Introduction

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This supplement has been developed to reflect the concepts presented at a recent conference on the use of combination regimens to treat acne.

Acne is a multifactoral disease of the pilosebaceous follicle. Improved understanding of the pathophysiologic features of acne has led to an increase in early initiation of treatment with a combination regimen. The multiple etiologies of acne include abnormal desquamation of follicular keratinocytes, androgen-stimulated excess sebum production, proliferation of the anaerobe *Propionibacterium acnes*, and immune and inflammatory responses.

Most acne regimens used today are a combination of treatments. All antiacne regimens should be tailored to resolve current and future acne lesions by targeting the underlying pathologies. Accordingly, the major strategies for acne therapy are to normalize keratinocyte desquamation, reduce excess sebum production, inhibit the proliferation of *P acnes*, prevent immune responses, and diminish inflammation. Because most acne treatments target only 1 or 2 of these pathogenic factors, combination therapies using drugs with complementary mechanisms of action are increasingly recognized as an effective strategy for treating acne.

A key underlying strategy in acne management is to minimize local irritation, a common complication of many topical acne treatments. Acne therapies that restore skin hydration or the epidermal barrier should be important considerations, especially when treating with a combination of topical therapies. For example, with retinoids, the choice of vehicle can be as important as the active agent itself because the inclusion of occlusive moisturizers, humectants, and emollients may help restore epidermal barrier function and improve tolerability.

Although the prevalence and pathophysiology of acne are similar, patients with darker skin types are at greater risk for developing postinflammatory hyperpigmentation than patients with lighter skin types. Combination acne regimens in this patient population should be tailored to minimize that risk by balancing early aggressive treatment with the use of products that are gentle and nonirritating. Postinflammatory hyperpigmentation is commonly managed with combinations of topical retinoids and hydroquinone.

The ideal combination regimen in the treatment of acne is one that targets the predominant underlying pathologies of the patient's condition (tailored to the individual's particular circumstances), while optimizing tolerability and limiting adverse events.

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Combination Therapy Is the Standard of Care

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Acne is a multifactorial disease characterized by abnormalities in sebum production, follicular epithelial desquamation, bacterial proliferation, and inflammation. Despite these multiple pathogenic factors, most current therapies for acne do not target all 4 areas of acne pathophysiology. Combination therapies using agents with complementary mechanisms of action increasingly are recognized as an effective strategy for treating acne. Several common regimens have shown this multiple-target efficacy, including the combination of a topical antibiotic with benzoyl peroxide. In combination, these agents produce greater and faster results than when each is used as monotherapy. For both initial treatment and maintenance therapy, the ideal combination regimen is often a topical antibiotic and benzoyl peroxide product plus a retinoid that is appropriate for the patient's skin type. Combination regimens should be tailored to the individual patient, bearing in mind the number and types of prevailing lesions and the skin type. Because the vehicle for each agent may have an impact on tolerability, one should pay attention to the combination of vehicles and patient care practices to maximize tolerability.

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The treatment goals for acne include resolving current symptoms, preventing future lesions and scarring, and treating postinflammatory hyperpigmentation.[1] These goals may be met most effectively by choosing a therapeutic regimen that targets as many of the 4 major pathogenic factors of acne as possible: (1) excess sebum production, (2) abnormal desquamation of follicular keratinocytes, (3) proliferation of *Propionibacterium acnes*, and (4) immune and inflammatory responses. Because most agents do not target all 4 pathogenic factors, combination therapies with complementary mechanisms of action are often used in the treatment of acne (Table).[2,3] The goal in designing such a regimen is to achieve optimal efficacy while minimizing the risk for adverse events (AEs).[1]

In addition to targeting the underlying pathogenesis, several patient factors require consideration when selecting an appropriate acne regimen. The severity of the patient's acne is important, with the predominance of type and number of lesions key in determining severity.[1] Other factors to be evaluated include the patient's age, skin type, coexisting medical conditions, and concomitant medications. The patient's lifestyle and level of motivation, along with the potential impact of the therapy on quality of life, also are relevant when selecting an acne regimen.

Agents That Reduce Sebum Production

No topical agent available today has been shown to reduce the production of excess sebum by sebaceous glands. Options for oral therapies to reduce excess sebum include isotretinoin and various antiandrogenic agents for women.

Isotretinoin, a naturally occurring metabolite of vitamin A, is the only agent that targets all 4 pathogenic factors of acne.[1,4] This agent inhibits sebaceous gland differentiation and proliferation, reduces sebaceous gland size, and lowers sebum excretion by 90% or more.[1,4,5] Isotretinoin also normalizes follicular epithelial desquamation, reduces comedogenesis, suppresses proliferation of *P acnes*, and possesses antiinflammatory activity.[1] Although it is uncommon to prescribe other antiacne medications with oral isotretinoin, some physicians initiate isotretinoin therapy in combination with an oral antibiotic for the first few weeks.[5]

Isotretinoin is indicated for refractory acne or severe nodular acne.[4] It also is used in patients with moderate to severe acne (with the potential to leave permanent scars), refractory inflammatory acne, and chronic acne prone to relapse.[5] Oral isotretinoin can achieve dramatic improvement in severe nodulocystic acne, with most cases responding to a single 4- to 6-month course of therapy.[5] The benefits of this therapy, however, must be weighed against its considerable AE profile and extreme teratogenic potential.

