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A review of the use of combination therapies for the treatment of acne vulgaris

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Acne is a disease of the pilosebaceous unit, involving abnormalities in sebum production, follicular epithelial desquamation, bacterial proliferation, and inflammation. The major classes of therapeutic agents are topical and systemic retinoids, antimicrobial agents, and systemic hormonal drugs. Combination therapy with a topical retinoid and an antibiotic can normalize follicular epithelial desquamation and reduce bacterial proliferation. The new retinoids (eg, adapalene) have an additional antiinflammatory action along with their effect on the preclinical microcomedo and, coadministered with a topical or an oral antibiotic, are a rational initial therapy for all but the most severe forms of acne. Retinoids can also be used alone for long-term maintenance to prevent the reemergence of comedones and inflammatory acne lesions and to spare the use of antibiotics, thus helping to reduce the risk of bacterial resistance. (J Am Acad Dermatol 2003;49:S200-10.)

Acne vulgaris is the most common dermatologic disorder, affecting approximately 85% of individuals at some time between the ages of 12 and 24 years. Although acne is most prevalent in this age group, the disease is reported in 8% of adults aged 25 to 34 years and in 3% aged 35 to 44 years.[1] In the United States alone, more than 50 million people are estimated to be affected by some form of acne, with over 17 million experiencing acne vulgaris. A third of these patients require medical treatment.[2] The high prevalence of the disease results in 20% of all visits to dermatologists being for acne.

Acne can persist for many years, and although it lacks the urgency of a life-threatening condition, its long-term ramifications can be significant. The disease is physically and psychologically scarring, and sufferers often have significantly impaired psychosocial development, reduced self-esteem, and emotional distress caused by perceived disfigurement. These effects can be less related to the severity of the disease than to the patient's own perception.[3] Thus effective treatment is extremely important to reduce the severity and potential for recurrence of the disease. Most patients have both noninflammatory and inflammatory acne lesions. In mild cases, noninflammatory lesions predominate, with occasional papules or pustules, whereas moderate cases exhibit more papules and pustules. Nodular lesions dominate the most severe of cases.[2-6]

This article reviews the available treatments for acne, on the basis of their effects on the pathogenic factors that underlie the disease. There is increasing evidence that the combination of topical retinoids with topical or oral antimicrobials is a rational and effective approach for treating all but the most severe forms of acne. An algorithm is proposed for the optimal use of single and combination therapies covering the spectrum of acne symptoms and severity.

THE PATHOGENESIS OF ACNE

The pathogenesis of acne is multifactored, involving seborrhea, microbial proliferation, inflammation, and abnormal desquamation of follicular epithelium (Fig 1).[7] Excessive sebum production, brought about by hormonal changes (in particular, an increase in the production of androgens associated with the onset of puberty[2]) is followed by abnormal desquamation of follicular corneocytes. The mixture of cells and sebum creates an environment for the proliferation of *Propionibacterium acnes*. Chemotactic factors released by *P acnes* attract lymphocytes and neutrophils, as well as producing other proinflammatory molecules.[8,9] Recently, the role of Toll-like

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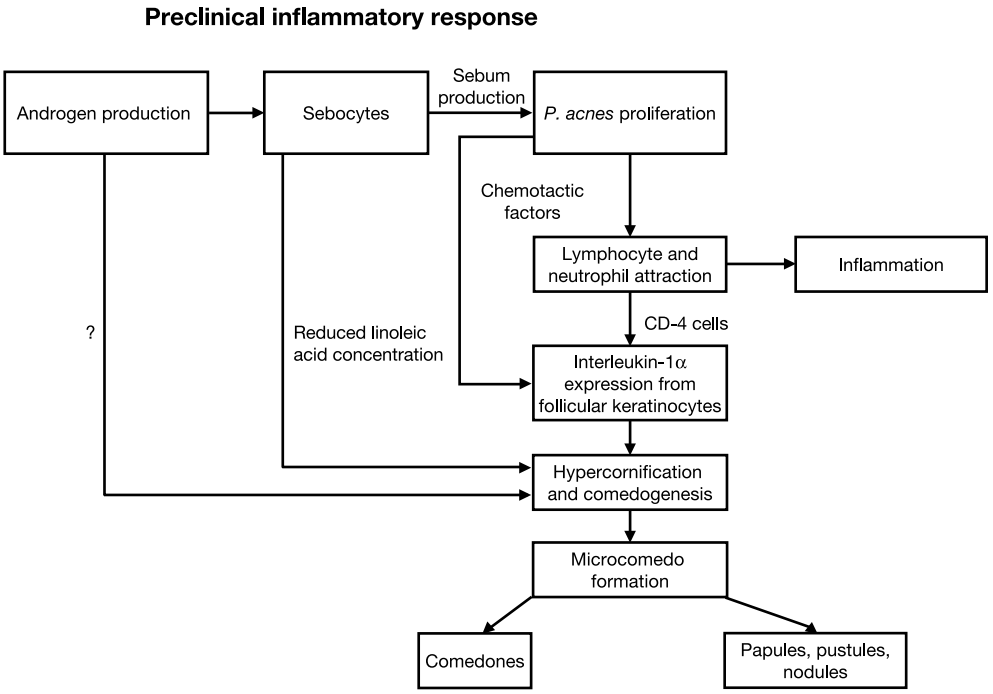

