New Treatments and Therapeutic Strategies for Acne

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Successful management of acne requires careful patient evaluation followed by consideration of several patient and medication factors when selecting a particular therapeutic regimen. Within the last few years, several new agents for the treatment of acne have become available that afford greater flexibility in the treatment of this prevalent dermatologic disorder. These include adapalene, tazarotene, 2 new topical tretinoin formulations, azelaic acid, a new sodium sulfacetamide formulation, and an oral contraceptive recently approved by the Food and Drug Administration for the treatment of acne. After a brief overview of the pathophysiology of acne and existing therapies, this review evaluates the new antiacne agents and how they can be integrated into a successful treatment strategy that takes into account acne severity and predominant lesion type as well as age, skin type, lifestyle, motivation, and the presence of coexisting conditions.

Arch Fam Med. 2000;9:179-187

Acne vulgaris is the most common skin condition encountered by physicians, and it affects an estimated 17 million people in the United States.[1] Within the last few years, several new agents for the treatment of acne have become available. This review provides a brief discussion of the pathophysiology of acne, principles for successful management, and an overview of existing therapies. This is followed by a discussion of the new antiacne agents and how they fit into a successful acne treatment strategy.

ACNE, ITS PATHOGENESIS, AND TREATMENT GOALS

Acne vulgaris is a multifactorial disease affecting the pilosebaceous follicles. It arises from the interplay of 4 pathogenic factors: sebum production, follicular hyperkeratinization, microbial colonization of the pilosebaceous unit by *Propionibacterium acnes*, and the release of inflammatory mediators into the follicle and surrounding dermis.[2-5] Acne begins in the prepubertal period, when increased amounts of adrenal androgens cause enlargement of the sebaceous glands and increased production of sebum on the face, chest, and back. Acne severity is often correlated with the amount of sebum produced. In follicles affected with acne, there is also increased desquamation of follicular keratinocytes and increased cohesiveness of the corneocytes due to an altered pattern of keratinization. The resulting follicular obstruction by the combination of sebum and desquamated epithelial cells causes the formation of a microcomedone, the precursor lesion of acne. This is also a suitable environment for the proliferation of *P acnes*, an anaerobic diphtheroid that colonizes sebum-rich follicles and uses lipids found in sebum as a nutrient source.[5,6] Lipases released from *P acnes* hydrolyze sebum triglycerides into free fatty acids, which are an irritant to the follicular wall and the surrounding dermis after follicular rupture.[6] *P acnes* also release chemotactic factors and proinflammatory mediators that contribute to the observed inflammatory response. The clinical results of these pathophysiological events include noninflammmatory open (blackheads) and closed comedones (whiteheads), as well as inflammatory papules, pustules, and nodules.

Although acne is not a life-threatening disease, it has significant physical and psychological ramifications such as permanent scarring, poor self-image, social inhibition, depression, and anxiety.[7] Therefore, the primary goals of acne treatment are prevention of scarring and alleviation of clinical

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symptoms. Treatment of existing scars and postinflammatory hyperpigmentation are also important goals of therapy, although they are more difficult to achieve.[8] Effective treatment should be directed at a combination of the 4 pathogenic factors.[9]

STRATEGIES FOR SUCCESSFUL ACNE MANAGEMENT

Patient Factors

Successful management of acne requires careful patient evaluation followed by consideration of several "patient factors" and "medication factors" in choosing a particular therapeutic regimen. Most patients have a mixture of noninflammatory and inflammatory lesions. The predominance of one type, along with the number of lesions, plays a role in determining acne severity. In addition, other factors to be considered include age, skin type (dry, oily, or combination), coexisting conditions, patient motivation, lifestyle, menstrual regularity and premenstrual flareups, evidence of hirsutism, effect of acne, and potential therapies on the patient's quality of life. If the patient is taking birth control pills, it is important to determine the brand, as certain formulations contain agents (eg, androgenic progestins) that may provoke acne. Exposure to comedogenic substances such as tars, polyvinyl chloride, or other substances used for hair care should also be determined. Other medications that may cause acne include corticosteroids, androgens, iodides, bromides, lithium, trimethadione, halothane, vitamin B_{12}, and hyperalimentation therapy. In addition, mechanical trauma can aggravate a patient's acne. Incorporation of these factors into the choice of a specific therapeutic regimen can enhance patient compliance, which is essential for the success of acne treatment.[10]

While acne is generally considered an affliction of adolescence, a steadily increasing number of older patients (particularly women) have been seeking treatment for acne.[11] This is a more demanding, articulate group of patients with high expectations for improvement. Furthermore, they may have a low tolerance for adverse effects of therapy, such as erythema or scaling, and greater concern about scarring and postinflammatory hyperpigmentation.

