swinyer L, et al. Efficacy and tolerability of combined topical treatment of acne vulgaris with adapalene and clindamycin: a multicenter, randomized, investigator-blind study. J Am Acad Dermatol In press.
17. Kaidbey K, Kligman AM, Yoshida H. Effects of intensive application of retinoic acid on human skin. Br J Dermatol 1975;92:693-701.
18. Cunliffe W, Grosshans E, Belaich S, Meynadier J, Alirezai M, Thomas L. A comparison of the efficacy and safety of lymecycline plus adapalene gel 0.1% versus lymecycline plus gel vehicle in patients with acne vulgaris. J Am Acad Dermatol In press.

ANTIMICROBIAL THERAPY

Consensus: Antibiotic Therapy Primarily Affects Inflammatory Lesions

- Oral and topical antibiotics usually should not be used as monotherapy
- Antibiotics are generally well tolerated, but are associated with rare instances of severe adverse events (minocycline)
- Antibiotics should be combined with topical retinoids to enhance efficacy against comedones and inflammatory acne lesions
- Benzoyl peroxide alone significantly improves inflammatory acne
- Topical benzoyl peroxide or azaleic acid treatment may be added to antibiotics to reduce the potentialof developing *P acnes* resistance

Antimicrobials have been a mainstay of acne treatment for more than 30 years and an active area of research for much of this time. In the past two decades, a substantial armamentarium of topical and systemic agents has been developed and utilized in the treatment of acne. The choice between topical and systemic agents is generally based on the presence, extent, and severity of inflammatory lesions. For optimizing results, antimicrobial agents should be combined with topical retinoids. This will increase efficacy, shortening treatment duration, and help to prevent antibiotic resistance.

Indications

The primary indication for systemic antibiotics is moderate-to-severe inflammatory acne.[1-3] The preferred agents include tetracyclines and derivatives; macrolides, co-trimoxazole (not used in Europe due to availability of trimethoprim), and trimethoprim may represent acceptable alternatives.[2] Due to lack of efficacy or safety considerations, the following antibiotics should not routinely be used in acne: cephalosporins, fluoroquinolones, aminoglycosides, chloramphenicol, sulfonamides, and gyrase inhibitors.[4]

Topical antibiotics and benzoyl peroxide are indicated in patients with mild to moderate inflammatory acne.[5] Azelaic acid is indicated in mild comedonal acne and mild forms of papulopustular acne.[5] It is highly desirable to combine topical antimicrobial agents with topical retinoids. Benzoyl peroxide combined with topical antibiotics reduces the risk of development of resistant strains of *P acnes*.[6]

Mechanism of action

Oral antibiotics reduce the number of *P acnes* and *Staphylococcus epidermidis.*[2,4,7-9] *P acnes* is thought to trigger the inflammatory response in acne and thus has an important role in the pathogenesis of inflamed acne lesions. In addition to interfering with the growth and/or metabolism of propionibacteria, antibiotics also have an anti-inflammatory activity (inhibiting neutrophil chemotaxis, cytokine production, and macrophage functions).[2,10-17] Tetracyclines also decrease prostaglandin production, inhibit nitric oxide synthetase, and increase the expression of dismutase superoxide enzyme (minocycline). Moreover, minocycline and doxycycline inhibit the formation of inflammatory granuloma.

Benzoyl peroxide is a powerful antimicrobial agent that rapidly destroys both bacterial organisms and yeasts.[4,18] It has both a greater and more rapid effect in suppressing *P acnes* compared with topical antibiotics.[19] After a few days, the organisms are reduced by 90% and fatty acids are decreased by 40% (in comparison, these effects are obtained with antibiotics only after several weeks of therapy).[1,4,19-20] In contrast to antibiotics, there is no evidence that microorganisms become resistant to benzoyl peroxide.[4,21-22] Benzoyl peroxide and antibiotics have an indirect effect on comedogenesis through their effects on *P acnes,* because activation of the immune system by *P acnes* intensifies comedogenesis.[4]

Antibiotics do have an effect on comedones, but probably less so than topical retinoids.[4] However, the effect on comedones increases when antibiotics are combined with zinc and benzoyl peroxide.[23]

The mechanism of action of azelaic acid is controversial; most studies suggest this agent reduces *P acnes*, whereas some demonstrate only a modest degree of bacterial suppression. Mild comedolytic activity and a mild anti-inflammatory effect have been found in well controlled, large-scale studies.[4,24-25] An additional mechanism of azelaic acid may be to help reduce postinflammatory hyperpigmentation in susceptible persons.

Clinical experience

Oral antibiotics. Oral erythromycin and tetracyclines have a long history of safety and efficacy in the management of inflammatory acne.[3,4] The increasing antimicrobial resistance to erythromycin and other macrolides limits use of these agents to cases where tetracyclines are contraindicated or not tolerated (eg, pregnant or breast-feeding women and young children).[4,26-29] Sulfamethoxazole/trimethprim (TMP/SMX) or TMP alone[30] may be considered a third-line agent, but is generally used for acne resistant to tetracycline and erythromycin.[21] Comparative studies of oral antibiotics have generally shown little or no significant differences between the available alternatives. Second generation tetracyclines (such as minocycline, doxycycline, and lymecycline) induce a quicker clinical response than first generation tetracyclines.

As with other acne therapies, the clinical effect of oral antibiotics typically requires 4 to 8 weeks.[32] Once the appearance of new inflammatory lesions has decreased or stopped, the dose may be gradually tapered or withdrawn.[32] Topical retinoid therapy should be continued to maintain remission.

Oral antibiotics are generally well-tolerated, and severe side effects are uncommon (Table III).[4,22] Adverse reactions involving the gastrointestinal tract may occur with the tetracyclines and the macrolides, particularly erythromycin (occurring in as many as 30% of patients, depending on dose).[3,4,31] Typically, these side effects are mild and transient and rarely of clinical significance. Tetracyclines can inhibit skeletal growth in the developing fetus and cause discoloration in teeth when used in children younger than 10 years; for these reasons, tetracyclines should be avoided in pregnant women and young children.[31] Minocycline is uncommonly associated with a characteristic discoloration that localizes to scars and sun-exposed areas and, rarely, benign intracranial hypertension and drug-induced lupus.[21,33-35] Candidiasis can occur with antibiotic therapy in women.[31] In one study, lymecycline demonstrated efficacy comparable to minocycline and appears to have a better safety profile.[36]

Topical antibiotics

Topical antibiotics are slower acting and are generally less effective than oral antibiotics. Clindamycin and erythromycin are the most popular topical antibiotics in acne.[37] In a review of the literature, Eady et al found that topical tetracycline is not effective and should not be used any more as acne therapy.[38] Clindamycin and erythromycin were both effective against inflammatory acne in topical form in concentrations of 1% to 4% with or without the addition of zinc.[39,40]

In general, topical antibiotics should not be used as monotherapy due to their relatively slow onset of action and the potential for bacterial resistance if used for extended periods. Topical antibiotic therapy should be discontinued once improvement is seen. If no improvement is observed within 6 to 8 weeks, the agent should be discontinued and alternate therapy should be considered.[44]

Side effects are typically minor, but may include

Table III. Oral antibiotics for acne

First line	Dose*	Efficacy	Advantage	Disadvantages
Tetracycline	500 mg 2×/day	++	Inexpensive	Poor absorption with food
Doxycycline	50-100 mg 2×/day	++	OK with food	Photosensitivity
Lymecycline	150-300 mg 1×/day	++	OK with food	
Minocycline	50-100 mg 2×/day	+++	OK with food	
				Dizziness**, rarely benign intracranial hypertension**, blue teeth and bruises; very rare hepatitis, lupus-like syndrome, mucosal skin pigmentation. More expensive.
Alternatives				
Erythromycin	500 mg 2×/day	+	OK with food	GI upset (not long term)
TMP/SMX	800 SMX/160 TMP	++		Drug rash, rarely severe allergic reactions
TMP	300 mg 2×/day	++		Drug rash

*Dose varies depending on body weight.
**Can occur with all tetracyclines, but more so with minocycline.
+++ very effective, ++ effective, + less effective.
Adapted with permission from White GM. Standard oral antibiotics for acne. 1999;14:29-57.

erythema, peeling, itching, dryness, and burning. Pseudomembranous colitis is rare, but has been observed after topical treatment with clindamycin hydrochloride and clindamycin phosphate.[45,46]

Benzoyl peroxide

Benzoyl peroxide is a safe and effective agent for treating acne, and has efficacy that is maintained over years of use.[4,47] Benzoyl peroxide is available in a variety of formulations and in concentrations ranging from 1% to 10%. The gel formulations may be preferred over creams and lotions due to better stability and more consistent release of the active ingredient. Benzoyl peroxide cleansers may be considered for adolescent boys, both to enhance compliance (the cleanser may be conveniently applied in the shower) and to cover large skin areas such as the chest and back. In general, fair-skinned or young patients should start with preparations of lower strength, particularly for the face. As with all topical medications, the medication should be applied to the entire affected area, usually in the morning and the evening, and not only to the visible lesions.

Benzoyl peroxide provides good efficacy against superficial inflammatory lesions, with rapid bacteriostatic—possibly bactericidal—action. Indeed, in the literature review by Eady discussed previously, none of the topical antibiotics tested was more effective than benzoyl peroxide. [4,6,38] Benzoyl peroxide also has the advantage of not being associated with antimicrobial resistance. Benzoyl peroxide in combination with erythromycin or clindamycin has been shown to be more effective and better tolerated than benzoyl peroxide alone.[45-52] This is perhaps not surprising, because the combination agents have a greater effect in reducing *P acnes* (Fig 10).[43] However, it should be noted that the magnitude of reduction in *P acnes* has not been proven to be always related to clinical effectiveness. The role of benzoyl peroxide and the benzoyl peroxide combination products is primarily antimicrobial.

The primary limitation of benzoyl peroxide for some acne patients is concentration-dependent cutaneous irritation or dryness and bleaching of clothes. Benzoyl peroxide can induce an irritant dermatitis with erythema, scaling, and itching; these side effects occur primarily within the first days of treatment and subside with continued use.[38] Benzoyl peroxide can also bleach hair, clothes, and bed linens.[21] It is probably preferable to combine benzoyl peroxide with other topical medications that have different modes of action. The best match is with topical retinoids; this is an excellent choice for patients with mild to moderate acne. It is probably preferable to use a topical retinoid in the evening, and benzoyl peroxide or a topical antibiotic in the morning, because this will minimize the risk for possible inactivation of either or both drugs.

Optimizing therapy with oral antibiotics

The following general guidelines are useful when utilizing oral antibiotic therapy in acne:

- Use only in moderate to severe acne
- In general, avoid antibiotic monotherapy

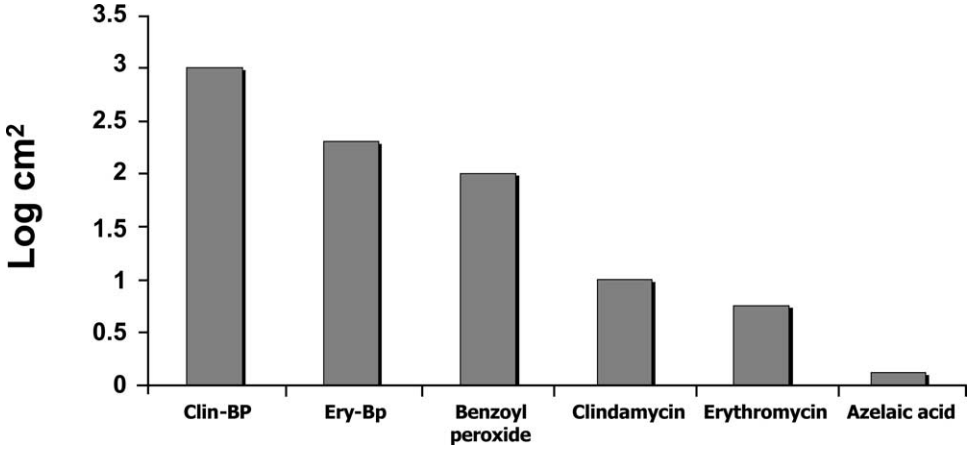

Fig 10. Reductions in *P acnes* with topical therapy
Reprinted with permission from Leyden JJ. The evolving role of *P acnes* in acne. Semin Cutan Med Surg 2001;20:139-43.

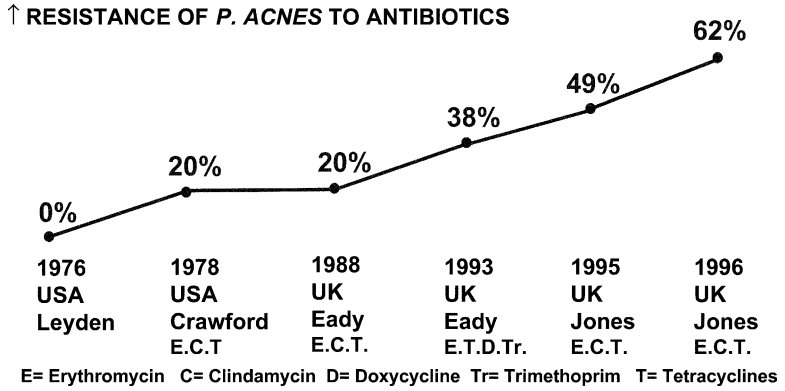

Fig 11. Antibiotics and acne: the facts. Data from Cooper AJ. Systemic review of *Propionibacterium acnes* resistance to systemic antibiotics. Med J Austral 1998;169:259-61.