Fig 1. Proposed scheme for the pathogenesis of acne.

receptor activation by *P acnes* cell wall peptidoglycan provides a molecular explanation for inflammation in acne.[10] *P acnes* can also induce follicular keratinocytes to release interleukin-1, which causes keratinocytes to proliferate and contribute to the formation of the preclinical microcomedo.[11]

TREATMENTS FOR ACNE

Most dermatologists agree that the choice of agents used to treat acne involves the integration of multiple factors such as the severity of lesions present, duration of disease, past and present response to therapy, and tendency for scarring and postinflammatory pigmentation. Therapy is therefore tailored to the individual patient depending on the nature and severity of their acne.[12] A wide range of systemic and topical treatments are available, covering all disease variants (Fig 2). No single topical acne therapy is effective in treating all 4 of these pathogenic factors. Also, of the commonly prescribed therapies, only systemic isotretinoin and hormonal therapy (such as cyproterone acetate spironolactone, and the combinations of ethinyl estradiol with norgestimate and levonorgestrel) are effective in sebosuppression.

Topical retinoids were once believed to be limited to treating comedonal acne because of concern for aggravating the inflammatory phase. However, combinations of topical retinoids and antimicrobials are now more commonly prescribed. Systemic retinoids are used for severe inflammatory acne and in the event of treatment failure.

Systemic treatments

Oral antibiotics are highly effective for inflammatory acne, and are widely used in clinical practice. Oral retinoids are usually given in cases of severe acne, or for patients in whom inflammatory or pustular acne does not respond to other approaches.

Oral antibiotics. Oral antibiotics prescribed for acne include the tetracyclines (tetracycline, minocycline, doxycycline, and lymecycline), erythromycin, clindamycin and cotrimoxazole, all of which target *P acnes*. In addition to their antimicrobial actions, tetracycline and erythromycin also possess some inherent antiinflammatory activity. These oral antibiotics are well-established, effective agents in the management of moderate to severe acne.[12,13] However, all systemic antibiotics can be associated with gastrointestinal disturbance, vaginal candidiasis, pseudomembranous colitis, and, in the case of minocycline, vestibular disturbances as well as phototoxicity with doxycycline.[13] They have also been associated with effects on the central nervous system, such as pseudotumor cerebi and immune disturbances, such as lupus erythematous.[14] The potential emergence of bacterial resistance is also problematic.

Oral retinoids. The development of retinoid therapy for acne began with systemic therapy with oral vitamin A (retinol). This was reported to signif-

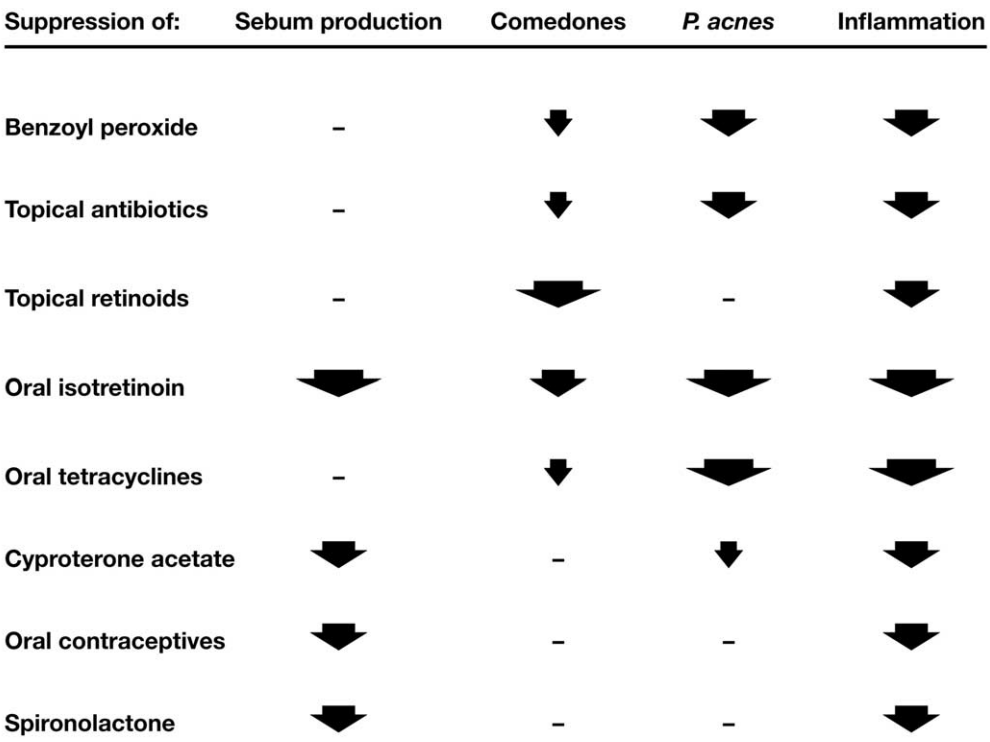

Fig 2. Acne therapies and their associated activities.

icantly reduce the number of acne lesions over a treatment period of 3 to 4 months.[15] In the late 1970s, systemic isotretinoin was found to be extremely effective for severe nodulocystic acne and for patients who are unresponsive to other therapies. This therapy is extremely effective in treating severe acne, being the only agent that affects all areas of acne pathophysiology. If there were not significant side effects, this agent would be the ideal treatment for acne.