Medication Factors

The patient's skin type and preferences should be considered in the choice of vehicle for topical agents. Those vehicles with a higher proportion of alcohol (eg, solutions and some gels) are often preferred by patients with oily skin; patients with dry skin may prefer a vehicle that offers greater moisturization, such as a cream, lotion, or ointment.[6] There are also questions regarding the compatibility of the various vehicles and agents with cosmetics, which may be important to some patients.[10] In addition, solutions and washes can be more easily applied to large areas of the skin such as the back, even though they are drying. Suggesting how the recommended therapy can be incorporated into the patient's skin care regimen is important because patients often have questions regarding the application of various medications. Tailoring treatment recommendations to fit within the patient's lifestyle will increase the likelihood of compliance. Patient education regarding use of the drug, rationale for the specific therapy chosen, and realistic expectations for improvement are also key to treatment success.

RATIONALE FOR SELECTION OF APPROPRIATE ANTIACNE AGENTS

In all cases, the objective in choosing a specific agent or agents should be to achieve maximum efficacy and tolerability with minimum risk of adverse effects.[9] For noninflammatory acne or for mild to moderate inflammatory acne, topical therapy may be sufficient and minimizes potential adverse effects associated with the use of systemic agents. Moderate to severe inflammatory disease not responding to topical combination therapy warrants the addition of oral agents to the regimen. In designing a topical therapeutic regimen, attention to the specific formulations available is warranted. Existing preparations of some topical agents can cause significant local irritation, which decreases tolerability and, consequently, compliance. Rational use of combination therapy in the management of acne requires consideration of the pathogenic factors and an understanding of how the various antiacne agents target one or more of these factors (**Table**).[9] Regimens should be designed to take advantage of the synergistic effects of agents with different mechanisms of action that can target a combination of the pathogenic factors.

OVERVIEW OF EXISTING THERAPIES

Historically, the existing armamentarium of antiacne agents has included topically applied or systemically administered antimicrobials or retinoids. The ideal agent would target each of the pathogenic factors without producing adverse effects; however, the antiacne agents currently available target only 1 or 2 of the pathogenic factors. Apart from isotretinoin, there is no agent with broad spectrum action in acne. There is a clear-cut need for new, safe, and effective agents in the treatment of acne.

COMEDOLYTIC AGENTS

Tretinoin

Topical tretinoin (all-trans-retinoic acid) is a highly effective comedolytic agent. It normalizes follicular keratinization, promotes drainage of preexisting comedones, and inhibits the formation of new ones.[1,12] There also may be a decrease in inflammatory lesions due to inhibition of microcomedone formation. Maximal clinical improvement may not be apparent until after 3 or 4 months of use. Tretinoin is effective as monotherapy for noninflammatory acne or mild to moderate inflammatory acne. It has also been used effectively in combination with either topical antibiotics, benzoyl peroxide (BPO), or systemic antibiotics, presumably because of its ability to increase the penetration and enhance the efficacy of other agents.[9,12,13] Another

benefit of such combinations is the apparent decrease in the irritation from tretinoin by the addition of a topical antimicrobial agent.[9]

The most common adverse effect associated with existing topical tretinoin preparations is local irritation. Patients may also experience erythema, dryness, and peeling. These effects often resolve after approximately 3 weeks.[6] Tretinoin should only be used in combination with BPO when applied 1 to 2 hours before or after application of BPO to avoid irritation and to increase efficacy. Tretinoin also induces a mild thinning of the stratum corneum that may increase sensitivity to sunlight, necessitating proper sunscreen use.[14] Finally, an exacerbation of inflammatory lesions (pustular flare) within 2 to 4 weeks of initiation of therapy may also occur.[9] To minimize local irritation, therapy should start with a mild formulation and the concentration should be gradually increased. In summary, topical tretinoin is a mainstay in the treatment of acne, but its adverse effect profile warrants careful patient management to optimize efficacy and tolerability.

Pathogenic Factors Targeted by Different Antiacne Agents

Agent	Sebum Production	Hyperkeratinization	*Propionibacterium acnes* Proliferation	Inflammation
Topical agents				
Adapalene	Unknown	Yes	Unknown	Possibly
Azelaic acid	No	Yes	Yes	Possibly
Benzoyl peroxide	No	Yes (indirectly)	Yes	Possibly
Erythromycin	No	No	Yes	Possibly
Sodium sulfacetamide	No	No	Yes	No
Tazarotene	No	Yes	Unknown	No
Tretinoin	No	Yes	Unknown	No
Systemic agents				
Erythromycin	No	No	Yes	Possibly
Isotretinoin	Yes	Yes	Yes (indirectly)	Yes
Oral contraceptives	Yes (indirectly)	No	No	No
Tetracylines	No	No	Yes	Yes