- Combine with topical retinoids to improve clinical outcomes. Add benzoyl peroxide if antibiotics must be used longer than 2 months.
- The usual minimum duration of therapy is 6 to 8 weeks with a maximum of 12 to 18 weeks; however, if the patient cannot tolerate other therapies and a therapeutic effect is apparent, antibiotic therapy may be continued indefinitely.
- If retreatment is necessary, use the same antibiotic if it was effective—otherwise, use an alternative antibiotic
- It may be helpful to use benzoyl peroxide for a minimum of 5 to 7 days between antibiotic courses to reduce resistant organisms from the skin
- Avoid concomitant use of oral and topical therapy with chemically dissimilar antibiotics
- Stress the importance of good compliance to patients
- Can be combined with anti-androgenic hormonal therapy in women when hormonal therapy is indicated

The dosing of oral antibiotics for acne is somewhat variable. However, a common initial approach includes tetracycline 1 g daily, one hour before meals. After one or two months, marked improvement of inflammatory lesions should be apparent. At this point, the dose may be decreased, usually to 500 mg ever day, for an additional one to two months. With doxycycline and minocycline, the dose may start at 100 mg or 200 mg daily and be followed by 50 mg every day after improvement is observed. However, many physicians do not reduce the dose but simply stop the oral therapy completely when appropriate. Lymecycline is given in a dose of 150 to 300 mg daily before meals, erythromycin 1 g with meals, TMP/SMX as 2 tablets daily (800 mg/SMX and

160 mg/TMP) and TMP 300 mg twice a day.[48] Often, the dose of a specific antibiotic in a particular patient is based on the prescribing physician's clinical experience and preferences.

In acne, antibiotics are typically administered for a prolonged period of time; however, a good response should be obtained in 3 to 6 months. Thereafter, antibiotic therapy should be tapered with an attempt to discontinue exposure. In some patients a quick flare does occur, even with the use of appropriate maintenance therapy. As a result, longer-term oral antibiotic or oral isotretinoin therapy may be required. Long-term therapy may lead to resistant bacteria, not only of *P acnes,* but also coagulase-negative staphylococci on the skin, *Staphylococcus aureus* in the nares, streptococci in the oral cavity, and enterobacteria in the gut. In addition, carriage of erythromycin-resistant propionibacteria has been linked to a poor clinical response in acne patients.[27,29]

Antimicrobial resistance

Antimicrobial resistance due to antibiotic therapy for acne poses a significant threat; Eady et al[28] found that antibiotic therapy in acne patients enhances the development of antimicrobial resistance in close contacts of these patients. Thus, antibiotic anti-acne therapy can affect a wide range of microbes in a large population. *P acnes* resistance was relatively rare until after the widespread use of topical antibiotics.[27,49-50] Antibiotic resistance has steadily increased in recent years (Fig 11). By the late 1980s, resistant strains had become common; now, resistant strains may be found in a large percentage of patients, and multidrug resistance is common.[27] Not many laboratories grow *P acnes*; however, resistant organisms may be suspected in patients who fail to improve.

P acnes resistance is readily disseminated, as evidenced by the finding that resistant strains occur in about 50% of close contacts of acne patients with a resistant organism. In addition, mutations that were first described in the United Kingdom are now present worldwide.[51] Globally, there are some differences in P acnes resistance patterns, which may reflect differences in the use of oral and/or topical antibiotics.[51] In the United States, there has been widespread use of many topical and systemic antibiotics for many years; this nation has a high level of resistance, including emerging resistance to minocycline and doxycycline.

In summary, it is likely that *P acnes* resistance is clinically relevant in some, and possibly 25% of patients receiving antibiotics, and will continue increasing unless significant steps are taken to minimize the selection pressures on *P acnes*. These steps may include limiting the use of antibiotics to shorter periods; using combined therapy benzoyl peroxide and topical antibiotics; using topical retinoids to speed improvement while targeting the microcomedone; and avoiding long-term use of antibiotics for maintenance therapy. However, it should be noted that many patients may require periodic courses of antibiotic therapy to control acne flares.

REFERENCES

1. Thielitz A, Helmdach M, Roepke EM, Gollnick H. Lipid analysis of follicular casts from cyanoacrylate strips as a new method for studying therapeutic effects of antiacne agents. Br J Dermatol 2001;145:19-27.
2. Meynadier J, Alirezai M. Systemic antibiotics for acne. Dermatology 1998;196:135-9.
3. Cunliffe WJ, Gollnick H. Acne: diagnosis and management. London: Martin Dunitz, Ltd; 2001.
4. Plewig G, Kligman AM. Acne and rosacea. 3rd ed. New York: Springer-Verlag; 2000.
5. Gollnick H, Schramm M. Topical therapy in acne. J Eur Acad Dermatol Venereol 1998;11(suppl 1):S8-S12, discussion S28-S29.
6. Eady EA, Bojar RA, Jones CE, Cove JH, Holland KT, Cunliffe WJ. The effects of acne treatment with a combination of benzoyl peroxide and erythromycin on skin carriage of erythromycin-resistant propionibacteria. Br J Dermatol 1996;34:107-13.
7. Kligman AM. Acne vulgaris: tricks and treatments. Part II. The benzoyl peroxide saga. Cutis 1995;56:260-1.
8. Goltz RW, Kjartansson S. Oral tetracycline treatment on bacterial flora in acne vulgaris. Arch Dermatol 1966;93:92-100.
9. Marples RR, Williamson P. Effects of systemic demethylchlortetracycline on human cutaneous microflora. Appl Microbiol 1969; 18:228-38.
10. Eady EA, Cove JH, Holland KT, Cunliffe WJ. Superior antibacterial action and reduced incidence of bacterial resistance in minocycline compared to tetracycline-treated acne patients. Br J Dermatol 1990;122:233-44.
11. Esterly NB, Furey NL, Flanagan LE. The effect of antimicrobial agents on leukocyte chemotaxis. J Invest Dermatol 1978;70:51-5.
12. Martin RR, Warr JA, Couch RB, Yeager H, Knight V. Effects of tetracycline on leukotaxis. J Infect Dis 1974;129:110-115.
13. Meynadier J, Guillot B. Tretinoine— erythromycine base: leur activite anti-inflammatoire. Gaz Med France 1983;90:2551-4.
14. Dreno B. Action du chlorhydrate de minocycline (Mynocine) sur le chimiotactisme des polynucleaires chez l'acnéique. Nouv Dermatol 1991;10:757-60.
15. Esterly NB, Koransky JS, Furey NL, Trevisan M. Neutrophil chemotaxis in patients with acne receiving oral tetracycline therapy. Arch Dermatol 1984;120:1308-13.
16. Webster GF, McGinley KJ, Leyden JJ. Inhibition of lipase production in Propionibacterium acnes by subminimal inhibitory concentrations of tetracycline and erythromycin. Br J Dermatol 1981;104:453-7.
17. Unkles SE, Gemmel GC. Effect of clindamycin, erythromycin, lincomycin and tetracycline on growth and extracellular lipase production by propionibacterium in vitro. Antimicrob Agents Chemother 1982;21:39-43.
18. Webster GF, Leyden JJ, McGinley KJ, McArthur WP. Suppression of polymorphonuclear leukocyte chemotactic factor production in Propionibacterium acnes by subminimal inhibitory concentrations of tetracyclines and erythromycin. Antimicrob Agents Chemother 1982;21:770-2.
19. Gloor M, Pfahler E, Neumann W, Hoffler U, Hoffmann M, Schmidt U. [Topical treatment of acne vulgaris with erythromycin and benzoyl peroxide (author's transl)]. Z Hautkr 1982;57:867-78.

20. Kligman AM, Mills OH, McGinley KJ, Leyden JJ. Acne therapy with tretinoin in combination with antibiotics. Acta Dermatovener (Stockholm) 1975;74(Suppl):111-5.
21. Bojar RA, Cunliffe WJ, Holland KT. The short-term treatment of acne vulgaris with benzoyl peroxide: effects on the surface and follicular cutaneous microflora. Br J Dermatol 1995;132:204-8.
22. White GM. Acne therapy. Adv Dermatol 1999;14:29-57.
23. Cotterill JA. Benzoyl peroxide. Acta Derm Venereol (Stockholm) 1980;89(suppl):57.
24. Schachner L, Pestana A, Kittles C. A clinical trial comparing the safety and efficacy of a topical erythromycin-zinc formulation with a topical clindamycin formulation. J Am Acad Dermatol 1990;22:489-95.
25. Graupe K, Cunliffe W, Gollnick H, Zaumseil R. Efficacy and safety of topical azelaic acid (20% cream): an overview of results from European clinical trials and experimental reports. Cutis 1996; 57(1 Suppl):13-9.
26. Gollnick HP, Graupe K, Zaumseil RP. Comparison of combined azelaic acid cream plus oral minocycline with oral isotretinoin in severe acne. Eur J Dermatol 2001;11:538-44.
27. Espersen F. Resistance to antibiotics used in dermatological practice. Br J Dermatol 1998;139:4-8.
28. Eady EA. Bacterial resistance in acne. Dermatology 1998;196:59-66.
29. Eady EA, Jones CE, Tipper JL, Cove JH, Cunliffe WJ, Layton AM. Antibiotic resistant propionibacterium in acne: need for policies to modify antibiotic usage. Br Med J 1993;306:555-6.
30. Eady EA, Cove JH, Holland KT, Cunliffe WJ. Erythromycin resistant Propionibacteria in antibiotic treated acne patients: association with therapeutic failure. Br J Dermatol 1989;8:41-5.
31. Cunliffe WJ, Aldana OL, Goulden V. Oral trimethoprim: a relatively safe and successful third-line treatment for acne vulgaris. Br J Dermatol 1999;141:757-8.
32. Krowchuk DP. Treating acne. A practical guide. Med Clin North Am 2000;84:811-28.
33. Goulden V, Glass D, Cunliffe WJ. Safety of long-term high-dose minocycline in the treatment of acne. Br J Dermatol 1996;134:693-5.
34. Gough A, Chapman S, Wagstaff K, Emery P, Elias E. Minocycline induced autoimmune hepatitis and systemic lupus erythematosus-like syndrome. BMJ 1996;312:169-72.
35. Sturkenboom MC, Meier CR, Jick H, Stricker BH. Minocycline and lupus-like syndrome in acne patients. Arch Intern Med 1999; 159:493-7.
36. Grosshans E, Belaich S, Meynadier J, Alirezai M, Thomas L. A comparison of the efficacy and safety of lymecycline and minocycline in patients with moderately severe acne vulgaris. Eur J Dermatol 1998;8:161-6.
37. Johnson BA, Nunley JR. Topical therapy for acne vulgaris. How do you choose the best drug for each patient? Postgrad Med 2000;107:69-70,73-6,79-80.
38. Eady EA, Cove JH, Joanes DN, Cunliffe WJ. Topical antibiotics for the treatment of acne vulgaris: a critical evaluation of the literature on their clinical benefit and comparative efficacy. J Dermatol Treat 1990;1:215.
39. Shalita AR, Smith EB, Bauer E. Topical erythromycin versus clindamycin therapy for acne: a multicenter, double-blind comparison. Arch Dermatol 1984;120:351-5.
40. Kurokawa I, Nishijima S, Kawabata S. Antimicrobial susceptibility of *Propionibacterium acnes* isolated from acne vulgaris. Eur J Dermatol 1999;9:25-8.
41. Leyden JJ, Shalita AR. Rational therapy for acne vulgaris: an update on topical treatment. J Am Acad Dermatol 1986;15:907-15.
42. Parry MF, Rha CK. Pseudomembranous colitis caused by topical clindamycin phosphate. Arch Dermatol 1986;122:583-4.
43. Fisher AA. Adverse reactions to topical clindamycin, erythromycin and tetracycline. Cutis 1983;32:415,419,424,428.
44. Cunliffe W. Acne. London: Martin Dunitz, Ltd; 1989.
45. Eady EA, Farmery MR, Ross JI, Cove JH, Cunliffe WJ. Effects of benzoyl peroxide and erythromycin alone and in combination against antibiotic-sensitive and –resistant skin bacteria from acne patients. Br J Dermatol 1994;1331:331-6.
46. Lookingbill DP, Chalker DK, Lindholm JS, Katz HI, Kempers SE, Huerter CJ, et al. Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: combined results of two double-blind investigations. J Am Acad Dermatol 1997;37:590-5.
47. Packman AM, Brown RH, Dunlap FE, Kraus SJ, Webster GF. Treatment of acne vulgaris: combination of 3% erythromycin and 5% benzoyl peroxide in a gel compared to clindamycin phosphate lotion. Int J Dermatol 1996;35:209.
48. Leyden JJ. Current issues in antimicrobial therapy for the treatment of acne. J Eur Acad Dermatol Venereol 2001;15(suppl 3):51-5.
49. Landow K. Dispelling myths about acne. Postgrad Med 1997; 102:94-9, 103-4, 110-2.
50. Harkaway KS, McGinley KJ, Foglia AN, Lee WL, Fried F, Shalita AR, et al. Antibiotic resistance patterns in coagulase-negative staphylococci after treatment with topical erythromycin, benzoyl peroxide, and combination therapy. Br J Dermatol 1992; 126:586-90.
51. Forssman T. Antibiotic resistance in acne patients under antibiotic treatment in comparison to an untreated control group with retrospective assessment of therapy. Curr Probl Dermatol 1995;22:91-7.
52. Ross JI, Snelling EM, Eady EA, Cove JH, Cunliffe WJ, Leyden JJ, et al. Phenotypic and genotypic characterization of antibiotic-resistant Propionibacterium acnes isolated from acne patients attending dermatology clinics in Europe, the USA, Japan, and Australia. Br J Dermatol 2001;144:339-46.