Topical treatments

Topical treatments are generally recommended for mild to moderate acne. Many types of drugs are used, some being available over-the-counter in certain countries. The most frequently prescribed products are antibiotics and retinoids, with other agents including benzoyl peroxide, salicylic acid, azelaic acid, and alpha-hydroxy acids.

Topical antibiotics. Topical antibiotics, including clindamycin and erythromycin, are available in a number of forms, including solutions, lotions, gels, and saturated pads, as well as in combination with benzoyl peroxide. These agents reduce the population of *P acnes* in the pilosebaceous duct and have a mild comedolytic effect, reducing *P acnes* and interleukin-1 production. They also demonstrate a mild antiinflammatory effect by suppressing leukocyte chemotaxis.[16] In clinical trials with topical and systemic antibiotics, a small (20%) but consistent reduction in the number of comedones was reported. This contrasts with a 60% reduction reported with tretinoin, adapalene and tazarotene.[17] All topical antibiotics can cause some measure of irritation, but other adverse effects are less significant than is the case for systemic antibiotics.[16]

Topical retinoids. Retinoids are the most effective "comedolytic" agents for the treatment of acne. These agents target comedogenesis by normalizing desquamation of the follicular epithelium, preventing the formation of new microcomedo precursor lesions, thus minimizing the formation of both inflammatory acne lesions and comedones. They also promote the clearing of preexisting comedones.[15] Topical retinoids are ideal for targeting the microcomedone, the primary lesion in acne, before they become inflammatory lesions or comedones.

In the past, topical retinoids were primarily used in patients with comedonal (noninflammatory lesions) acne.[13,18] However, topical retinoids also demonstrate activity in inflammatory acne by direct immunomodulatory effects and by reversing the microcomedo, the precursor of both inflammatory and noninflammatory lesions.[19] Consequently, clinical studies have shown that topical retinoids are effective in the treatment of both inflammatory and noninflammatory acne lesions. With the advent of the

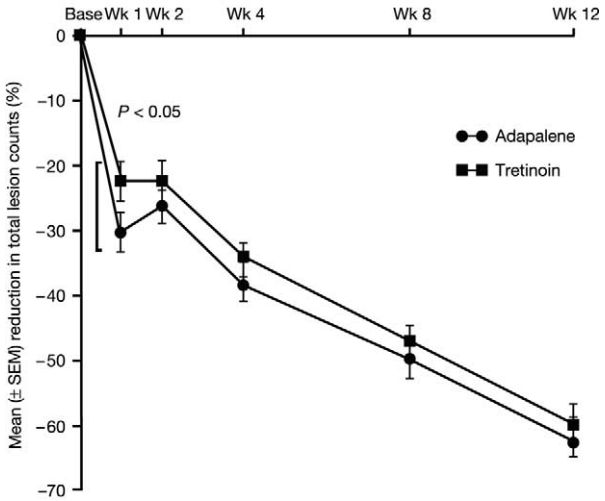

Fig 3. Efficacy of adapalene versus tretinoin: percentage change in total lesion counts from baseline after 12 weeks of treatment with adapalene 0.1% gel and tretinoin 0.025% gel: combined results from 5 randomized trials. Reprinted with permission from the *British Journal of Dermatology*.[24]

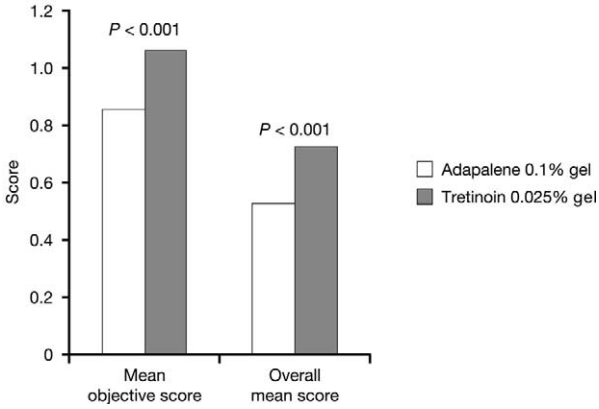

Fig 4. Tolerability of adapalene versus tretinoin: mean objective score and overall mean score for side effects reported with adapalene 0.1% gel and tretinoin 0.025% gel: combined results from 5 randomized trials.[24] Mean objective score = average score among erythema, scaling and dryness. Overall mean score = average score among erythema, scaling, dryness and burning and pruritus (immediate or persistent).

more tolerable topical retinoids this gives them the potential to be initiated together with antimicrobials from the start of therapy for inflammatory acne, rather than their present perceived use to clear mainly comedones after an initial course of therapy with antibiotics.