ANTIMICROBIAL AGENTS

Benzoyl peroxide is a potent topical bactericidal agent that reduces the population of *P acnes* by generating reactive oxygen species in the sebaceous follicle.[9] It rapidly improves both inflammatory and noninflammatory lesions and has therefore been a first-line choice in the therapy of mild acne and a mainstay in acne therapy in general. It is available in a wide variety of concentrations and preparations. Benzoyl peroxide is very effective in combination with either topical antibiotics or tretinoin (described above).[13] When combined with tretinoin or 3% erythromycin, BPO can have a synergistic effect on inflammatory acne.[9] The major adverse effect of BPO is local irritation, which is often most pronounced during therapy initiation. Erythema and dryness may also occur. Allergic contact dermatitis, necessitating therapy discontinuation, has been reported in approximately 1% to 3% of patients.[14] Patients should be informed that the drug bleaches clothing and bed linens. This may present a problem, particularly when it must be applied to the chest or back.

ANTIBIOTICS

Topical Antibiotics

Topical antibiotics are useful in the treatment of mild to moderate inflammatory acne. They reduce the population of *P acnes* in sebaceous follicles and also demonstrate antiinflammatory properties by suppressing chemotaxis and decreasing the percentage of proinflammatory free fatty acids in surface lipids.[9] Topical antibiotics available for use include erythromycin, clindamycin, sodium sulfacetamide, and salicylic acid. Erythromycin and clindamycin have been shown to be of equivalent efficacy for treating moderate acne.[9,14] They are often used effectively in combination with BPO or tretinoin. Sodium sulfacetamide is an antibacterial agent that has been used in antiacne preparations for many years. Until recently, it has only been available in combination with sulfur 5% as a keratolytic agent. Salicylic acid is effective against comedones and inflammatory lesions, but may be less effective in patients who cannot tolerate topical tretinoin. All topicals should be applied to the entire face rather than to individual lesions.

All of the topical antibiotics can cause local irritation to some extent.[6] Although more commonly associated with systemic clindamycin, diarrhea, abdominal pain, bloody diarrhea, and colitis (including pseudomembranous colitis) have also been associated with topical clindamycin.[15,16] In addition, sodium sulfacetamide products may cause rare hypersensitivity. The development of resistance of *P acnes* to topical antibiotics has become more prevalent and may result in loss of efficacy.[14,17,18] Studies have demonstrated that resistance to erythromycin may be reduced by using the drug in combination with BPO.[9,14]

Systemic Antibiotics

Systemic antibiotics such as erythromycin and tetracycline, or the derivatives doxycycline and minocycline, are most often used for moderate to severe inflammatory acne not responding to topical combinations, acne involvement of areas where topical agents cannot be easily applied (back), or for acne with high scarring potential. The primary mechanism of action of these agents in acne treatment is the suppression of *P acnes* growth, which reduces the production of inflammatory factors.[14] Many of these agents, such as tetracycline and erythromycin, also possess intrinsic anti-inflammatory activity.[6,14]

Erythromycin

Oral erythromycin is comparable to tetracycline in its therapeutic effect on acne,[6,14] although resistance of *P acnes* to erythromycin seems to be

more common than that produced by tetracyclines.[17,18] The most common adverse effect associated with erythromycin is gastrointestinal (GI) tract irritation, which may be alleviated to some degree by taking the drug with food or milk.

Tetracycline, Doxycycline, and Minocycline

Tetracycline and its derivatives are the most commonly used oral medications for acne vulgaris. Tetracycline hydrochloride is known to penetrate sebocytes and keratinocytes to reach the follicular canal.[6] As with topical antibiotics, development of resistance of *P acnes* to tetracycline is a potential problem,[18,19] and this should be suspected if a patient's acne worsens after several months of treatment. Doxycycline is a lipophilic tetracycline derivative with demonstrated efficacy in the treatment of inflammatory acne. Like tetracycline, resistance of *P acnes* to doxycycline has been reported.[18] Minocycline, also a lipophilic derivative of tetracycline, achieves excellent penetration into the follicular canal and is often effective in cases of acne that have not responded to treatment with other oral antibiotics.[6] There are fewer reports of resistance of *P acnes* to minocycline than with tetracycline and doxycycline. While tetracycline should be taken on an empty stomach, doxycycline and minocycline can be taken with food, which should decrease GI tract upset.

Adverse effects of tetracyclines are well known and include GI tract upset, vaginal yeast infection, and possible decreased efficacy of oral contraceptives. In addition, doxycycline is associated with photosensitivity. Unlike less lipophilic tetracyclines, minocycline is associated with vestibular adverse effects such as headache, dizziness, ataxia, and drowsiness,[14,15] and may cause phototoxicity. Tetracyclines as a class should not be used in pregnant patients or in those younger than 9 years to avoid the risks of tooth discoloration and bone growth retardation in the fetus or child.[15] One adverse effect of minocycline use is a gray-blue discoloration of the skin, particularly in inflamed areas.[20] A rare hepatitis resembling serum sickness and a reaction resembling lupus erythematosus can be associated with tetracycline use, particularly minocycline.[21] Finally, although rare, intracranial hypertension is also a serious adverse effect of tetracycline use.