HORMONAL THERAPY

Indications

Hormonal therapy is an excellent option for women, especially if oral contraception is desirable. Sometimes, hormonal therapy is used as an alternative to repeated courses of isotretinoin. Hormonal therapy may also be warranted for female patients with severe seborrhea, clinically apparent androgenic alopecia, seborrhea/acne/hirsutism/alopecia (SAHA) syndrome, late-onset acne (acne tarda), and with proven ovarian or adrenal hyperandrogenism.

Hormonal therapy may consist of antiandrogens (cyproterone acetate, chlormadinone acetate, spironolactone, drospirenone, desogestrel, flutamide), agents that block ovarian and adrenal androgen production (estrogens, oral contraceptives, cyproterone acetate, gonadrotropin-releasing hormone (GnRH) agonists, low-dose glucocorticoids) and, possibly in the future, inhibitors of enzymes that are involved in androgen metabolism in the skin.

Androgens in acne

The etiology of acne is multifactorial; however, increased sebum production due to androgens acting at the sebaceous follicle is a prerequisite for acne

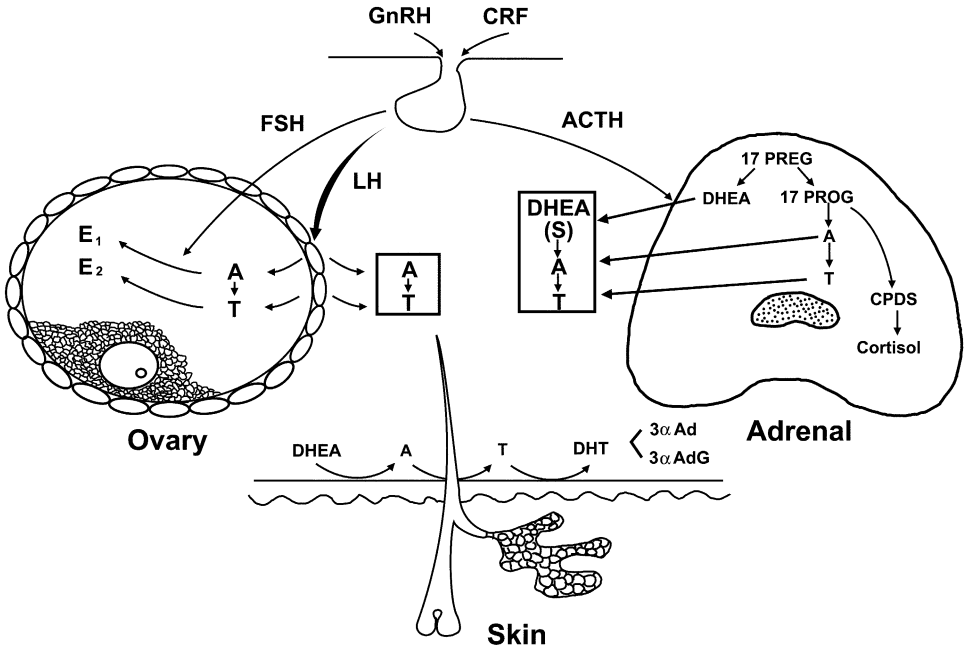

Fig 12. Sources of androgens in women. Reprinted from Lucky A. Hormonal correlates of acne and hirsutism. Am J Med 1995;98:89S-94S, with permission from Excerpta Medica Inc.

in all patients.[1-3] Before the onset of puberty, the adrenal glands produce increasing amounts of dehydroepiandrosterone sulfate (DHEAS), which, in turn, can be metabolized to more potent androgens in the skin that cause the sebaceous glands to enlarge and increase sebum production.[3,4] The serum level of DHEAS correlates with the severity of comedonal acne in prepubertal girls.[5,6] In addition, acne severity has been correlated with sexual maturity in both girls and boys.[5,7] Thus, hormonal influences have an important role in the pathogenesis of acne.

Both boys and girls may have acne that is related to increased sensitivity of the sebaceous gland to androgens.[8] In girls, excess ovarian and adrenal production of androgens may also rarely cause acne, particularly when it has a late onset, is persistent, or is associated with hirsutism.[8] Girls with acne may have high circulating androgen levels, particularly in free testosterone and DHEAS; low sex hormone-binding globulin may also be observed.[9,10]

Screening for an endocrine disorder

An endocrine evaluation may be indicated for women with acne who have proven resistant to conventional therapy; when there is a sudden onset of severe acne; and in women with acne associated with hirsutism, irregular menstrual periods, or signs of hyperandrogenism (SAHA syndrome). Androgen evaluation may also be warranted in women who have relapse shortly after isotretinoin therapy.[8] A medical history and physical examination should be performed to elicit any symptoms or signs of hyperandrogenism.

Screening tests for hyperandrogenism include serum DHEAS, total testosterone, free testosterone, luteinizing hormone/follicle stimulating hormone (LH/FSH) ratio, prolactin, and 17-hydroxyprogesterone.[8,11-13] These tests should be obtained in the luteal phase of the menstrual cycle (within two weeks before the onset of menses). Excess androgens may be produced by either the adrenal gland or the ovary. Serum DHEAS can be used to screen for an adrenal source of excess androgen production. Patients with a serum DHEAS >8000 ng/mL (~21.7 μmol/L) may have an adrenal tumor and should be referred to an endocrinologist for further evaluation. Some adrenal tumors may also produce testosterone. Values of DHEAS in the range of 4000 ng/mL to 8000 ng/mL (10.8-21.7 μmol/L) may be associated with congenital adrenal hyperplasia, which is more 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.[11,12]

An ovarian source of excess androgen can be suspected in cases where the serum total testosterone level is elevated. Serum total testosterone in the range of 150 ng/dL to 200 ng/dL (520-700 nmol/L) or an increased LH/FSH ratio (>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. Greater elevations in serum testosterone may indicate an ovarian tumor and appropriate referral should be made. There is a significant amount of variation in an person's serum androgen levels. In cases where abnormal results are obtained, repeat testing is recommended before proceeding with therapy or a more extensive work-up.[11,12,14] Sources of androgens in women are illustrated in Figure 12.

Specific hormonal therapies

The goal of hormonal therapy is to oppose the effects of androgens on the sebaceous gland and probably follicular keratinocytes as well. This can be accomplished with the use of estrogens, antiandrogens (androgen receptor blockers), or agents designed to decrease the endogenous production of androgens by the ovary or adrenal gland, such as oral contraceptives, glucocorticoids, or GnRH agonists.

Estrogens

Estrogens are particularly valuable in female patients with clinical evidence of hyperandrogenism. Any estrogen given 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. Estrogens suppress the ovarian production of androgens by suppressing gonadotrophin release; they also stimulate hepatic synthesis of sex hormone binding globulin (SHBG).[6,15,16] Although some patients will respond to lower-dose agents containing 0.035 to 0.050 μg of ethinyl estradiol or its esters, higher doses of estrogen are often required.[17,18]

If estrogen therapy is indicated and the physician is unfamiliar with its usage or side effects, it is best to work with a gynecologist. Breast examinations and Pap smears may be recommended for women receiving chronic estrogen therapy; however, the recommendations of these examinations vary from country to country depending on age, sexual activity, and other factors. The incidence of more serious side effects, such as clotting and hypertension, that follow the use of estrogens is fortunately rare in young healthy females. Nevertheless, the physician and patient should be aware of the potential risk of adverse events, and the risk/benefit ratio should be carefully considered before undertaking estrogen therapy.

Anti-androgens

Anti-androgens, or androgen receptor blockers, include cyproterone acetate, drospirenone, spironolactone, and flutamide. With all anti-androgens, pregnancy should be avoided during therapy.

Cyproterone acetate. Cyproterone acetate (CPA) is a progestational anti-androgen that blocks the androgen receptor. It is combined (2 mg) with ethinyl estradiol (35 μg or 50 μg) in an oral contraceptive formulation that is widely used in Europe for the treatment of acne (Dianette, Diane-35). Cyproterone acetate is not available in the United States. Overall improvement in 75% to 90% of patients treated with CPA 50 to 100 mg daily (with or without ethinyl estradiol 50 μg) has been reported.[19,20] Cyproterone has a dual action, inhibiting ovulation and blocking androgen receptors. Both spironolactone and cyproterone acetate should be used only in women, because they lead to feminization in men.[21] Side effects include menstrual abnormalities, breast tenderness and enlargement, nausea/vomiting, fluid retention, leg edema, headache, and melasma; cyproterone acetate can also be associated with tiredness, headache, nausea, changes in body weight, liver dysfunction and, rarely, blood clotting disorders.[22] Chlormadinone acetate is available in several European countries and is only slightly less efficacious than CPA.

Spironolactone. Spironolactone functions both as an androgen receptor blocker and an inhibitor of 5α-reductase. In doses of 50 to 100 mg twice a day, it has been shown to reduce sebum production and improve acne.[23] In countries with no effective anti-androgenic medications containing cyproterone acetate or chlormadinone acetate, spironolactone may be used for female patients with therapy-resistant acne, although it has not been approved for this disorder. Most commonly, spironolactone is used in countries that do not have access to other anti-androgen drugs. In general, spironolactone should be reserved for cases resistant to conventional therapy.[24] In a recent retrospective review of spironolactone therapy in 85 women with acne, 33% of patients were cleared of acne, 33% had marked improvement, 27.4% showed partial improvement, and 7% had no improvement.[22] Spironolactone is administered in doses of 25 to 100 mg twice daily. Recently, a derivative drospirenone has become available to European physicians.

Side effects are dose-dependent and include potential hyperkalemia, irregular menstrual periods, breast tenderness, headache and fatigue. Hyperkalemia is rare in young healthy patients. Although breast tumors have been reported in rodents treated with spironolactone, this drug has not been directly linked with the development of cancer in humans.[25]

Because spironolactone is an antiandrogen, there is a risk of feminization of a male fetus if this medication is taken by a pregnant woman. Risk to a fetus and the symptoms of irregular menstrual bleeding can be alleviated by combining treatment with an oral contraceptive. Side effects can be minimized if therapy is initiated with a low dose (25-50 mg daily). Effective maintenance doses are in the range of 25 to 200 mg per day. Response in acne may take as long as three months as with other hormonal therapies.[26]

Flutamide. Flutamide blocks the androgen receptor and is approved for treatment of prostate cancer. It has been used at doses of 250 mg twice a day in combination with oral contraceptives for the treatment of acne or hirsutism in females. In one study, improvement in acne was noted in 11 of 15 patients.[27] In a comparative trial between flutamide and spironolactone, Cusan et al reported that flutamide therapy was superior in reducing total acne and seborrhea after just 3 months.[28] Cases of fatal hepatitis have been reported and monitoring of liver function is required.[29] As with all anti-androgens, pregnancy should be avoided due to the risk of feminization of a male fetus. Use of flutamide in the treatment of acne is very much limited by its side effect profile; thus, it is used very little.

In our opinion, topical antiandrogens have not yet proven beneficial in the treatment of acne.

Blocking ovarian androgens: Oral contraceptives

Estrogens are most commonly used to treat acne in combination with a progestin in an oral contraceptive to avoid the risk of endometrial cancer associated with unopposed estrogens. Oral contraceptives also suppress ovarian production of androgens by direct gonadotropin suppression and the prevention of ovulation.[6,15]

Some progestins also have intrinsic androgenic activity, which has been hypothesized to aggravate acne. The level of progestin required to produce androgenic effects in various systems is several orders of magnitude greater than that which is present in modern day oral contraceptives. Of the second-generation progestins, ethynodiol diacetate, norethindrone, and levonorgesterol had the lowest androgenic activity. The third generation progestins (desogestrel, norgestimate, and gestodene) have the lowest intrinsic androgenic activity.[30] These agents are also metabolized to levonorgestrel. Currently, gestodene is not available in the United States. There is controversy in the literature as to whether there is an increased risk of venous thromboembolism associated with oral contraceptives containing desogestrel and gestodene. However, the risk of myocardial infarction may be lower with these oral contraceptives compared with those containing a second-generation progestin. An oral contraceptive containing ethinyl estradiol and norgestimate has been studied in the treatment of acne in two placebo-controlled double-blind studies.[31] Two recent low-dose estradiol plus levonorgestrel oral contraceptives have shown comparable efficacy to estrodial plus norgestimate for the treatment of acne. Oral contraceptive therapy was associated with statistically significant improvement over the placebo group in total lesions, inflammatory lesions, and global assessment. In addition, a reduction of free testosterone and increase in sex-hormone binding globulin was noted.