Topical retinoids have been prescribed for more than 30 years in the treatment of acne vulgaris, with topical tretinoin the first agent to be used.[20] First-generation compounds included retinol (vitamin A) and metabolic derivatives, such as retinaldehyde, all-*trans*-retinoic acid (tretinoin) and 13-*cis*-retinoic acid (isotretinoin). After these, second-generation monoaromatic compounds were developed. These are synthetic analogues to first-generation compounds, in which a portion of the molecule is altered. More recently, the development of polyaromatic third-generation retinoids, in which the basic molecule is extensively modified, resulted in compounds such as adapalene, arotinoid, and tazarotene.[21,22]

Tretinoin has been the mainstay of topical retinoid therapy for decades. However, its use has been limited by the occurrence of pustular flaring in some, and irritation shortly after initiation of therapy, particularly in sensitive skinned patients.[23] Local irritation is less of a problem with the third-generation topical retinoids that have been introduced recently, such as adapalene.

Several clinical trials have compared adapalene with tretinoin, and a metaanalysis has been conducted of 5 trials involving a total of 900 patients.[24] After 12 weeks of therapy, results showed that both agents were equally effective in reducing the total number of acne lesions, but adapalene had a faster onset of action (Fig 3), and was associated with significantly less skin irritation (Fig 4). Although mild irritation was reported for both treatment groups specific irritancy tests have confirmed that adapalene has a low potential for causing skin irritation and causes significantly less irritation than tretinoin.[25] This may be because adapalene has intrinsic antiinflammatory activity that may lessen the irritant effect and enhance tolerability.

In a clinical trial comparing tazarotene 0.1% gel and tretinoin 0.1% microsponge gel, tazarotene treatment was associated with a significantly greater incidence of treatment success and reduction in noninflammatory lesions than tretinoin.[26] However, tazarotene treatment was not associated with any clinically meaningful increase in tolerability. Indeed, a short-contact method of applying tazarotene has recently been studied in a randomized, vehicle-controlled trial in an effort to reduce skin irritation to tazarotene.[27] Although tazarotene was more efficacious than placebo local skin irritation was reported by a significant number of patients receiving tazarotene.

Topical retinoids can effectively reduce the number of comedones and inflammatory lesions. Studies using topical retinoids as monotherapy have shown not only significant reductions in comedones, but also a significant reduction in papulopustular lesions (Fig 5).[28-30] Fig 6 illustrates the effect of topical retinoid therapy on moderate inflammatory facial acne

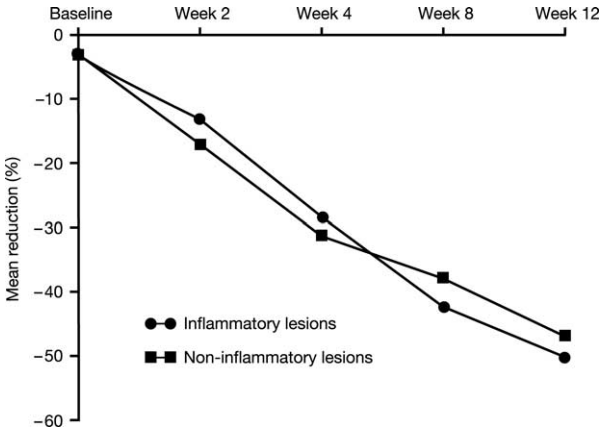

Fig 5. Efficacy of adapalene gel 0.1% in reducing inflammatory and noninflammatory acne lesions. Modified with permission from Mosby.[26]

lesions over a 12-week treatment period. The benefit of all topical retinoids in the inflammatory phase of acne is most likely due to their effect on the microcomedo, the precursor stage of both inflammatory and noninflammatory lesions. The recently described effect in down-regulation of Toll-like receptor expression is a new finding that supports the potential for benefit in inflammatory acne.[10]

Benzoyl peroxide. Benzoyl peroxide is frequently used as a first-line therapy for mild to moderate acne. It has been recognized as an effective antiacne therapy for many years and is available over-the-counter (in some countries) and as prescription preparations with a variety of vehicles. Benzoyl peroxide has a strong antibacterial effect and can significantly reduce colonization of *P acnes*, with no evidence to date of acquired bacterial resistance. However, benzoyl peroxide can cause skin irritation and drying[31,32] and in 1% of patients, contact allergy may develop.[33] It may also cause bleaching of clothes. Also, benzoyl peroxide has only very mild comedolytic properties.[34]

Other products. Salicylic acid is keratolytic and may help to combat comedones by breaking down follicular plugs and by reducing the rate of follicular desquamation. It is used in 5% to 10% preparations and may be used as an adjunct to other therapies. However, it is also an irritant, causing erythema and peeling,[29,35] and even exacerbations of inflammatory acne lesions.

Azelaic acid is a naturally occurring dicarboxylic acid that inhibits DNA synthesis of keratinocytes and is reported to have comedolytic activity.[36,37] It is also reported to have some antimicrobial effects on *Staphylococcus epidermidis* and *P acnes*.[2] However, its action is dose dependent and at higher concentrations, some burning can occur.[6] One isolated European study indicated that a 20% azelaic acid preparation applied 3 times per day was as effective as topical or systemic antibiotics,[38] but these results have not been confirmed.