In summary, orally administered erythromycin or tetracyclines are effective in the management of moderate to severe acne. However, as systemic agents, they are associated with more significant and diverse adverse effect profiles than many topical agents. These agents are increasingly associated with the development of resistance to *P acnes*.

AGENTS TO SUPPRESS SEBUM PRODUCTION

Isotretinoin (13-cis retinoic acid) is the most effective agent available for severe inflammatory acne or nodulocystic acne.[14] It is the only drug that affects all 4 pathogenic factors of acne.[22,23] Isotretinoin produces an 80% reduction in sebum excretion, comedogenesis, and ductal and surface *P acnes* within 4 to 8 weeks of use and demonstrates anti-inflammatory activity.[22] Doses of 0.5 to 1.0 mg/kg per day are typical and treatment duration is usually 20 weeks. Improvement may continue for up to 5 months after ending therapy; the physician can use this time to decide whether a second treatment course is needed. Relapse can occur in 15% of patients, particularly in younger ones.

Isotretinoin is a known teratogen. Given this, a negative pregnancy test must be obtained from female patients of childbearing potential prior to and throughout therapy, and education regarding the need for adequate contraception during and for 1 to 2 months after therapy is imperative.[23] Therapy should be started on day 2 or 3 of the menstrual cycle. Two methods of contraception are recommended from 1 month before therapy and continuing until 1 month after discontinuation of therapy. Other adverse effects of isotretinoin include anemia and/or thrombocytopenia, pruritis, exuberant granulation tissue, cheilitis, epistaxis, dry skin, ocular and vaginal dryness, arthralgia, secondary skin infection with *S aureus*, depression, and, rarely, pseudotumor cerebri and skeletal hyperostoses.[14,23] Occasionally, patients may have mildly to moderately raised liver function test results. Some of the adverse effects are treatable: dryness and irritation are treatable with emollients, while pain or stiffness of the bones and joints can be controlled with aspirin or nonsteriodal anti-inflammatory drugs. Hypertriglyceridemia is usually mild and can be controlled by dietary management and weight control. Elevations of serum triglycerides or liver enzymes may occur, but are not usually clinically significant.[22] Baseline liver function tests and fasting lipid profile are suggested, with recommendations for follow-up monitoring ranging from every 4 to 8 weeks to less frequently if baseline values are normal.[22]

NEW ANTIACNE AGENTS

During the past few years, several new agents have become available for the treatment of patients with acne vulgaris. These include new retinoids, new tretinoin formulations, azelaic acid, a new formulation of sodium sulfacetamide, and an oral contraceptive containing a second-generation progestin.

New Topical Retinoids

Retinoids encompass vitamin A (retinoic acid), its analogs, and any agent that exerts a physiological action by interacting with retinoic acid receptors and binding proteins.[23] Newer agents with retinoid activity include adapalene (Differin; Galderma Laboratories, Ft Worth, Tex), tazarotene (Tazorac; Allergan Inc, Irvine, Calif), and 2 new formulations of tretinoin with less irritation potential than current dosage forms (Retin-A Micro; Ortho Pharmaceuticals, Raritan, NJ, and Avita Cream; Penederm Inc, Foster City, Calif).

Adapalene

Adapalene is a synthetic naphthoic acid derivative with retinoid activity. It has a distinctly different chemical structure from tretinoin and in-

teracts with a unique set of receptors. It is a potent modulator of cellular differentiation, keratinization, and inflammatory processes, whose mechanism of action is believed to be similar to that of other retinoids.[24] Interestingly, adapalene has been shown to possess moderate to potent anti-inflammatory activity when compared with corticosteroids and nonsteroidal anti-inflammatory drugs in several in vitro and in vivo preclinical studies.[25] In the same models, tretinoin and isotretinoin were found to have either weak or no anti-inflammatory activity.

Several clinical studies have demonstrated that adapalene 0.1% gel is equally or more effective than 0.025% tretinoin gel (the most potent tretinoin formulation available) in reducing the number of acne lesions.[26-29] Results of a small European trial in male patients showed that 0.1% adapalene gel and 0.025% tretinoin gel were equally effective in reducing total comedo counts, while the 0.1% adapalene gel was significantly better than the 0.025% tretinoin gel in reducing inflammatory lesions and total lesion count.[29] The global assessment of efficacy showed no difference between the 2 treatments. Results of a larger multicenter European trial comparing 0.1% adapalene gel and 0.025% tretinoin gel applied once daily for 12 weeks showed comparable efficacy for the treatment of mild to moderate acne.[26]

In a US trial, Shalita et al[27] compared the same 2 regimens in patients with mild to moderate acne. Adapalene gel 0.1% produced greater reductions in noninflammatory, inflammatory, and total lesion counts than 0.025% tretinoin gel at week 12. The mean percent reductions in these types of lesions were 49% vs 37% for total lesions, 46% vs 33% for noninflammatory lesions, and 48% vs 38% for inflammatory lesions in adapalene and tretinoin gel treatment groups, respectively.