All combination oral contraceptives reduce free testosterone and have a positive effect on acne; to date, no single preparation has been shown to be superior to another. In some cases, acne may be aggravated by contraceptives containing only a progestin, such as nedroxyprogesterone injections or levonorgesterol implants. Co-Cyprindiol (Dianette®) contains 25 mcg of estrogen.

The most serious side effect of oral contraceptives, thromboembolism, has largely been eliminated by the reduced doses of estrogen used in modern formulations. In general, oral contraceptives are well tolerated by most women. The most common adverse events include nausea/vomiting, breast tenderness, headache, spotting/breakthrough bleeding, edema of the venous system of the lower extremities, and with some, weight gain. These are often transient, and resolve after the first few months of therapy. A transient flare of inflammatory acne may also accompany the initiation of oral contraceptive therapy. Pill selection should be based on minimizing side effects and maximizing ease of compliance.[32]

Blocking adrenal androgen production: Glucocorticoids

Glucocorticoids in low doses can suppress the adrenal production of androgens. They are indicated in patients (male or female) who have an elevation in serum DHEAS associated with an 11- or 21-hydroxylase deficiency. Glucocorticoids may also be used in acute flare of acne or in very severe acne for a few weeks. Low-dose prednisone (2.5 mg or 5 mg) or dexamethasone (0.25-0.75 mg) can be given orally at bedtime daily or every other day to suppress adrenal androgen production.[2,13,33] Adrenal suppression is possible, particularly if dexamethasone is used.[14] Patients should be followed for signs of adrenal suppression with ACTH (cosyntropin) stimulation tests

performed 2 to 3 months after initiation of therapy. Plasma cortisol should rise to >16 μg/dL thirty minutes after an injection of 250 μg/m^2 of ACTH. The effect of glucocorticoids on reduction of adrenal androgen production can be monitored with periodic assessment of serum DHEAS.

The combination of glucocorticoids and estrogens has been used in recalcitrant acne in women, based on the inhibition of sebum production by this combination.[2,34,35] The mechanism of action is probably related to a greater reduction of plasma androgen levels by combined therapy than is produced by either drug alone. The doses of estrogen used in these studies, however, were 80 to 100 μg, which is much higher than the dose of estrogen in most oral contraceptives.

Gonadotropin-releasing hormone agonists

GnRH agonists such as nafarelin, leuprolide, and buserelin inhibit ovarian androgen production by blocking the cyclic release of LH and FSH from the pituitary. The net effect is suppression of ovarian steroidogenesis. These agents cannot be given orally and are available as nasal sprays or injectables. GnRH agonists have demonstrated efficacy in the treatment of acne and hirsutism in females, both with and without endocrine abnormalities.[36] Their use is limited by their expense and side effect profile, which includes menopausal symptoms, headache, and bone loss.

Inhibiting androgen metabolism: 5α-reductase inhibitors

There are no therapies currently available that inhibit the local production of androgens within the sebaceous gland. An inhibitor of 5α-reductase would block the local conversion of testosterone to dihydrotestosterone. Specific inhibitors of the type 1 5α-reductase are being developed.[37] If sebum production is mediated by dihydrotestosterone and not testosterone, these agents may inhibit sebum production and, hence, be beneficial in the treatment of acne.

Hormonal therapy in women with normal serum androgens

It is important to note that hormonal therapy can be very effective in females with acne whether their serum androgens are abnormal. Although females with acne may have higher serum androgens compared with women without acne, these levels are mostly within the normal range. Hormonal therapies seem to work best in adult females and sexually active teens with persistent inflammatory papules and nodules that commonly involve the lower face and neck. Often, these women report that their acne flares before their menstrual periods and consists of a few tender, deep-seated, inflammatory papules and nodules. The skin may or may not be oily. Comedones are often present on the forehead and chin. These patients often note little improvement in their acne despite multiple courses of various antibiotics.

In cases such as this, oral antibiotics can be discontinued and hormonal therapy initiated with the use of oral contraceptives because they block both the ovarian and adrenal production of androgens. In addition, use of oral contraceptives is recommended if treatment with spironolactone is anticipated. If the patient's acne has not improved significantly after 3 to 6 cycles, spironolactone can be added. It is recommended to initiate treatment with a low dose such as 25 to 50 mg twice daily. The dose can be increased if the patient is not having significant breast tenderness or headache. On the whole, oral antibiotics do not significantly affect the enterohepatic circulation of sex hormones.[11]

Achieving optimal results with hormonal therapy

Appropriate patient selection is the key to achieving good results with hormonal therapy. The hormonal approach is useful for women with endocrine abnormalities and those who have proven nonresponsive to more conventional therapies. Use of oral contraceptives may be useful for women who require medical therapy to control their menstrual period, and/or those who desire contraception.

Hormonal therapy is aimed at reducing sebum production. Sebum production is, however, only one facet of the pathogenesis of acne. For this reason, it is rare that hormonal therapy is used alone in the treatment of acne. In most cases, hormonal therapy should be combined with other anti-acne therapies, including antibiotics and topical retinoids. The addition of a topical combination benzoyl peroxide/antibiotic agent is often helpful if mild inflammatory acne persists. Sometimes oral antibiotics may be prescribed in conjunction with oral contraceptives. There is recent evidence that antibiotics do not significantly affect the enterohepatic circulation of sex hormones.[11] It is recommended, however, that the physician seek the advice of their national family planning organizations if they coprescribe oral antibiotics and the contraceptive pill. In many cases, hormonal therapy represents an effective alternative to the use of isotretinoin. In resistant cases, however, isotretinoin may be indicated.

Consensus Recommendations: Hormonal Therapy

Excellent choice for women who need oral contraception for gynecologic reasons

Use early in female patients with moderate to severe acne or with SAHA symptoms

Useful as a componenet of combination therapy in women with or without endocrine abnormalities

Sometimes used in women with late-onset acne

REFERENCES

1. Leyden JJ. New understandings of the pathogenesis of acne. J Am Acad Dermatol 1995;32(suppl):15-25.
2. Pochi PE. Hormones and acne. Semin Dermatol 1982;1:265.
3. Pochi PE. The pathogenesis and treatment of acne. Ann Rev Med 1990;41:187-98.
4. Stewart ME, Downing DT, Cook JS, Hanson JR, Strauss JS. Sebaceous gland activity and serum dehydroepiandrosterone sulfate levels in boys and girls. Arch Dermatol 1992; 128:1345-8.
5. Lucky AW, Biro FM, Huster GA, Leach AD, Morrison JA, Rotterman J. Acne vulgaris in premenarchal girls. Arch Dermatol 1994; 130:308-14.
6. Lucky A, Henderson T, Olson W, Robisch DM, Lebwohl M, Swinger LJ. Effectiveness of norgestimate and ethinyl estradiol in treating moderate acne vulgaris. J Am Acad Dermatol 1997; 37:746-54.
7. Lucky AW, Biro FM, Huster GA, Morrison JA, Elder N. Acne vulgaris in early adolescent boys: Correlations with pubertal maturation. Arch Dermatol 1991;127:210-6.
8. Beylot C, Doutre MS, Beylot-Barry M. Oral contraceptives and cyproterone acetate in female acne treatment. Dermatology 1998;196:148-52.
9. Lucky AW, McGuire J, Rosenfield RL, Lucky PA, Rich BH. Plasma androgens in women with acne vulgaris. J Invest Dermatol 1983;81:70-4.
10. Vexiau P, Husson C, Chivot M, Brerault JL, Fiet J, Julien R, et al. Androgen excess in women with acne alone compared with women with acne and/or hirsutism. J Invest Dermatol 1990;94: 279-83.
11. Thiboutot D. Hormones and acne: pathophysiology, clinical evaluation, and therapies. Semin Cutan Med Surg 2001;20:144-53.
12. Thiboutot D. Endocrinological evaluation and hormonal therapy for women with difficult acne. J Eur Acad Dermatol Venereol 2001;15(suppl 3):57-61.
13. Lucky A. Hormonal correlates of acne and hirsutism. Am J Med 1995;98:89S-94S.
14. Cunliffe WJ, Gollnick H. Acne: diagnosis and management. London: Martin Dunitz, Ltd; 2001.
15. Rothman KF, Lucky AW. Acne vulgaris. Adv Dermatol 1993;8: 347-74; discussion, 375.
16. Hammerstein J, Meckies J, Leo-Rossberg, Moltz L, Zielske F. Use of cyproterone acetate (CPA) in the treatment of acne, hirsutism, and virilism. J Steroid Biochem 1975;6:827-36.
17. Strauss J, Pochi PE. Effect of cyclic progestin-estrogen therapy on sebum and acne in women. JAMA 1964;190:815.
18. Imperato-McGinley J, Gautier T, Cai LO, Yee B, Epstei J, Pochi P. The androgen control of sebum production. Studies of subjects with dihydrotestosterone deficiency and complete androgen insensitivity. J Clin Endocrinol Metab 1993;76:524-8.
19. Van Wayjen R, van den Ende A. Experience in the long-term treatment of patients with hirsutism and/or acne with cyproterone acetate-containing preparations: efficacy, metabolic, and endocrine effects. Exp Clin Endocrinol Diabetes 1995;103:241-51.
20. Gollnick H, Albring M, Brill K. Efficacitè de l'acètate de cyprotèrone oral associe à l'èthinylestradiol dans le traitement de l'acné tardive de type facial. Ann Endocrinol 1999;60:157-66.
21. Sawaya ME, Hordinsky MK. The antiandrogens: when and how they should be used. Dermatol Clin 1993;11:65-72.
22. Shaw JC. Low-dose adjunctive spironolactone in the treatment of acne in a retrospective analysis of 85 consecutively treated patients. J Am Acad Dermatol 2000;43:498-502.
23. Goodfellow A, Alaghband-Zadeh J, Carter G, Cream JJ, Holland S, Scully J, et al. Oral spironolactone improves acne vulgaris and reduces sebum excretion. Br J Dermatol 1984;111: 209-14.
24. Plewig G, Kligman AM. Acne and rosacea. 3rd ed. New York: Springer-Verlag; 2000.
25. Shaw J. Spironolactone in dermatologic therapy. J Am Acad Dermatol 1991;24:236-43.
26. Marcoux D, Thiboutot D. Hormonal therapy for acne. J Cutan Med Surg 1996;1(Suppl 1):52-6.
27. Cusan L, Dupont A, Belanger A, Tremblay RR, Manhes G, Labrie F. Treatment of hirsutism with the pure antiandrogen flutamide. J Am Acad Dermatol 1990;23:462-9.
28. Cusan L, Dupont A, Gomez FL, Tremblay RR, Labrie F. Comparison of flutamide and spironolactone in the treatment of hirsutism: a randomized controlled trial. Fertil Steril 1995;61: 281-7.
29. Wysowski D, Freiman J, Tourtelot J, Horton M. Fatal and nonfatal hepatotoxicity associated with flutamide. Ann Intern Med 1993; 118:860-4.
30. Speroff L, DeCherney A. Evaluation of a new generation of oral contraceptives. Obstet Gynecol 1993;81:1034-47.
31. Redmond GP, Olson WH, Lippman JS, Kafrissen ME, Jones TM, Jorizzo JL. Norgestimate and ethinyl estradiol in the treatment of acne vulgaris: a randomized, placebo-controlled trial. Obstet Gynecol 1997;89:615-22.
32. Koulianos GT. Treatment of acne with oral contraceptives: criteria for pill selection. Cutis 2000;66:281-6.
33. Marynick SP, Chakmakjian ZH, McCaffree DL, Herdon JH. Androgen excess in cystic acne. N Engl J Med 1983;308:981-6.
34. Saihan E, Burton J. Sebaceous gland suppression in female acne patients by combined glucocorticoid-oestrogen treatment. Br J Dermatol 1981;103:139.
35. Pochi P, Strauss J. Sebaceous gland inhibition from combined glucocorticoid-estrogen treatment. Arch Dermatol 1976; 112:1108.
36. Faloia E, Filipponi S, Mancini V, Morosini P, De Pirro R. Treatment with a gonadotropin-releasing hormone agonist in acne or idiopathic hirsutism. J Endocrinol Invest 1993;16:675-7.
37. Chen W, Zouboulis CC, Orfanos CE. The 5 α-reductase system and its inhibitors. Recent development and its perspective in treating androgen-dependent skin disorders. Dermatology 1996;193:177-84.