Alpha-hydroxy acids are reported to offer some improvement for acne, but there is a paucity of data to demonstrate the benefit of this class of drugs.[6]

THE RATIONALE FOR COMBINATION THERAPIES

Because of the multifactorial nature of the pathogenesis of acne, a combination of different classes of drugs that affect different areas of pathophysiology makes sense. No single therapy is able to counter the growth of *P acnes* inflammation and comedogenesis as effectively as antibiotics and retinoids in combination.[1,19,23]

CLINICAL STUDIES ON COMBINATION THERAPIES

Clinical studies have assessed the efficacy and safety of combination medications for acne. These studies demonstrate significantly greater and faster results with the combination therapy than with the single agents alone. Combinations of topical antibiotics plus topical benzoyl peroxide, topical retinoids plus topical or oral antibiotics, and topical retinoids plus topical benzoyl peroxide and antibiotics have all been investigated.

Topical antibiotic plus benzoyl peroxide

A combination of the topical antibiotic, erythromycin, and benzoyl peroxide (Benzamycin) was reported to have an additive effect compared with administration of either agent as monotherapies.[39] Similar results were reported with a combination gel of clindamycin and benzoyl peroxide.[40,41] Although both agents are effective against *P acnes*, bacterial growth is only a single factor in the complex pathogenesis of acne. In terms of treating comedones, the combination is not optimal, as both benzoyl peroxide and antibiotics are only mildly comedolytic. However, these combinations do prevent the emergence of resistant strains of *P acnes* and are a good choice for combination with topical retinoids. Drug combinations that treat bacterial colonization, have antiinflammatory effects and control comedogenesis (eg, an antibiotic-retinoid combination) are more rational and effective strategies.[1,19,23]

Combination therapies with topical retinoids

Topical retinoids have been combined with oral or topical antibiotics or benzoyl peroxide with the aim of more effectively treating comedones and inflammatory acne lesions. The mechanisms of action of the drugs are complementary. Retinoids are

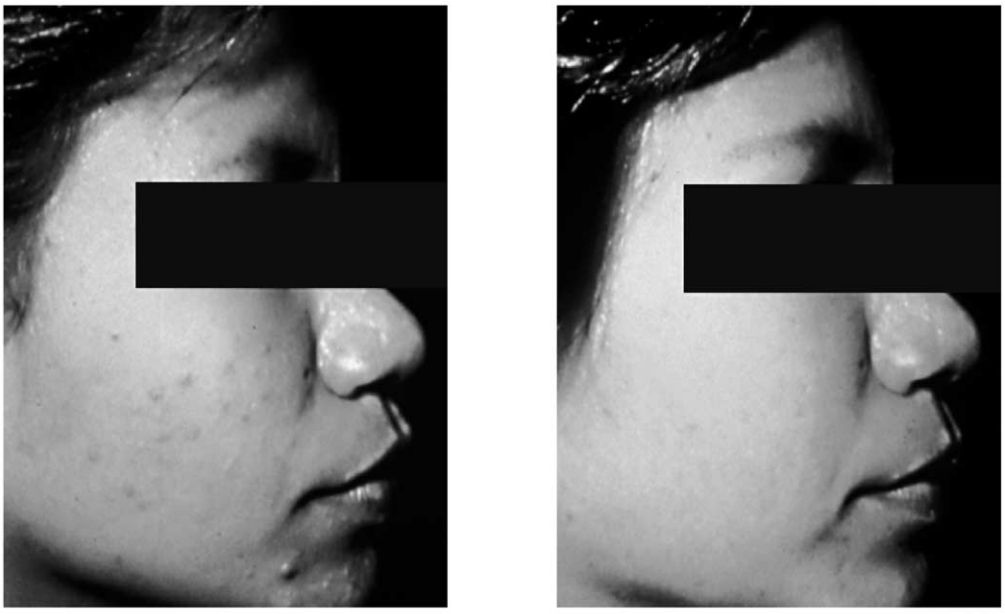

Fig 6. Effect of topical retinoid monotherapy on moderate inflammatory facial acne lesions.

comedolytic and antiinflammatory, antibiotics are antimicrobial, antiinflammatory, and mildly comedolytic (by mechanisms different to those of retinoids), and benzoyl peroxide is antimicrobial and mildly comedolytic. These complimentary actions of the retinoids and antimicrobials may help to explain the significantly greater and faster results obtained with the combination therapy. Both comedones and inflammatory lesions demonstrate greater reductions during treatment with the combination of an antibiotic plus a topical retinoid compared with either agent used alone.[42-45] As a result of the action of normalizing desquamation and reducing comedogenesis, topical retinoids also allow other topical therapies to penetrate more effectively into the subcutaneous follicle and thus treat bacterial colonization more effectively.[20]