The most common adverse effects observed with adapalene are those typical of topical retinoids, including erythema, scaling, dryness, and burning. In comparative trials, 0.1% adapalene gel was better tolerated than 0.025% tretinoin gel, with a lower incidence and decreased severity of the typical local irritative symptoms.[27-30] These symptoms may be expected to occur in 10% to 40% of patients treated once daily with 0.1% adapalene gel.[25] It is possible that differences in the mechanism of action of adapalene at the molecular level compared with that of tretinoin may account for its more favorable tolerability profile.[31]

Tazarotene

Tazarotene is a synthetic acetylenic retinoid which, when applied in a topical, nonalcoholic gel formulation, rapidly penetrates into the skin, where it is immediately converted into its active metabolite, tazarotenic acid, which binds to nuclear retinoic acid receptors.[11,32] The binding to these receptors affects the expression of genes involved in cell proliferation, cell differentiation, and inflammation. At the cellular level, the result may be a modification of several acne pathogenic factors, including the accumulation and cohesion of corneocytes and inflammation.

Both the 0.1% and the 0.05% topical gel formulations of tazarotene have been shown to be significantly more effective than vehicle in 2 large-scale clinical studies.[11] Both concentrations of tazarotene produced greater reductions in the number of noninflammatory lesions and in the number of total lesions than did vehicle gels. The 0.1% gel also caused a significant reduction in the number of inflammatory lesions. In general, the 0.1% gel was more effective than the 0.05% preparation in reducing the number of acne lesions. In another study, the treatment success rate at week 12 was significantly higher in the 0.1% tazarotene gel-treated group (68%) compared with the vehicle-treated group (40%).[33]

The adverse effects reported in these trials were those typical of topical retinoids, including erythema, pruritus, burning, and stinging. These were dose related and mostly mild to moderate in severity. It has been postulated that differences in tazarotene's molecular mechanism of action compared with other topical retinoids may lead to less local irritation.[32] However, there are no comparative trials with other topical retinoids to confirm this. Results of human dermal safety studies have shown no evidence of allergic sensitization, phototoxicity, or photosensitization with tazarotene.[11] Tazarotene has also been approved for the treatment of psoriasis.[34-36]

NEW TRETINOIN FORMULATIONS

Tretinoin Gel Microsphere

Tretinoin gel microsphere 0.1% (Retin-A Micro) is a formulation that uses a novel delivery system designed to improve the tolerability of topical tretinoin. This system, also currently used in cosmetic, sunscreen, and prescription products, consists of macroporous beads approximately 10 to 25 µm in diameter.[38,39] Tretinoin is incorporated into these spongelike spheres, or microsponges, and is gradually released over a sustained period.[39,40] This may permit a more targeted delivery of tretinoin to the upper layers of the skin, primarily the epidermis, by holding the bulk of the applied product on the skin's surface. These properties may limit irritation and consequently increase patient compliance, while retaining tretinoin's effectiveness. Reductions in dose or administration frequency are also treatment possibilities that should further enhance compliance.

In a large-scale, 12-week study of patients with acne, the 0.1% tretinoin microsphere–treated group exibited significantly greater reductions in inflammatory, noninflammatory, and total number of lesions than the vehicle-treated group.[39] Mild erythema and mild to moderate peeling peaked during the initial 2 weeks of therapy, yet these symptoms practically disappeared by week 4. During this time, no more than 3% of patients had scores indicative of a severe irritation rating.[41] In a second, 14-day study evaluating tolerability only, a split-face comparison was made with a commercial 0.1% tretinoin cream formulation. The microsphere for-

mulation was significantly better tolerated and less irritating than the 0.1% cream and, by the end of the study, 92% of the patients preferred the microsphere formulation.[39] Additionally, a cumulative 21-day irritation evaluation in subjects with normal skin also showed that 0.1% tretinoin gel microsphere had a lower irritation profile than 0.1% tretinoin cream.[41]

Tretinoin Polymer Cream

Tretinoin cream 0.025% (Avita) is a formulation of tretinoin and a liquid polymer compound called polyolprepolymer-2 (PP-2). Polyolprepolymer-2 is composed of large polymer molecules that can modify topical drug delivery by retaining the drug on and in the upper layers of the skin and within the pilosebaceous unit.[42] Theoretically, limiting drug migration into deeper layers of the epidermis may reduce tretinoin-induced irritation.[38] Results of a preclinical study using a hamster ear model demonstrated that a tretinoin formulation containing PP-2 reduces the penetration of tretinoin into the epidermis and dermis while allowing selective drug delivery to the pilosebaceous unit.[42]