ORAL RETINOIDS

Consensus: Oral Isotretinoin is the Mainstay of Therapy for Severe Acne

- Targets all pathophysiologic factors in acne
- May achieve dramatic results even in severe disease
- Now used more frequently in moderate, nonresponsive acne
- Side effects are common, but usually manageable
- Education is vital (side effects, teratogenicity, adverse psychiatric events, monitoring)
- Variable rate of recurrence; retreatment may be necessary

Indications

Isotretinoin, an oral retinoid, is indicated for severe nodular acne and moderate or severe acne unresponsive to topical therapy.[1,2] Virtually all dermatologists also use oral isotretinoin in patients with moderate to severe acne that scars physically and psychologically, inflammatory acne resistant to conventional therapy, and chronic acne prone to relapse.[2] It is also used in gram-negative folliculitis, pyoderma faciale, and severe acne rosacea.[2,3]

Mechanism of action

Oral isotretinoin is a retinoid preparation that decreases the size and secretion of the sebaceous glands, normalizes follicular keratinization and prevents the formation of new comedones, indirectly inhibits *P acnes* growth via changes of the follicular milieu, and exerts an anti-inflammatory effect.[3-10] During oral isotretinoin therapy, sebum production is reduced by 90% or greater. As a result, *P acnes* levels decrease substantially.[8] However, both sebum and *P acnes* levels increase again after isotretinoin is stopped.[10] Thus, oral isotretinoin is unique among current acne treatments in that it affects all of the pathogenic factors involved in this disease.

Clinical experience

The effect of oral isotretinoin in severe nodulocystic acne can be dramatic (Fig 13); most cases of severe acne respond to a single 4- to 6-month therapeutic course.[3,11-13] In general, pustules clear more rapidly than papules or nodules. Also, lesions on the face, upper arms and legs tend to respond more quickly than truncal lesions.[14]

Oral isotretinoin is first line treatment in severe acne and may also be used in patients who have failed conventional treatment (eg, a combination of topical retinoids, benzoyl peroxide and topical or systemic antibiotics and, when appropriate, hormonal therapies).[15] In general, results are not evident for 1 to 2 months after start of therapy; similarly, therapeutic benefits continue for several months after discontinuation of therapy.[15] In a few cases, complete clearing may occur 1 to 2 months after oral isotretinoin is stopped, usually without additional treatment.[15]

Dosing

Although oral isotretinoin doses range from 0.1 to 2.0 mg/kg,[2,3,7,15] doses >1.0 mg/kg/day are rarely used. In general, treatment continues until a cumulative dose of 120 to 150 mg/kg is achieved; it is thought that this may reduce the potential for relapse but much more work is required to confirm this suggestion.[2,3] To minimize potential side effects, particularly flare, many of us give a dose of no more than 0.5 mg/day for the first month. If the patient has no tolerability problems, this may be followed by 1.0 mg/kg/day for the rest of a 16- to 20-week course of therapy.[2,3,16] Resolution of acne may take longer and relapse may be more likely with lower doses.[3,17-19] In some cases with severe acne involving deep nodules, a longer treatment period (24-32 weeks) may be needed. Rarely, an even longer period is required.

It is uncommon to coprescribe other anti-acne medications with oral isotretinoin; however, some of us coprescribe a nontetracycline antibiotic such as erythromycin for the first few weeks of isotretinoin therapy, and one of us routinely continues tetracycline therapy on those started on isotretinoin. If the patient has severe inflammatory lesions, acne fulminans, or pyoderma faciale, oral prednisone (0.5-1.0 mg/kg/day for 2-6 weeks, usually before initiation of isotretinoin) may be necessary.[20] Topical keratolytics and drying agents should be avoided because isotretinoin has a drying effect on mucocutaneous tissues.

Adverse events

Common adverse events with oral isotretinoin therapy include dry, chapped lips and dry skin and eyes.[15,21] Secondary skin infection with *S aureus* is not uncommon and should be treated with topical antiseptics or oral antibiotics. Some patients have muscle aches and backaches, and some have mild headaches at the start of therapy, but these often resolve during the course of treatment. Nosebleeds and skin fragility may also occur. Any patient with severe headache, decreased night vision, or signs of adverse psychiatric events, which may be drug related should immediately stop taking isotretinoin.[22-24] In addition, serum lipids should be routinely monitored. Oral isotretinoin is a

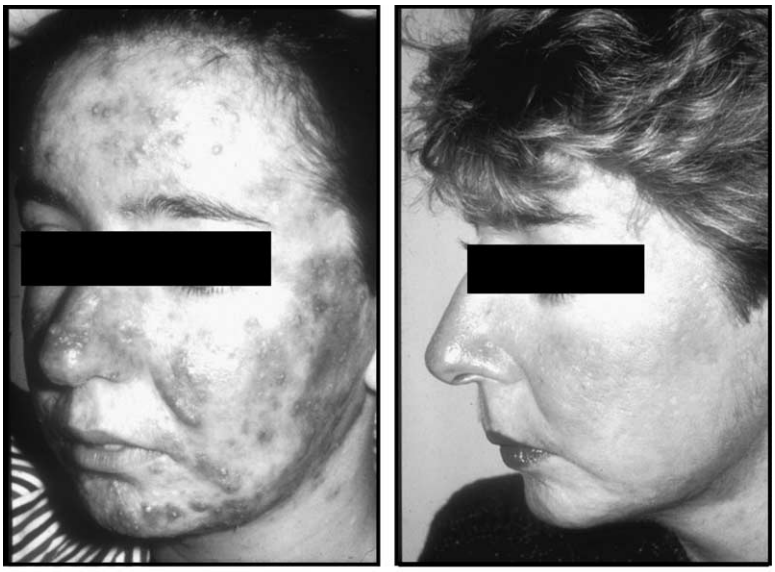

Fig 13. Effect of oral isotretinoin on severe acne.

potent teratogen, and women of child-bearing age must not start therapy until a negative pregnancy test result has been obtained. Adequate contraception is essential before and during oral isotretinoin therapy, as well as for 6 weeks post-therapy. Therapy should start on the first, second, or third day of the menstrual period once the results of the pregnancy test have been obtained.[25] Discussion on potential adverse psychiatric events should also be recorded in the notes.

It is important to inform the patient and family of the teratogenicity issues and the potential for mood swings and depression during isotretinoin therapy.[22-24] Most physicians document that pregnancy issues and drug-induced mood changes and depression have been discussed with the patient. Psychosocial events associated with severe acne frequently show improvement, however, once isotretinoin takes effect. Nevertheless, some patients with acne who have depression do not show improvement. This could be due to ineffective coping strategies, acne scarring, isotretinoin therapy, or other unrelated reasons.[26]

Some physicians definitely consider that oral isotretinoin does produce, very occasionally, significant mood changes, depression, and other significant psychiatric side effects. It is very important to discuss these issues with patients, and the information should be shared with their family and friends. The reader is referred to three recent reviews on this important topic.[22,27,28]

Rarely, long-term oral retinoid therapy may be complicated by skeletal changes, including osteoporosis and osteophyte formation.[15,29-31] One prospective study measured bone density and calcium metabolism in young men receiving oral isotretinoin for cystic acne and in a group of healthy volunteers. The researchers concluded that a loss of bone density occurred in the absence of measurable alterations of calcium metabolism and was therefore likely to be a direct effect of retinoids on bone. They suggested that further studies of retinoid-induced osteoporosis and bone density in patients with cystic acne are needed.[32]

Recently, randomized double-blind studies have compared a new micronized formulation of oral isotretinoin with the standard formulation. The newer formulation has improved bioavailability, minimal food effect, and may be associated with a lower rate and severity of adverse events (particularly mucocutaneous side effects and hypertriglyceridemia).[33,34] The new formulation is also teratogenic.

Optimizing therapy with oral retinoids

It is critical to educate patients or parents of children about oral isotretinoin, focusing on the benefits and the risks (for example, the likelihood of significant improvement, the time before clinical effects will be seen, the potential for acne flare, and the potential side effects). Some patients are reassured to learn that isotretinoin is a naturally occurring endogenous compound.[35,36]

Because of oral isotretinoin's mechanism of action, it is very drying; therefore, it is important to educate patients about ways to minimize this side

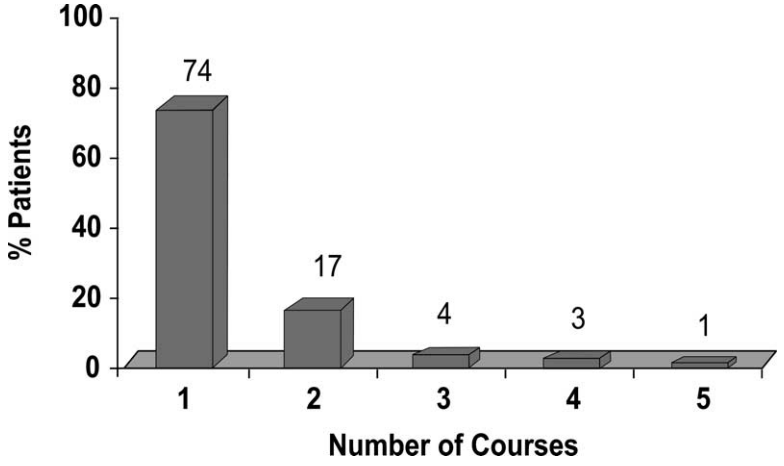

Fig 14. Percent of patients requiring multiple courses of isotretinoin. Reprinted with permission from Cunliffe WJ, Layton A, Knaggs HE. In: Saurat JH, editor. Retinoids: 10 years on. Basel (Switzerland): Karger; 1991. p. 272-80.

effect. For example, avoiding hot showers and drying soaps, as well as frequent application of moisturizers can help prevent dry, chapped skin, and patients who wear contacts may need to switch to soft lenses or eyeglasses because of conjunctival dryness.[15,21] Patients should also be advised to take oral isotretinoin with food. As much as 40% of oral isotretinoin is absorbed when the drug is taken with food, whereas only about 20% is absorbed on an empty stomach.[33]

It is very important for patients, particularly women, to understand the teratogenic effects of oral isotretinoin. They should also know that the risk for teratogenicity exists only while the retinoid is in the body; after the retinoid is cleared (typically 6 weeks after discontinuation of isotretinoin) there is no longer a risk.[15] A patient information form is available from the manufacturer to assist with patient counseling. At baseline, and monthly in some countries, pregnancy tests are recommended for females receiving isotretinoin therapy. As a reminder, counseling must include provision of both oral and written information concerning the hazards of taking isotretinoin during pregnancy, and of the need for effective contraception.

Other laboratory monitoring that is recommended during oral isotretinoin therapy includes a baseline fasting cholesterol level, triglyceride level, and standard liver function tests.[14,15] The frequency of blood tests while on oral isotretinoin therapy varies from country to country. However, blood work should be checked at baseline and possibly at weeks 4 and 8. If the initial test results are normal and there is no elevation of the isotretinoin dose, no further testing may be needed unless the patient has known risk factors.[14,21] If relevant elevations occur, reducing the dosage or, in rare instances, discontinuing isotretinoin therapy should be considered.[2,14]

Recurrence

Recurrence of acne is not uncommon after oral isotretinoin therapy; some patients are successfully retreated with conventional therapies, but a significant number require retreatment with isotretinoin (Fig 14).[37-39] According to a recent study conducted in the health maintenance organization setting, only 38% of patients had no acne at the 3-year follow-up after the first course of oral isotretinoin.[40] Among the remaining patients, acne was controlled with topical therapy in 17%, topical therapy plus oral antibiotics in 25%, and a second course of isotretinoin in 20%.[40] Notably, relapse was more likely to occur in patients 16 years or younger and in women versus men.[35,40] Furthermore, recurrence is more common in patients with less than nodular acne.

In a study of 229 patients treated with oral isotretinoin and followed for 5 years, 30% of patients relapsed. Factors that contributed to relapse included low-dose isotretinoin therapy (0.1 and 0.5 mg/kg), severe acne, a prolonged history of acne, and being a female older than 25 at the onset of therapy.[37] Other factors linked with relapse include younger age at time of treatment, and truncal acne.[3,15,16,41,42] Relapse is most common in the first year after isotretinoin therapy; relapse after 3 years is relatively uncommon.[37] Maintenance therapy with topical retinoid therapy may reduce the relapse rate by controlling microcomedo formation.