Topical retinoids combined with topical antibiotics. Topical retinoids in combination with topical antibiotics, particularly clindamycin and erythromycin, have been demonstrated in numerous clinical trials to be more effective than either agent given alone for patients with mild to moderate acne.[42,44,46] The concurrent use of topical clindamycin with the topical retinoid tretinoin has been shown to be more effective in reducing lesion counts than either agent used as monotherapy. In a study of 64 patients, topical clindamycin gel 1% was combined with topical tretinoin gel 0.025%, and the results were compared with those from the individual therapies. After 8 weeks of treatment, patients receiving combination therapy showed a numerical improvement in both comedone and inflammatory lesion counts over the patients receiving tretinoin alone and a significant improvement over those with clindamycin alone.[44] The combination was better tolerated than tretinoin alone, possibly because clindamycin is believed to decrease the irritant effects of tretinoin.[46] Published as a study in this supplement, a recent clinical trial has shown that the combination regimen of clindamycin topical lotion 1% plus adapalene gel 0.1% was significantly more effective than clindamycin plus vehicle for the treatment of mild to moderate acne vulgaris.[42] With the adapalene combination, total, inflammatory and noninflammatory acne lesions were all significantly reduced in number, a significantly greater and faster efficacy response was seen, and no significant tolerability burden was reported. Fig 7 illustrates the effect of clindamycin and adapalene combination therapy on mild inflammatory facial acne lesions over a 12-week treatment period.

Inflammatory acne of moderate severity was shown to respond well to sequential use of topical tretinoin 0.05% and topical erythromycin 2%, with clinical improvements in papules, pustules and comedones.[15,45] The combination was synergistic and well tolerated. Trials have also been carried out on gel preparations containing tretinoin 0.025% plus erythromycin 4% in a combined formulation. A 14-

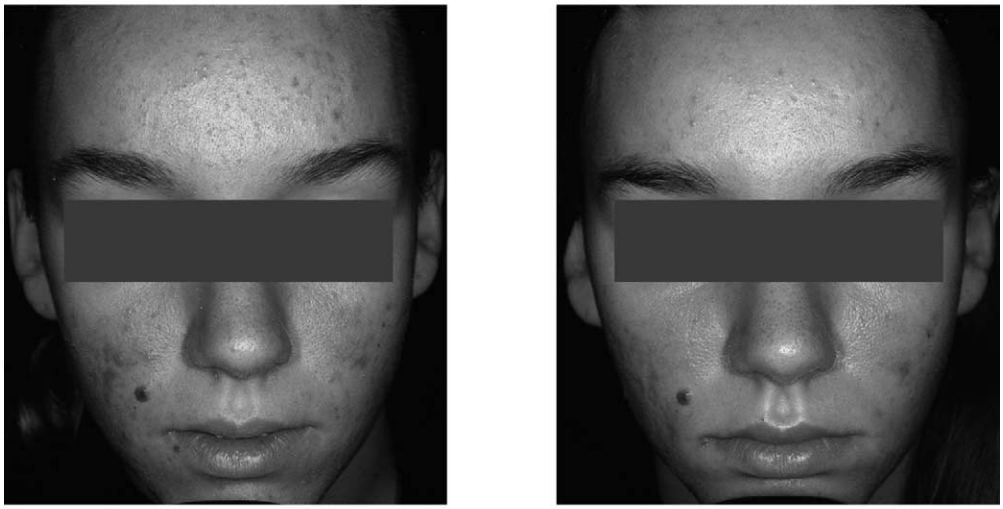

Fig 7. Effect of clindamycin plus adapalene combination therapy on mild inflammatory facial acne lesions.

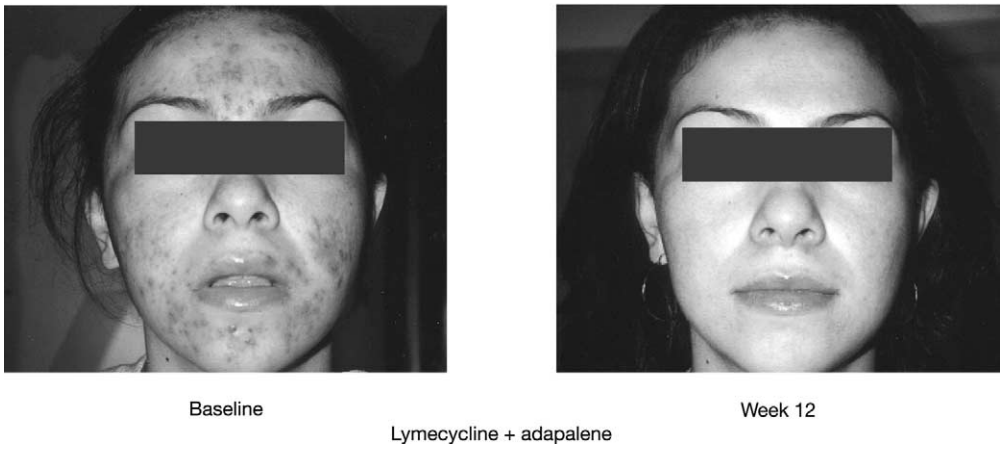

Fig 8. Effect of lymecycline plus adapalene combination therapy on facial acne lesions.

week, open, multicenter trial in 1324 general practice patients confirmed the good efficacy and tolerability profile of this retinoid-antibiotic combination. However, in this case, no direct comparisons were made with the individual agents as monotherapy.[47]