The results of several comparative trials demonstrate that tretinoin formulations containing PP-2 are comparable in efficacy with commercially available formulations of tretinoin in the treatment of mild to moderate acne.[43,44] Specifically, 0.025% tretinoin cream containing PP-2 was as effective as the commercial 0.025% tretinoin cream in a 12-week multicenter study for mild to moderate acne.[43] A similar study demonstrated comparable efficacy between the 0.025% tretinoin gel formulation containing PP-2 and the commercial 0.025% tretinoin gel.[44]

Patch test studies in humans have demonstrated that tretinoin formulations containing PP-2 produce less irritation than seen with currently available tretinoin formulations. Similarly, the results of a randomized, double-blind, split-face study comparing 0.025% tretinoin gel containing PP-2 with the currently available 0.025% gel formulation showed less overall irritation associated with the formulation containing PP-2. The PP-2–containing formulation may be better tolerated and produce less cutaneous irritation. It should be noted that only the cream formulation of tretinoin containing PP-2 is currently available.

AZELAIC ACID

Azelaic acid (Azelex; Allergan Inc) is a dicarboxylic acid that was first developed for use in the treatment of benign hyperpigmentation disorders. It has been used in the treatment of acne in Europe for several years, but has also demonstrated efficacy in the treatment of hyperpigmentary disorders and rosacea.[45-50] Azelaic acid is structurally unrelated to any of the conventional acne therapies. It possesses bacteriostatic properties in vitro against a variety of aerobic and anaerobic microorganisms, including *P acnes* and *Staphylococcus epidermidis*.[50-52] Two to 3 months of treatment with azelaic acid can reduce follicular microbial colonization by more than 97%.[53-55] Azelaic acid does not seem to induce microbial resistance, even with prolonged exposure.[51] In addition to antimicrobial properties, azelaic acid has a significant ability to normalize keratinization.[50] It also decreases superoxide anion and hydroxy radical generation by neutrophils, which may contribute to its ability to reduce inflammation.[11]

In controlled comparisons with active agents, administration of topical 20% azelaic cream twice daily for 5 or 6 months was comparable in efficacy to topical 5% BPO gel, 0.05% tretinoin cream, and 2% erythromycin cream in patients with comedonal or mild to moderate inflammatory acne.[50] A good-to-excellent clinical response (an approximately 50% decrease in noninflamed and/or inflamed lesion counts) was achieved in 65% to 85% of patients with comedonal or mild to moderate inflammatory acne when treated with azelaic acid or the other antiacne agents.[46,50,56-58] In these studies, the overall time-response relationship for lesion count reduction was similar to the antibiotics studied, but somewhat slower than that of BPO.[46,56] Azelaic acid is also effective when combined 15% and 20% glycolic acid lotions, as this combination therapy has been demonstrated to be at least as effective as 0.025% tretinoin cream in reducing lesion counts and in overall global improvement.[59]

Many animal and human studies have demonstrated that azelaic acid exhibits no systemic toxicity after either oral or topical administration.[46,50,52] There are no reports of teratogenicity and it is classified as pregnancy category B. The most frequent adverse effects with topical use are mild transient erythema and cutaneous irritation, characterized by scaling, pruritus, and a mild burning sensation. These effects are clinically noteworthy in 5% to 10% of patients and usually subside after 2 to 4 weeks of treatment. The rate of local adverse effects with azelaic acid is lower than that observed with BPO or tretinoin.[56,58,60] Combining 20% azelaic acid cream with 15% and 20% glycolic acid lotions does not produce increased irritation; in fact, this combination produced less irritation than 0.025% tretinoin cream.[59]

Because azelaic acid can lighten skin, there is the possibility that bleaching of the normal skin color can occur; however, evidence from preclinical and clinical studies suggests that this is not harmful.[46] Based on the results of the Kaidbey and Kligman test for phototoxicity, the modified Draize test for photoallergy, and postmarketing drug safety surveillance data, azelaic acid does not pose any particular risk of phototoxicity or photosensitivity.[46] Finally, incubation of *P acnes* and *S epidermidis* with sublethal concentrations of azelaic acid for 1272 hours does not induce resistant mutants or phenotypically adapted strains.[51]

NEW SULFACETAMIDE FORMULATION

Sodium sulfacetamide is an antibacterial agent that has been used in antiacne preparations for many years. It is believed to block bacterial growth by acting as a competitive antagonist of para-aminobenzoic acid. A new formulation of sodium sulfacetamide without sulfur has recently become available. This is a

lotion containing 10% sodium sulfacetamide in an aqueous base (Klaron Lotion; Dermik Laboratories Inc, Collegeville, Pa). The lack of sulfur and alcohol in this new product may decrease its potential to cause local irritation in comparison with existing sodium sulfacetamide–containing products.