Consensus Recommendations: Oral Isotretinoin

Indications
Severe nodulocystic acne/severe acne variants
And, after conventional therapy has failed:
Inflammatory acne with scarring
Moderate-to-severe acne frequently relapsing
Acne with severe psychological distress
Typical dose: 0.5 to 1.0 mg/kg daily in two divided doses, with a cumulative of 120 to 150 mg/kg per treatment course (4-6 months)
A lower (<0.5 mg/kg) dose may be used but is associated with a higher relapse rate
Patient counseling is critical

REFERENCES

1. Ortonne JP. Oral isotretinoin treatment policy. Do we all agree? Dermatology 1997;195(suppl 1):34-40.
2. Cunliffe W, van de Kerkhof P, Caputo R, Cavicchini S, Cooper A, Fyrand OL, et al. Roaccutane treatment guidelines: results of an international survey. Dermatology 1997;194:351-7.
3. Leyden JJ. The role of isotretinoin in the treatment of acne: personal observations. J Am Acad Dermatol 1998;39(suppl):S45-S49.
4. Ward A, Brogden RN, Heel RC, Speight TM, Avery GS. Isotretinoin: a review of its pharmacological properties and therapeutic efficacy in acne and other skin disorders. Drugs 1984;28:6-37.
5. King K, Jones DH, Daltry DC, Cunliffe WJ. A double-blind study of the effects of 13-cis-retinoic acid on acne, sebum excretion rate, and microbial population. Br J Dermatol 1982;107:583-90.
6. Farrell LN, Strauss JS, Stranieri AM. The treatment of severe cystic acne with 13-cis-retinoin acid: evaluation of sebum production and the clinical response in a multiple dose trial. J Am Acad Dermatol 1980;3:602-11.
7. Plewig G, Gollnick H, Meigel W, Wokalek H. [13-cis retinoic acid in the oral therapy of acne conglobata. Results of a multi-center study.] Hautarzt 1981;32:634-46.
8. Leyden JJ, McGinley KJ, Foglia AN. Qualitative and quantitative changes in cutaneous bacteria associated with systemic isotretinoin therapy for acne conglobata. J Invest Dermatol 1986;86:390-3.
9. Pigatto PD, Fioroni A, Riva F, et al. Effects of isotretinoin on the neutrophil chemotaxis in cystic acne. Dermatologica 1983;167: 16-8.
10. Strauss JS, Stranieri AM. Changes in long-term sebum production from isotretinoin therapy. J Am Acad Dermatol 1982;6:751-5.
11. Peck GL, Olsen TG, Yoder FW, Strauss JS, Downing DT, Pandya M, et al. Prolonged remissions of cystic and conglobate acne with 13-cis-retinoic acid. N Engl J Med 1979;300:329-33.
12. Pochi PE. 13-cis-retinoic acid in severe acne. N Engl J Med 1979; 300:369-80.
13. Jones DH, Blanc D, Cunliffe WJ. 13-cis-retinoin acid and acne. Lancet 1980;2:1048-9.
14. Johnson BA, Nunley JR. Use of systemic agents in the treatment of acne vulgaris. Am Fam Physician 2000;62:1823-30, 1835-6.
15. Di Giovanna JJ. Systemic retinoid therapy. Dermatol Clin 2001; 19:161-7.
16. Layton AM, Knaggs H, Taylor H, Cunliffe W. Isotretinoin for acne vulgaris—10 years later: a safe and successful treatment. Br J Dermatol 1993;129:292-6.
17. Hermes B, Praetel C, Henz BM. Medium dose isotretinoin for the treatment of acne. J Acad Dermatol Venereol 1998;11:117-21.
18. Seukeran DC, Cunliffe WJ. Acne vulgaris in the elderly: the response to low-dose isotretinoin. Br J Dermatol 1998;139:99-101.
19. Bellosta M, Vignini M, Miori L, Rabbiosi G. Low-dose isotretinoin in severe acne. Int J Tissue React 1987;9:443-6.
20. Wolverton SE. Retinoids. In: Wolverton SE, Wilkin JK, eds. Systemic drugs for skin diseases. Philadelphia: Saunders; 1991. p. 187-218.
21. Meigel WN. How safe is oral isotretinoin? Dermatology 1997; 195(suppl 1):22-8.
22. Jick S, Kremers H, Vasilakis-Scaramozza C. Isotretinoin use and risk of depression, psychotic symptoms, suicide and attempted suicide. Arch Dermatol 2000;136:1231-6.
23. Lamberg L. Acne drug depression warnings highlight need for expert care. JAMA 1998;810:57.
24. Maddin S. FDA warning about isotretinoin. Skin Therapy Letter 1998;3:3-5.
25. Mitchell AA, Van Bennekom CM, Louik C. A pregnancy prevention program in women of childbearing age receiving isotretinoin. N Engl J Med 1995;333:101-6.
26. Kellet SC, Gawkrodger DJ. The psychological and emotional impact of acne and the effect of treatment with isotretinoin. Br J Dermatol 1999;140:273-82.
27. Jacobs DG, Deutsch NL, Brewer M. Suicide, depression, and isotretinoin: is there a causal risk? J Am Acad Dermatol 2001;45:S168-S175.
28. Wysowaski DK, Pitts M, Beitz J. An analysis of reports of depression and suicide in patients treated with isotretinoin. J Am Acad Dermatol 2001;45:515-9.
29. Margolis D, Attie M, Leyden J. Effects of isotretinoin on bone mineralization during routine therapy with isotretinoin for acne vulgaris. Arch Dermatol 1996;132:769-74.
30. Leachman SA, Insogna KL, Katz L, Ellison A, Milstone LM. Bone densities in patients receiving isotretinoin for cystic acne. Arch Dermatol 1999;135:961-5.
31. Kindmark A, Rollman O, Mallmin H, et al. Oral isotretinoin therapy in severe acne induces transient suppression of biochemical markers of bone turnover and calcium homeostasis. Acta Derm Venereol 1998;78:266-9.
32. Leachman SA, Insogna KL, Ellison A, Milstone LM. Bone density in patients receiving isotretinoin for cystic acne. Arch Dermatol 1999;135:961-5.
33. Strauss JS, Leyden JJ, Lucky AW, Lookingbill DP, Drake LA, Hanifin JM, et al. Safety of a new micronized formulation of isotretinoin in patients with severe recalcitrant nodular acne: a randomized trial comparing micronized isotretinoin with standard isotretinoin. J Am Acad Dermatol 2001;45:196-207.
34. Strauss JS, Leyden JJ, Lucky AW, Lookingbill DP, Drake LA, Hanifin JM, et al. A randomized trial of the efficacy of a new micronized formulation versus a standard formulation of isotretinoin in patients with severe recalcitrant nodular acne. J Am Acad Dermatol 2001;45:187-95.
35. White GM. Acne therapy. Adv Dermatol 1999;14:29-57.
36. Saurat JH. Oral isotretinoin where now, where next? Dermatology 1997;1S-3S.
37. Stainforth JM, Layton AM, Taylor JP, Cunliffe WJ. Isotretinoin for the treatment of acne vulgaris: which factors may predict the need for more than one course? Br J Dermatol 1993;129:297-301.
38. Jones DH, Cunliffe WJ. A follow-up study of 13-cis-retinoic acid therapy in cystic acne. In: Cunliffe WJ, Miller AJ, eds. Retinoid therapy. Lancaster: MTP Press; 1984. p. 241-51.
39. Harms M, Masouye I, Radeff B. The relapses of cystic acne after isotretinoin treatment are age-related: a long-term follow-up study. Dermatologica 1986;172:148-53.
40. White GM, Yao J, Wolde-Tsadik G. Recurrence rates after one course of isotretinoin. Arch Dermatol 1998;134:376-8.
41. Layton AM, Stainforth JM, Cunliffe WJ. Ten years' experience of

oral isotretinoin for the treatment of acne vulgaris. J Dermatol Treat 1993;4:S2-S5.

42. Cunliffe WJ, Layton A, Knaggs HE. In: Saurat JH, editor. Retinoids: 10 years on. Basel (Switzerland): Karger; 1991. p. 274-80.

GENERAL MANAGEMENT STRATEGIES IN ACNE

Today there are a number of very effective anti-acne therapies; in addition, the management of the acne patient is enhanced by a number of general strategies. Before treatment, a thorough history should be taken, documenting current skincare habits and any use of acne medication.[1-3] Knowledge of which acne medications the patient has previously used may help establish response and tolerability patterns. Ask whether specific factors, including exercise, stress, or pressure seem to exacerbate acne; it is possible that such factors can be modified or eliminated. There is also a familial predilection for persistent acne, which should be determined. Finally, the history should include questions about acne scarring in the family, because aggressive therapy may be warranted for patients at risk of scarring.[3] Figure 15 illustrates typical improvement in acne with therapy over time.

Diet

Although general lore associates many foods with the development of acne, studies to date have not shown that diet has an etiologic role in acne.[2,4] The myth that diet affects acne is widespread among both the general public and medical students.[5,6] Notably, the majority of foods linked to acne are tasty (chocolate, nuts, candy, soft drinks, etc). In a study of chocolate ingestion among acne patients, acne was unaffected in the majority of patients, improved in a few, and worsened in a few.[2,4] In addition, there is no scientific validity to the belief that high intake of carbohydrate and/or fat influences sebum production or acne; however, low calorie intake does decrease DHEAS.[2]

Zinc: An alternative oral therapy

Zinc, which inhibits chemotaxis, 5-α reductase and tumor necrosis factor-α production, and induces superoxide dismutase, exhibits some effectiveness against noninflammatory lesions, but does not affect comedones. In a randomized, comparative study, Dreno et al found that the effect of zinc (30 mg) on inflammatory lesions was approximately 17% lower than that of minocycline (100 mg).[7] However, patients with a good response have no zinc deficiency demonstrated either in blood or skin. Zinc may be safely used in summer (no phototoxicity). It is typically administered in a dose of 200 mg daily without food. Adverse events may include gastralgia and nausea. Zinc may be considered as an alternative to tetracyclines.

Skin care

Many persons also believe that acne is related to poor hygiene.[2,5] Furthermore, patients with acne tend to wash their skin excessively in an attempt to reduce oiliness. Yet there is no evidence that lack of washing is associated with acne or that frequent washing improves the condition.[2] Too-vigorous cleansing and scrubbing can aggravate the inflammatory phase of acne. Normal washing does not affect the follicular reservoir of lipids—the site of acne pathology. It is helpful for dermatologists to discuss these common misconceptions, particularly with adolescents, who may already feel unclean and unacceptable because of teasing from their peers. Patients should cleanse their acne skin areas twice daily at the most, using warm water and fingers (avoiding rough cloths and other scrubbing materials). Abrasives cause physical disruption of the follicle and are associated with an increase in lesions.

Patient education concerning skin care should focus on gentle cleansing. Moisturizers may be useful for persons with dry skin or irritation due to a topical medication. In addition, patients should be taught to select noncomedogenic skincare products and cosmetics.[3] In general, lotions and oil-based products are more comedogenic than gel-based products and foundations containing silicone derivatives (cyclomethicone, dimethicone); similarly, loose powder may be less comedogenic than pressed powder.[3,8] Antibacterial soaps, which contain agents such as chlorhexidine or triclosan, do not affect *P acnes*.

In addition these soaps can be irritating; for these reasons, antibacterial soaps are not indicated in acne. The exception is the benzoyl peroxide wash, which does suppress *P acnes*.[2,9]

Counseling

For optimal results, patients with acne require education about treatment and expectations. For example, it is important to help the patient understand the typical time required before results are clearly observed (ie, most treatment regimens require several weeks of consistent use before results are seen). In addition, patients should know about the risk of acne worsening before improvement is evident—

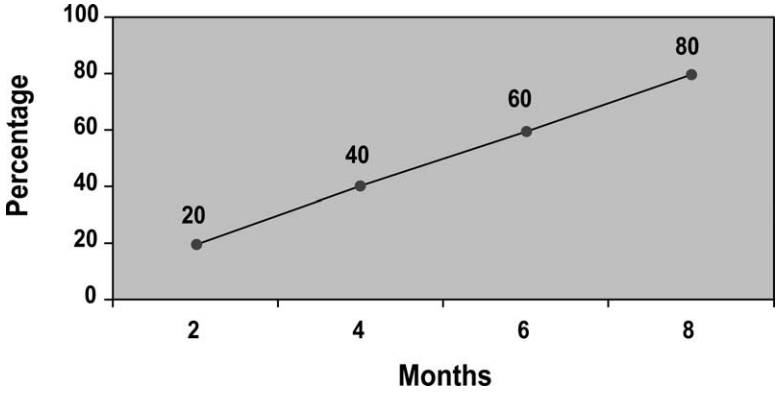

Fig 15. Typical improvement during acne therapy.

they should be reassured and encouraged to continue therapy. The importance of compliance and ongoing therapy to maintain remission should also be emphasized. Finally, patients should be taught the proper use of medications (topical agents should be spread over the entire involved area and oral medications should be taken as directed). Spot treatment of visible lesions does not achieve optimal results.[3] Patients may also need education about how to best apply topical therapies to hard-to-reach areas such as the back.