Retinoids combined with oral antibiotics. Combination therapies including topical retinoids and oral antibiotics also have a role to play in the treatment of moderate and severe inflammatory acne. The oral antibiotics tetracycline, doxycycline, minocycline and lymecycline are used in clinical practice in combination with topical tretinoin or adapalene to treat such cases.[13] Topical tretinoin in combination with oral tetracycline resulted in increased efficacy and a faster therapeutic response in reducing *P acnes* in the first 2 weeks of use than when either agent was given as monotherapy.[48] The combination of topical tretinoin and oral tetracycline was also more effective than either drug given alone.[49] Published as a study in this supplement, a recent clinical trial investigated the clinical profile of the combination of adapalene and lymecycline (tetracycline available in Europe) for acne vulgaris.[43] The combination of adapalene gel 0.1% and lymecycline produced a faster and a significantly greater reduction in the number of comedones, inflammatory and noninflammatory lesions, as well as total lesions than lymecycline alone in patients with moderate to moderately severe acne vulgaris. Fig 8 illustrates the effect of lymecycline and adapalene com-

bination therapy on facial acne lesions over a 12-week treatment period.

Retinoids combined with benzoyl peroxide. Combination therapy with topical retinoids and benzoyl peroxide exploits the same underlying principles as that with topical retinoids and topical antibiotics. The efficacy of such combinations, in particular tretinoin with benzoyl peroxide, has been demonstrated.[50] In an open study of 400 patients with moderate to severe acne, 88.1% of those receiving a combination of tretinoin and benzoyl peroxide achieved 80% to 90% clearing of acne lesions after 6 to 8 weeks of therapy. Both of these agents are irritants, and so common clinical practice is to apply the first drug in the morning and the other at night to minimize skin irritation. In fact, in this study, the combination of tretinoin and benzoyl peroxide resulted in less irritation than when tretinoin was used as monotherapy. Also, a 21-day patch test study has shown that adapalene can be coadministered with benzoyl peroxide, clindamycin, and erythromycin with little or no evidence of irritancy compared with significantly higher levels reported with similar tretinoin combinations.[51]

Topical retinoid plus a combination of benzoyl peroxide and topical antibiotic. Treatment with a topical retinoid and a benzoyl peroxide–antibiotic combination has been described as a sequential rather than a combination treatment. Because of the possibility of chemical incompatibility, the first agent has to be applied in the morning and the other in the evening. Sequential use of tretinoin and a combination of benzoyl peroxide and erythromycin (Benzamycin) has demonstrated superior efficacy than any of the 3 products used as monotherapy.[52] In a 10-week study, proportional reductions in mean comedone counts were similar for the combination and tretinoin groups. However, proportional reductions in inflammatory lesions were 65% in the combination group compared with approximately 30% in the tretinoin group.

Incidence of antibiotic resistance

In any treatment regimen that uses antibiotics, the potential for bacterial resistance is of considerable concern. Strains of *P acnes* resistant to erythromycin are reported to be on the increase, as is cross-resistance to erythromycin and clindamycin.[13] Erythromycin-resistant strains of *P acnes* have been reported to be present in 51% of patients treated with oral erythromycin and 42% of patients treated with topical clindamycin (in patients previously treated with oral erythromycin), compared with 3% of untreated control subjects. A major concern is the potential transfer of antibiotic resistance to other organisms for which erythromycin may be prescribed, including *Staphylococcus*, *Chlamydia*, *Legionella*, and *Campylobacter sp*.[53]

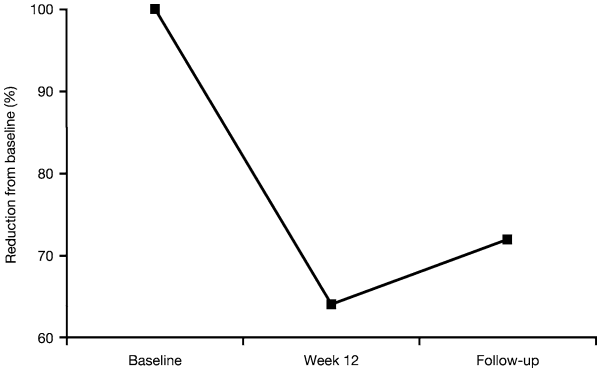

Fig 9. Importance of maintenance therapy to prevent the recurrence of inflammatory acne lesions: reduction in microcomedone counts with 0.025% tretinoin. Reprinted with permission from the *British Journal of Dermatology*.[55]

However, combination therapy that incorporates benzoyl peroxide with an antibiotic has been reported not to promote resistant strains. It has been suggested that, although the addition of benzoyl peroxide to the therapy can be drying or increase irritation, the 3-way combination of retinoid, benzoyl peroxide and antibiotic may be suitable for patients who require topical treatment but have previously developed resistant strains of *P acnes*[16] or require prolonged antibiotic treatment.

To minimize the potential for microbial resistance, antibiotic therapy should be stopped if possible once the formation of new inflammatory lesions has been curtailed. In my opinion, long-term maintenance therapy (>3 months) with antibiotics is no longer desirable; rather, patients should be treated with topical retinoids alone or in combination with topical benzoyl peroxide or benzoyl peroxide-antibiotic combinations. This approach minimizes the potential for developing bacterial resistance by shortening the exposure to antibiotics while providing faster and significantly greater reduction in acne lesions. This approach also helps to maintain remission without the need for long-term antibiotic therapy in many patients. It is important, however, not to stop topical retinoid therapy once the clearance of acne lesions occurs, but to maintain their use to control the relapse of symptoms. Studies are under way to investigate the hypothesis that maintenance therapy can be achieved with topical retinoids as monotherapy.