No published clinical trials are available evaluating the efficacy or safety of this new formulation of sodium sulfacetamide. However, hypersensitivity reactions are the most significant adverse effects associated with products containing sodium sulfacetamide. Though rare, reactions such as Stevens-Johnson syndrome or exfoliative dermatitis can be severe or life-threatening and patients must be monitored carefully for any signs of sensitivity. Use of any product containing sodium sulfacetamide is contraindicated in patients with a known sensitivity to sulfonamides. However, the manufacturer's labeling for the product states that in controlled clinical trials, adverse reactions associated with the use of 10% sodium sulfacetamide lotion were infrequent and restricted to local events.[61] The total incidence of adverse reactions reported in these studies was less than 2%. Only 1 of 105 patients treated with 10% sodium sulfacetamide lotion had adverse reactions of erythema, itching, or edema. Safety studies demonstrated that sodium sulfacetamide lotion possesses a low or minimal potential for irritation and no detectable potential for contact sensitization or phototoxicity under the conditions tested. Additional clinical studies investigating the safety and efficacy of 10% sodium sulfacetamide lotion compared with other topical antibiotics are in progress.

CLINDAMYCIN/BPO TOPICAL GEL

This new antiacne treatment is a combination product of 1% clindamycin and 5% BPO (Clindoxyl gel; Steifel Research Institute, New York, NY). Unlike other antibiotic/BPO combination products, this combination gel does not require refrigeration. It is currently awaiting approval from the FDA.

Recently, the combination of clindamycin and BPO has been reported to be efficacious in controlling acne and superior to either individual agent used alone.[62] In these double-blind, randomized, parallel, vehicle-controlled trials, patients were treated for 11 weeks with a nightly application of 1% clindamycin gel, 5% BPO gel, or the combination gel. Efficacy was determined by lesion counts and assessment of global response. With the combination product, the mean reduction of inflammatory lesions was significantly greater than vehicle at weeks 2, 5, 8, and 11 and significantly greater than each of the individual ingredients at weeks 8 and 11.

In this study, safety was evaluated by reporting adverse effects and scoring of irritancy parameters. All of the study preparations were well tolerated and received excellent overall tolerance ratings from 95% of the patients. The only adverse event reported in the clindoxyl group was a transient, slight stinging on initial application.

ORAL ESTROGEN/PROGESTIN

The beneficial effects of oral contraceptives on acne have been noted for many years.[5] Oral contraceptives are thought to exert their antiacne effect by decreasing the amount of circulating androgens.[9] Specifically, they have been shown to increase sex hormone–binding globulin and decrease free testosterone in healthy women.[63-65] In addition, the estrogen component may decrease the production of ovarian androgens by suppressing the secretion of the pituitary gonadotrophins.[65] The triphasic, combination oral contraceptive, norgestimate-ethinyl estradiol (Ortho Tri-Cyclen; Ortho, Raritan, NJ) is the first low-dose oral contraceptive to receive Food and Drug Administration approval for the treatment of acne. Antiandrogenics such as spironolactone (usually 50 to 100 mg/d) may be used for women with the history of new-onset or worsening acne in their adult years, for patients who report premenstrual flare-ups, and for women whose conditions have not responded to standard systemic antiacne treatments. Those women who typically benefit from treatment have moderately severe papular or small nodular lesions on the lower face and neck. Maximal clinical improvement is usually seen after only 2 to 3 months of use. Some oral contraceptives are better than others (the less adrogenic progesterones norgestimate and desogestrel), but almost any oral contraceptive will produce beneficial effects.

The efficacy of the norgestimate-ethinyl estradiol combination in the treatment of acne was demonstrated in 2 large 6-month placebo-controlled trials.[65,66] In each study, the active group was significantly better than the placebo group for all primary efficacy measures: inflammatory lesions (mean reduction, 51.4% vs 36.4% and 62% vs 38.6%), total lesions (mean reduction, 46.4% vs 33.9% and 53.1% vs 26.8%), and investigator's global assessment (83.3% vs 62.5% improved and 93.7% vs 65.4% improved). No significant adverse effects were reported in these trials. The most common adverse effects associated with oral contraceptives are nausea, vomiting, breakthrough bleeding, weight gain, and breast tenderness. Rare but serious adverse effects include hypertension, thrombophlebitis, and pulmonary embolism. The use of spironolactone may cause irregular menses and increased breast tenderness. Low-dose corticosteroids can suppress adrenally produced androgens. Finally, systemic antibiotics change GI tract flora, which may result in decreased absorption of estrogen, thereby potentially compromising the efficacy of oral contraceptives.