Because acne manifests primarily on the face and at a time (adolescence) when patients are highly vulnerable to criticism from peers, it is linked with many emotional issues. It is not uncommon for patients with acne to feel angry, hostile, depressed, isolated, and anxious. It is important for dermatologists to have empathy for these feelings, and to indicate that such feelings are not unusual. In addition, the patient should know that acne is not caused by bad habits, bad living, or bad thoughts. Generally, psychotherapy is not needed for patients with acne. Indeed, successful anti-acne therapy often resolves emotional issues.[2,3,10,11]

Consensus Recommendations

- Perform careful patient history
- Teach patients about gentle skin cleansing
- Show appropriate application technique for topical therapies
- Help patients to have realistic expectations of therapy
- Show empathy for patients' distress due to acne

REFERENCES

1. Cunliffe WJ, Gollnick H. Acne: diagnosis and management. London: Martin Dunitz, Ltd; 2001.
2. Plewig G, Kligman AM. Acne and rosacea. 3rd ed. New York: Springer-Verlag; 2000.
3. Berson D. Office management and local treatment. Dermatologic Ther 1995;6:47-53.
4. Fulton JE, Plewig G, Kligman AM. Effect of chocolate on acne vulgaris. JAMA 1969;210:2071-4.
5. Tan JK, Vasey K, Fung KY. Beliefs and perceptions of patients with acne. J Am Acad Dermatol 2001;44:439-45.
6. Green J, Sinclair RD. Perceptions of acne vulgaris in final year medical student written examination answers. Australas J Dermatol 2001;42:98-101.
7. Dreno B, Moyse D, Alirezai M, Amblard P, Auffret N, Beylot C, et al. Multicenter randomized comparative double-blind controlled clinical trial of the safety and efficacy of zinc gluconate versus minocycline hydrochloride in the treatment of inflammatory acne vulgaris. Dermatology 2001;203:135-40.
8. Draelos ZK. Patient compliance: enhancing clinician abilities and strategies. J Am Acad Dermatol 1995;32:542-8.
9. Mills OH Jr, Kligman AM. A human model for assessing comedogenic substances. Arch Dermatol 1982;118:903-5.
10. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210-6.
11. Cotterill JA. Acne. Practitioner 1982;226:1227-36.

ADJUNCTIVE THERAPIES

Comedo extraction/Electrocautery

A variety of office procedures are useful adjuncts to the overall acne regimen.[1,2] Acne surgery can be important in the management of comedonal acne. Extracting comedones results in an immediate improvement, which patients appreciate.[2,3] Topical anesthesia may be needed for removing closed comedones. Extractors, light cautery, or laser puncture may be used to remove the comedo.[2] The beneficial results of acne surgery are enhanced by use of topical retinoids to prevent the development of new

lesions while existing comedones resolve; topical retinoids also facilitate expulsion of the comedo.

Skillful comedo extraction results in an immediate benefit. Open comedones may be extracted by gentle pressure around the follicular opening. Closed comedones may be incised with a large gauge needle or number 11 blade; the contents are then expressed through the opening.[2,3] The limitations of comedo extraction include incomplete extraction, refilling, and the risk of tissue damage. Macrocomedones are a frequent cause of therapeutic failure, and usually do not respond to oral or topical retinoids. Light cautery under local anesthesia can be very helpful.[2,4]

Chemical peels

Light chemical peels may also be useful in acne patients to help correct surface scarring and hyperpigmentation.[5-7] This should be attempted only after acne is brought under control. Peeling agents include alpha-hydroxy acids (glycolic acid), salicylic acid, and trichloroacetic acid. Salicylic acid may have anti-inflammatory effects.[8,9] Salicylic acid is lipid soluble and may penetrate into sebum-laden follicles more readily than water-soluble alpha-hydroxy acids.

Photodynamic therapy

Once a staple of acne therapy, older ultraviolet light treatments are now known to provide only fleeting benefit.[2] Prolonged use (particularly of ultraviolet-A) may enhance comedogenesis and damage skin. Phototherapy targets *P acnes*.[10,11] In patients with mild to moderate forms of acne, use of limited spectrum wavelengths, such as blue light (peak at 415 nm) and mixed blue and red light (peaks at 415 and 660 nm) have been associated with significant reductions in acne lesions after 4 to 12 weeks.[10,11]

Corticosteroids

Strong topical corticosteroids are limited by the potential for delayed side effects, including skin atrophy, papulopustular flares, perioral dermatitis, steroid rosacea, and rebound dermatitis.[1,2] However, a short course (7-10 days) may be useful as initial strategy in severe inflammatory acne (especially acne conglobata, acne fulminans). One of the primary benefits of this approach is to give the patient with severe acne hope that their disease may be controlled. Topical corticosteroids may also be used to treat granuloma pyogenicum-like and very localized lesions after oral isotretinoin therapy.[1,2]

Oral corticosteroids may be a preferred therapy in patients with very severe inflammatory disease, including acne conglobata, because a short course will immediately reduce the number of inflammatory lesions. As with topical steroids, this can have a significant positive psychologic benefit. In addition, reduction of pustular and hemorrhagic lesions can ameliorate pain. Oral steroids are also very useful in acne fulminans, often in combination with an oral antibiotic. This regimen may be followed by isotretinoin once improvement has been achieved. Finally, good results can be achieved with oral corticosteroids in patients with adrenal hyperplasia.[1,2]

Intralesional steroid injections can be helpful for large, inflammatory lesions of <2 weeks' duration.[1,2,12,13] However, there is a small risk of an atrophic scar. To minimize the potential for scarring, only larger lesions with significant elevation over the surrounding skin should be treated. The corticosteroid should be injected into the center of the lesion until the redness blanches.[1,2,12,13]

REFERENCES

1. Cunliffe WJ, Gollnick H. Acne: Diagnosis and management. London: Martin Dunitz, Ltd; 2001.
2. Plewig G, Kligman AM. Acne and rosacea 3rd ed. New York: Springer-Verlag. 2000.
3. Shalita AR, Harris H. Comedo extraction. Arch Dermatol 1972; 105:759-60.
4. Thomson KF, Goulden V, Sheehan-Dare R, Cunliffe WJ. Light cautery of macrocomedones under general anesthesia. Br J Dermatol 1999;141:595-6.
5. Szalay LV. Treatment of acne scarring by combined dermabrasion and chemical peel. Plast Reconstr Surg 1987;79:307-8.
6. Horton CE, Sadove RC. Refinements in combined chemical peel and simultaneous abrasion of the face. Ann Plast Surg 1987;19:504-11.
7. Monheit GD. The Jessner's-trichloroacetic acid peel. An enhanced medium-depth chemical peel. Dermatol Clin 1995;13: 277-83.
8. Davies M, Marks R. Studies in the effect of salicylic acid in normal skin. Br J Dermatol 1976;95:187-92.
9. Weirich EG, Longauer J, Kirkwood AH. Dermatopharmacology of salicylic acid in animals. III. Topical contra-inflammatory effect of salicylic acid and other drugs in animal experiments. Dermatologica 1976;152:87-99.
10. Papageorgiou P, Katsambas A, Chu A. Phototherapy with blue (415 nm) and red (660 nm) light in the treatment of acne vulgaris. Br J Dermatol 2000;142:973-8.
11. Cunliffe WJ, Goulden V. Phototherapy and acne vulgaris. Br J Dermatol 2000;142:855-6.
12. Callen JP. Intralesional corticosteroids. J Am Acad Dermatol 1981;4:149-51.
13. Levine RM, Rasmussen JE. Intralesional corticosteroids in the treatment of nodulocystic acne. Arch Dermatol 1983;119:480-1.

THE IMPACT OF ACNE ON QUALITY OF LIFE

Consensus: Acne Has a Very Significant Impact on Patients

- Negative effect on emotional well-being and social function is greater than that seen with more "serious" medical conditions such as
  - Asthma
  - Epilepsy
- Acne is often associated with anxiety, depression, and higher-than-average unemployment rates
- The emotional impact of acne is not always easy to assess clinically

Skin diseases can have a major impact on quality of life.[1,2] Comparisons with other chronic illnesses have shown that patients with acne have levels of social, psychologic, and emotional impairments that are similar to those reported by patients with more "serious" diseases, such as asthma, epilepsy, diabetes, or arthritis (Fig 16).[3] Both women and men find the effects of acne on appearance to be the most bothersome aspect of their disease.[4,5] In addition, the negative effects of acne occur in both older and younger patients.[6]

The disease also affects patients' functional abilities.[7] Patients with acne have a higher unemployment rate than adults without acne.[8] Patients with acne are also prone to embarrassment and social withdrawal, depression, anxiety, and anger.[9-12] In addition, younger patients with acne are subject to scorn, teasing, and stigmatization from their peers.[13] Some people still perceive acne to be a curse that accompanies bad attitudes or bad actions. However, there are a number of highly effective treatments for acne and, in many cases, cure is quite possible.[13]

The impact of acne on a particular patient is not always easy to judge clinically.[1,3,13] For example, even mild acne can pose a significant problem for some patients, diminishing their quality of life and, in some cases, their social functioning.[1] Fortunately, treatment can dramatically improve quality of life.[9] Therefore, it is important to achieve optimal results with acne therapies. Clinicians need to understand that the positive impact of effective treatment on quality of life is highly significant to patients.

Measurement of quality of life

Measurement of the impact of skin disease on quality of life is vital for research purposes, and is also valuable in clinical practice.[14] General health measures that have been used to assess a variety of diseases include the Short-Form 36 and the General Health Questionnaire.[15,16] These tools allow comparison of the impact of skin diseases with a spectrum of other diseases.[16,17] For instance, use of general health measures suggests that the impact of psoriasis is similar to that of cardiac disease.[16,18] As discussed previously, acne can cause emotional disability that is similar to asthma or epilepsy.

In general, skin diseases affect patients' lives in similar ways. Several validated dermatology questionnaires have been created to measure the impact of skin diseases.[16] Dermatology-specific measures include the Dermatology Life Quality Index (DLQI),[19] Skindex,[20] and the Dermatology Quality of Life Scales (DQOLS).[15,16,21] The DLQI was the first tool described, and has the most extensive experience.[15] Acne-specific measures include the Acne Disability Index (ADI), the Cardiff Acne Disability Index (CADI), the APSEA (Assessment of the Psychological and Social Effects of Acne), and the Acne-QOL; these can be used to monitor change during therapy.[7,22-25]

Quality of life and compliance

Understanding the relationship between compliance with therapy and the impact of a disease on a patient's life may help clinicians to devise strategies to improve compliance.[14] Poor compliance may occur in young persons and in patients with chronic disease who have had poor outcomes with other therapies. Notably, a study of patients taking oral isotretinoin suggested that compliance improved with the degree of disability due to disease. However, the compliance did not correlate with the clinical rating of severity of acne.[26]

Impact of acne treatment

Assessing quality of life at baseline provides important information about patients' perceptions. During treatment, quality-of-life assessment can provide additional information about efficacy and may help clinicians tailor therapy to the individual needs of each patient.

In a study assessing the effect of anti-acne therapy on 111 patients, Newton et al showed that treatment substantially improved scores on quality-of-life instruments.[27] Oral isotretinoin was prescribed for 79 patients, and 32 patients received oral or topical antibiotics, hormonal therapy, or a topical retinoid.[27] There was significant clinical improvement in all patients, particularly in those treated with oral isotretinoin (mean acne grade at baseline of 5.0 vs 0.7 at 4 months). Quality-of-life assessment at both 4-month and 12-month follow-up showed significant and substantial improvements in self-esteem

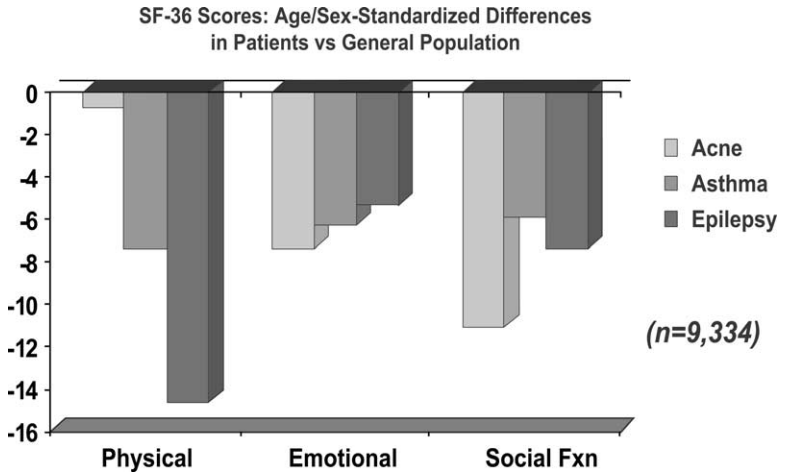

Fig 16. Quality of life scores for acne and other chronic illnesses Reprinted with permission from Mallon E, et al. The quality of life in acne. Br J Dermatol 1999;140:672-6.

and other indices measured by the DLQI and Short Form-36. This suggests that the disability caused by acne can be largely reversed by effective therapy.[27]

Topical retinoid therapy alone has also been shown to improve quality of life among patients with mild to moderate acne.[28] In a 12-week comparative study of adapalene gel 0.1% versus tretinoin gel 0.025%, topical retinoid therapy significantly reduced acne lesion counts (52% from baseline in adapalene-treated patients and 53% from baseline in tretinoin-treated patients). There was also a significant improvement of DLQI indices by the end of treatment (total score 3.95 at baseline vs 2.14 at week 12 for adapalene-treated patients and 5.13 vs 3.35 for tretinoin-treated patients). In addition, there were significant reductions in scoring for specific questions; as shown in Figure 17, patients' embarrassment or self-consciousness due to skin was markedly decreased.[28]

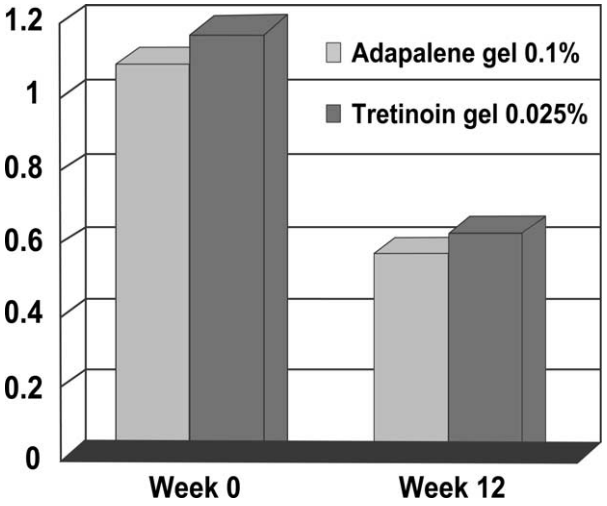

Fig 17. Impact of topical retinoid therapy on quality of life (DLQI results) score for embarrassment or self-consciousness due to skin. Data from Grosshans E, et al. Evaluation of clinical efficacy and safety of adapalene 0.1% gel versus tretinoin 0.025% gel in the treatment of acne vulgaris, with particular reference to the onset of action and impact on quality of life Br J Dermatol 1998;139(suppl 52):26-33.