Maintenance therapy for acne

The management of acne is a long-term process, as microcomedones and subsequently comedones

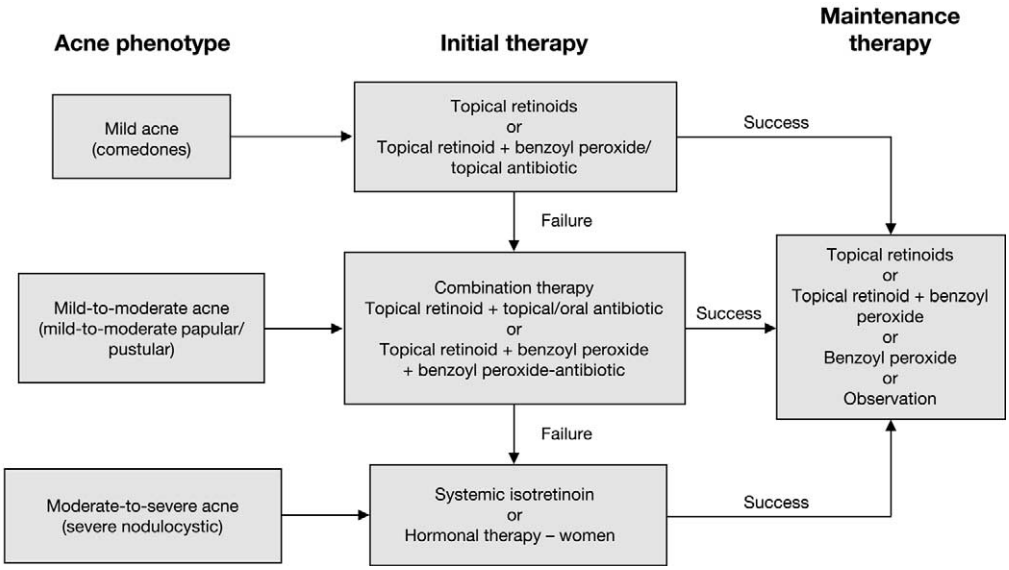

Fig 10. Proposed algorithm for the management of acne vulgaris in dermatology clinical practice.

and inflammatory lesions have been shown to return when treatment is withdrawn following successful initial therapy (Fig 9).[54,55] Antibiotics are less desirable for long-term use, because of the risk of antibiotic resistance discussed above. Maintenance therapy with topical retinoids may be effective in this situation; their comedolytic and antiinflammatory effects prevent the formation of microcomedones and subsequently noninflammatory and inflammatory lesions.

COMBINATION THERAPIES IN DERMATOLOGIC PRACTICE

An algorithm for managing acne, on the basis of clinical trial evidence, is shown in Fig 10. A stratified approach to care is recommended, whereby the selection of the initial therapy is based on the nature and severity of the patient's presenting lesions.[6,19,33] Mild acne can be treated with topical retinoids, and then by adding antibiotics or benzoyl peroxide-containing products if inflammatory lesions are present. As inflammation becomes more widespread or intense, topical retinoids and oral antibiotics make sense. With more severe acne in women, hormonal options are available, whereas for men, systemic isotretinoin is the only option. For a very large percentage of patients, perhaps as high as 80%, a topical retinoid with oral antibiotic therapy is sufficient. Adding benzoyl peroxide to the topical retinoid regimen helps to prevent emergence of resistant strains of *P acnes*. Patients in whom these therapies fail or those with more severe papular/pustular and severe nodular acne may require systemic isotretinoin. Once the initial therapy is successful, many patients can be transferred to maintenance therapy with topical retinoids to avoid long-term use of antibiotics.

OVERALL CONCLUSIONS

Acne pathogenesis involves abnormalities in sebum production, desquamation of follicular corneocytes, bacterial proliferation and inflammation. However, emerging evidence points to comedogenesis (the formation of the microcomedone) and its progression to comedones and inflammatory lesions as a central early aspect of pathophysiology. Controlling this aspect of pathophysiology is helpful, not only in eliminating acne lesions, but also in preventing relapse. Topical retinoids have significant antiinflammatory activity and tolerability profiles that make them suitable not only to treat comedones but also mild to moderate inflammatory acne lesions at the onset of treatment, when combined with topical or oral antimicrobials. These factors may also help explain the mechanism of action of topical retinoids on the maintenance of acne remission. Retinoids have been shown to reduce the migration of immune cells that release proinflammatory cytokines, which are implicated in the formation of microcomedones, in addition to their effects on clearing existing comedones and inflammatory acne lesions.

In summary, acne is a highly treatable disease. The use of combination therapies from the outset of therapy has the potential to improve treatment by producing greater and faster results and simplify management for the dermatologist, leading to

greater patient satisfaction and compliance with therapy.

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