ROLE OF NEW ANTIACNE AGENTS IN TREATMENT STRATEGIES

The new topical retinoids are at least equal in efficacy compared with existing topical retinoid preparations. More importantly, these agents may offer an advantage over existing topical retinoids in decreasing local irritation. Local irritation is the most common adverse effect associated with existing topical retinoids and can result in discontinu-

ation of therapy or other compliance problems. The newer agents may therefore improve compliance and, consequently, success of therapy. They are most appropriate for patients with mild to moderate comedonal and mixed inflammatory acne. Clinical experience may help dictate the proper choice among them for specific patients.

Because they are one of the few treatment modalities that affect the hormonal aspect of acne pathogenesis, and, indirectly, sebum production, oral contraceptives are an appropriate treatment option for female patients with moderate acne and no contraindications to hormonal therapy.[65,67,68] They may be particularly useful for patients who also desire contraception or whose acne is secondary to a hyperandrogenic disorder.[68]

Based on the results of comparative clinical trials and its favorable safety profile, azelaic acid may be an appropriate first-line treatment for mild to moderate acne. Azelaic acid can be continued as maintenance therapy after an oral antibiotic is tapered. Given its favorable tolerability profile, azelaic acid is a suitable choice for patients with sensitive skin. Its dual mechanism of action and efficacy in hyperpigmentary disorders also make it particularly useful for patients with combination acne or those who are prone to hyperpigmentation (eg, patients with darker complexions). Finally, because azelaic acid has no known interactions with other topical antiacne agents, it can be effectively used in combination therapy. This property gives physicians greater flexibility when developing individual treatment regimens.

The new formulation of sodium sulfacetamide (Klaron Lotion) is also an appropriate first-line treatment for mild to moderate inflammatory acne in patients with no known hypersensitivity. It can also be safely used in combination therapy with BPO, retinoids, oral antibiotics, or hormonal therapies, particularly in patients with sensitive skin. Because the development of resistant strains of *P acnes* has been primarily associated with erythromycin and tetracyclines, sodium sulfacetamide may be well-suited for patients who are resistant to other antimicrobial agents.[14,17-19]

AREAS OF NEED IN ACNE MANAGEMENT

In all situations, the primary goal of acne treatment is maximization of efficacy with the minimization of the risk of adverse effects. In the management of acne, a variety of established therapies with different mechanisms of action are available to accomplish this goal. However, successful treatment with these agents is sometimes limited by tolerability or resistance problems. For example, topical tretinoin is often associated with local irritation that can present a compliance problem for some patients. Benzoyl peroxide is also a local irritant and can bleach clothing. Topical and systemic antimicrobial agents may sometimes lose efficacy because of the development of resistant strains of *P acnes*. In addition, oral antimicrobial agents are associated with systemic adverse effects (primarily GI), which can result in compliance problems. Finally, isotretinoin is associated with several systemic adverse effects, the most significant of which is teratogenicity. Consequently, there is ample opportunity for new antiacne agents to contribute to our ability to safely and effectively manage this chronic disease.

Research can contribute to our understanding of the pathophysiology of acne. Such an understanding will facilitate the development of more effective acne therapies. For example, great strides are being made in retinoid research. As we learn more about the interaction of retinoids with the various retinoid receptors and the sequence of subsequent cellular responses, we may increase our understanding of the mechanisms involved in the development of follicular hyperkeratinization.

Apart from hormonal therapy and isotretinoin, little can be done to reduce sebum production. Sebum production is thought to be modulated in part by the androgen dihydrotestosterone. This hormone is produced from testosterone by the action of the 5-reductase enzyme. Research into the factors regulating sebum production will improve our understanding of this process and may lead to the identification of new therapeutic targets. For example, 2 isozymes of 5-reductase have been identified; type 1 predominates in human sebaceous glands.[69] If specific inhibitors of this isozyme can be developed that are safe and effective in reducing sebum production, these compounds may comprise a novel class of future antiacne agents.

Clinically, dermatologists have been aware of the development of antibiotic resistance in patients whose initial favorable response waned over time. Traditionally, antibiotics were periodically switched in an effort to regain control over the patient's acne. Additional epidemiologic studies are needed to track patterns of *P acnes* resistance to antibiotics. Data gained from such studies will aid in the development of guidelines for designing therapeutic regimens that can minimize the development of resistance.

SUMMARY

Successful management of acne requires careful pairing of individual patients with the appropriate antiacne agent(s) and individualized treatment regimens, along with appropriate patient education. A thorough patient evaluation takes into account acne severity and predominant lesion type as well as age, skin type, lifestyle, motivation, and the presence of coexisting conditions. Incorporation of these factors into the choice of a specific treatment program can enhance patient compliance and satisfaction, which is essential for the success of treatment. The recent introduction of several new agents affords greater flexibility in the treatment of acne. The availability of these new options to complement the existing ones should greatly facilitate the successful treatment of greater numbers of patients with acne with improved tolerability and patient satisfaction.

Accepted for publication October 26, 1999.

This work was supported in part by Allergan Inc (Irvine, Calif).

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