Counseling

Patients should be informed that there is the potential for a short-term negative impact on quality of life from acne therapies. For example, some topical agents are irritating and others may leave a white film on the face. There is also the potential for other side effects with anti-acne therapies. The dermatologist should discuss the risks versus the benefits of anti-acne therapy, focusing on why each agent was chosen and how it can benefit the patient.

Wider strategies for improving quality of life

Approximately 25% of patients with skin disorders have significant psychiatric morbidity as identified on the General Health Questionnaire. The most common psychiatric disorders in acne patients are anxiety and depression.[12] Health-related quality of life has been correlated with psychiatric morbidity, even more than clinical severity. It is important to be aware of the emotional well-being of patients with acne, and to be alert to death wishes and suicidal ideation. Because dermatologists often have the closest contact with patients who have acne, they are in a unique position to recognize psychiatric morbidity and take appropriate measures. Coun-

seling or brief psychotherapy, perhaps accompanied by psychotropic drugs, may be valuable for patients with acne who have depressive or anxiety disorders. The use of simple questionnaires may help dermatologists to recognize the presence of psychiatric distress and may help facilitate further inquiries and referral to a clinical psychologist.

Consensus Recommendations: Quality of Life

Effective treatment can dramatically improve patients' quality of life

Use of a simple QoL assessment tool can help clinicians optimize therapy and can detect the patient with mild disease who is psychologically distressed

REFERENCES

1. Picardi A, Abeni D, Melcchi CF, Puddu P, Pasquini P. Psychiatric morbidity in dermatological outpatients: an issue to be recognized. Br J Dermatol 2000;143:983-91.
2. Harlow D, Poyner T, Finlay AY, Dykes PJ. Impaired quality of life in adults with skin disease in primary care. Br J Dermatol 2000; 143:979-82.
3. Mallon E, Newton JN, Klassen A, Stewart-Brown SL, Ryan TJ, Finlay AY. The quality of life in acne: a comparison with general medical conditions using generic questionnaires. Br J Dermatol 1999:140:672-6.
4. Jowett S, Ryan T. Skin disease and handicap: analysis of the impact of skin conditions. Soc Sci Med 1985;20:425-9.
5. Shuster S, Fisher GH, Harris E, Binnell D. The effect of skin disease on self-image. Br J Dermatol 1978;99(Suppl 16):18-9.
6. Lasek RJ, Chren M-M. Acne vulgaris and the quality of life of adult dermatology patients. Arch Dermatol 1998;134:454-8.
7. Motley RJ, Finlay AY. How much disability is caused by acne? Clin Exp Dermatol 1989;14:194-8.
8. Cunliffe WJ. Acne and unemployment. Br J Dermatol 1986;115: 386.
9. Kellet SC, Gawkrodger DJ. The psychological and emotional impact of acne and the effect of treatment with isotretinoin. Br J Dermatol 1999;140:273-82.
10. Koo J. The psychosocial impact of acne: patients' perceptions. J Am Acad Dermatol 1995;32:S25-S30.
11. Wu SF, Kinder BN, Trunnell TN, Fulton JE. Role of anxiety and anger in acne patients: a relationship with the severity of the disorder. J Am Acad Dermatol 1988;18:325-33.
12. Aktan S, Ozmen E, Sanli B. Anxiety, depression, and nature of acne vulgaris in adolescents. Intl J Dermatol 2000;39:354-7.
13. Plewig G, Kligman AM. Acne and rosacea. 3rd ed. New York: Springer-Verlag; 2000.
14. Finlay AY, Dermatology patients: what do they really need? Clin Exp Dermatol 2000;35:444-50.
15. Finlay AY. Dermatology Life Quality Index: initial experience of a simple practical measure. In: Rajagopalan R, Sherertz EF, Anderson RT, eds. Care management of skin disease: life quality and economic impact. New York: Marcel Dekker; 1998. p. 85-94.
16. Finlay AY. Quality of life assessments in dermatology. Semin Cutan Med Surg 1998;7:291-6.
17. Klassen AF, Newton JN, Mallon E. Measuring quality of life in people referred for specialist care of acne: comparing generic and disease-specific measures. J Am Acad Dermatol 2000;43: 229-33.
18. Finlay AY, Khan GK, Luscombe DK, Salek MS. Validation of sickness impact profile and psoriasis disability index in psoriasis. Br J Dermatol 1990;123:751-6.
19. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210-6.
20. Chren M-M, Lasek RJ, Quinn LM, Mostow EN, Zyzanski SJ. Skindex, a quality-of-life measure for patients with skin disease: Reliability, validity, and responsiveness. J Invest Dermatol 1996; 107:707-13.
21. Morgan M, McCreedy R, Simpson J, Hay RJ. Dermatology quality of life scales – a measure of the impact of skin diseases. Br J Dermatol 1997;136:202-6.
22. Salek MS, Khan GK, Finlay AY. Questionnaire techniques in assessing acne handicap: reliability and validity study. Qual Lif Res 1996;5:131-8.
23. Clark SM, Goulden V, Finlay AY, Cunliffe WJ. The psychological and social impact of acne: a comparison study using three acne disability questionnaires [abstract]. Br J Dermatol 1997; 137(suppl 50):41.
24. Oakley AMM. The acne disability index: usefulness confirmed. Australas J Dermatol 1996;37:37-9.
25. Gupta MA, Johnson AM, Gupta AK. The development of an acne quality of life scale: reliability, validity and relation to subjective acne severity in mild to moderate acne vulgaris. Acta Derm Venereol (Stockh) 1998;78:451-8.
26. Mufleh L, Gonzalez M, Judodihardjo H, Finlay AY. Compliance is high in patients taking oral isotretinoin for acne. Br J Dermatol 1999;141(Suppl 55):87.
27. Newton JN, Mallon E, Klassen A, Ryan TJ, Finlay AY. The effectiveness of acne treatment: an assessment by patients of the outcome of therapy. Br J Dermatol 1997;137:563-7.
28. Grosshans E, Marks R, Mascaro JM, Torras H, Maynadier J, Alirezai M, et al. Evaluation of clinical efficacy and safety of adapalene 0.1% gel versus tretinoin 0.025% gel in the treatment of acne vulgaris, with particular reference to the onset of action and impact on quality of life. Br J Dermatol 1998:139(Suppl 52):26-33.

TREATMENT AND MANAGEMENT OF ACNE

In acne, the therapeutic approach should begin with a careful assessment of the patient's history and education, because there are many myths surrounding this disease. It is important to emphasize that acne is not infectious, is not caused by poor hygiene, and is not related to diet. Female patients should be informed that acne may worsen during the week before menses and patients of both sexes should be advised against picking at lesions. In addition, patients should receive instructions about proper skin care and application of topical medications. Patients also need to understand that, although most cases of acne can be cleared with existing medications, therapy requires time, and improvement may not be very apparent until after four to six weeks of therapy (sometimes longer). In fact, patients should be advised that, in the early weeks of therapy, their acne may appear to worsen. They

should be reassured that this apparent worsening is simply due to the medication acting on lesions that were previously unseen, and that it is not a reason to discontinue therapy.

Assessment of acne should include acne severity, lesion type, the presence or likelihood of scarring, the psychologic impact of the disease, and experience with anti-acne therapies (prescription and over-the-counter). The skin should be examined under a good light, and the dermatologist should determine the lesion types and overall disease severity. The psychologic impact of acne can be determined by questioning, or by use of one of several established techniques such as the acne disability index.

An algorithm for the pharmacologic treatment of acne is presented in Figure 18. As shown, topical retinoids are an appropriate first-line therapy for virtually all cases of acne except the most severe. Although not as effective, salicylic acid and azaleic acid may be acceptable alternatives for mild comedonal acne in patients who are unable to tolerate topical retinoid therapy, or in countries where topical retinoids are not available.

When inflammatory lesions are present, but the disease is still relatively mild, a topical antimicrobial agent should be combined with the topical retinoid to provide more rapid clearing. If topical retinoids are not available for combining with antimicrobial therapy, or if the topical retinoid is not tolerated by the patient, an alternative to the retinoid is azelaic acid.

For more severe moderate acne, it is appropriate to combine oral antibiotics with topical retinoids and/or benzoyl peroxide. Female patients may also be candidates for hormonal therapy, especially when they require oral contraception, have higher sebum levels, or there is familial evidence for androgenic alopecia or need for contraception or control of the menstrual period in addition to acne. In the most severe cases of acne, such as conglobate acne and significant nonresponsive disease, oral isotretinoin is the usual treatment of choice. Given the teratogenic risks associated with use of oral isotretinoin, however, it is essential that the dermatologist provide all female patients of child-bearing potential with comprehensive counseling before prescribing isotretinoin. As a reminder, counseling must include provision of both oral and written information concerning the hazards of taking isotretinoin during pregnancy, and of the need for effective contraception. Indeed, it is critical to remember the entire list of "musts" that female patients of child-bearing potential have to meet before receiving isotretinoin.

Maintenance therapy is very important in acne, because this disease tends to recur without an ongoing treatment regimen. Because they target microcomedones (the precursor lesions of acne), topical retinoids are recommended as maintenance therapy. Benzoyl peroxide may also be used as maintenance therapy in combination with topical retinoid, with the topical retinoid being used in the evening and benzoyl peroxide in the morning. Very long-term use of antibiotics, however, should be minimized whenever possible to reduce the potential for antimicrobial resistance.

Treatment of acne during pregnancy

Because acne most often occurs during the years that females are at the height of their child-bearing potential, dermatologists must caution their female patients to promptly inform all healthcare providers if pregnancy occurs. Indeed, acne patients who become pregnant should immediately advise their obstetrician of the medication they were taking on or about the time of contraception.

In most cases, the patient will simply be advised to stop therapy. Given the sophistication of obstetric care, and the availability of diagnostic tools, most patients will require nothing more than appropriate counseling. Clearly, however, the issue becomes much more serious if the patient has been taking oral isotretinoin

Oral isotretinoin must not be prescribed during pregnancy, and a female patient must avoid pregnancy for at least four weeks after stopping isotretinoin. It is the responsibility of the dermatologist and the pharmacist to ensure that the patient is not pregnant before starting oral isotretinoin, and that she use appropriate and adequate contraception throughout the course of treatment, and for at least four weeks after stopping isotretinoin therapy.

Should the patient request acne treatment during pregnancy, it is essential to make it quite clear that treatment will only be prescribed if the physician deems it to be necessary and advisable and that the patient agrees with this decision. Regulations relating to medication use during pregnancy vary from country to country. Thus, the dermatologist should check the appropriate product information.

In many countries, topical benzoyl peroxide and topical erythromycin can be prescribed as individual therapies. In some countries, use of azaleic acid is not prohibited during pregnancy. Topical retinoids are not recommended for use in pregnant patients. However, pharmacologic data suggest that percutaneous absorption of such topical acne therapies is minimal. Given the increasingly complex medical

and legal issues, however, minimal acne therapy is a prudent approach in this situation.

Some female patients do need to treat their acne during pregnancy, especially those with severe disease and those at risk of significant scarring. Oral tetracyclines, including doxycycline, lymecycline, and minocycline, are *not* recommended. Trimethoprim also is not recommended. Oral erythromycin (0.5 g twice daily) is the safest choice, followed by topical benzoyl peroxide or topical erythromycin. If the acne is very inflammatory, short courses of oral steroids may be used after the first trimester, but discussions with the obstetrician are essential before initiating therapy. Occasionally, macro comedones are the cause of the severe inflammatory acne. If so, the patient may need gentle cautery of the macro comedones under the eutectic mixture of local anesthetics. However, the safety of the eutectic mixture of local anesthetics during pregnancy remains in question.

Other patients who require counseling are those female patients definitely in need of acne therapy, but who are currently trying to become pregnant or intending to start a family in the near future.

The prescribed acne medication should be discussed in detail with the patient and the obstetrician, and with the general practitioner when appropriate.