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Indications and Activity of Acne Agents*

Treatment	Target				Lesion Type		
					Non-inflammatory	Inflammatory	
	Excess Sebum	Comedogenesis	*P acnes*	Inflammation	Comedonal	Papulopustular	Nodular Cysts
Hormonal							
Oral contraceptives	√			√	√	√	√
Topical							
Antibiotics		√	√	√	√	√	
Benzoyl peroxide		√	√	√	√	√	
Retinoids		√		√	√	√	
Oral							
Isotretinoin	√	√	√	√			√
Antibiotics		√	√	√		√	√

*P acnes indicates *Propionibacterium acnes*.

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Owing to the poor safety profile of isotretinoin, some physicians urge their peers to reserve isotretinoin as last-line therapy for refractory acne or severe acne.[5] For most patients, there are many other options that work better than isotretinoin with a higher degree of safety.

AEs observed with oral isotretinoin include dry chapped lips, dry skin and eyes, secondary skin infection with *Staphylococcus aureus*, muscle aches and backaches, nosebleeds, skin fragility, hypertriglyceridemia, and elevated liver function tests. Therefore, routine monitoring of serum lipids and liver function is recommended during isotretinoin therapy. In addition, some patients can experience psychiatric effects from isotretinoin, including depression and mood swings.[5]

Given the potent teratogenicity of isotretinoin, negative pregnancy test results must be obtained before women of childbearing age may begin therapy. Therapy should be initiated on the first, second, or third day of the menstrual period after the pregnancy test results have been obtained, and adequate contraception must be used before, during, and for 6 weeks after therapy.[5]

Hormonal Therapies—Antiandrogenic therapies for acne can be used in adult female patients to counteract the increased sebum production that results from increased sensitivity to androgen stimulation of the sebaceous follicle.[5] The 3 types of hormonal therapies used in acne are estrogens, androgen receptor blockers (eg, cyproterone, spironolactone, flutamide), and agents that inhibit ovarian or adrenal androgen production (eg, oral contraceptives [OCs], gonadotropin-releasing hormone agonists, low-dose glucocorticoids).[5] Because hormonal therapies are aimed at only one pathogenic factor of acne (ie, excess sebum production), they are rarely used as monotherapy in the management of acne.

Hormonal therapies are particularly useful in women with endocrine abnormalities (eg, hyperandrogynism, hirsutism), irregular menstrual periods, a desire for contraception, or an unresponsiveness to conventional therapies.[5] Several OCs are now approved for use in acne, but no single formulation has shown superiority over another.[4,5] A recent, randomized controlled trial showed 59% and 63% reductions in acne lesion count using 2 different formulations of OCs.[6] The most significant safety considerations when using OCs include cardiovascular risks and thromboembolism, especially in cigarette smokers; more common AEs tend to be transient and mild, such as nausea, vomiting, breast tenderness, headache, breakthrough bleeding and spotting, edema, or weight gain.[4,5]

Comedolytic Agents

Topical retinoids, which normalize the desquamation process, are among the most effective comedolytic agents available.[1,5,7,8] In randomized controlled trials, these agents have been shown to result in a moderate reduction in the number of comedones, with a mild effect on inflammatory lesions.[4] It is generally agreed that topical retinoids are effective therapy for comedonal acne and can be a component of maintenance therapy to sustain acne remission.[5]

Retinoids are vitamin A derivatives that prevent the development of future comedones by normalizing the keratinization process.[4,7] The 3 major topical retinoids are tretinoin, adapalene, and tazarotene. All of these agents are keratolytic, but there are differences in their anti-inflammatory effects, tolerability, and efficacy.

Tretinoin was first shown to be effective in the 1970s.[4] Therapy with the original formulations of tretinoin was limited by poor tolerability, characterized by peeling, burning, erythema, itching, and dryness.[5,9] These effects are dose related and vehicle related; tend to be more common in patients with sensitive skin, rosacea, or eczema[5]; and often improve after several weeks of therapy.[1] Shortly after the initiation of therapy, some patients develop an exacerbation of their inflammatory lesions, or "acne flare." These flares are usually temporary, resolving after a few weeks.[10] In addition, by inducing a mild thinning of the stratum corneum and relative exfoliation of keratinocytes, tretinoin may increase a patient's vulnerability to damage from UV radiation.[1]

Approaches to minimizing these AEs have been to initiate therapy with a low-dose formulation, gradually increasing the concentration,[1] and to develop newer formulations that offer improved tolerability.[5] One newer formulation is tretinoin gel microsphere, which contains tretinoin trapped within porous copolymer microspheres that selectively localize to the follicle and release tretinoin over time. The other formulation, polymerized tretinoin, delivers tretinoin in a controlled manner through a polyolprepolymer-2 vehicle.[5] Despite these advances, the use of tretinoin still is often limited by local skin irritation.[11]

Adapalene is a third-generation retinoid that has a distinctly different chemical structure than tretinoin.[1,5] This compound has unique affinity for the pilosebaceous unit[7] and moderate to potent anti-inflammatory activity.[1] A meta-analysis of 5 clinical trials found adapalene to have comparable efficacy to tretinoin but with a more favorable tolerability profile.[12] The percentage change in noninflammatory lesions was 58% with adapalene gel 0.1% (n=450) and 52% with tretinoin gel 0.025% (n=450).[12] By every measure of topical AEs, adapalene gel 0.1% was significantly ($P<.0001$) less irritating than tretinoin gel 0.025%.[12] Perhaps because the formulation is a water-based gel rather than an alcohol-based gel, adapalene seems to be the least irritating of the retinoid gel formulations.[13]

Tazarotene, a synthetic retinoid, is a prodrug that is converted to its active form, tazarotenic acid, once it penetrates the skin.[1] In clinical trials, tazarotene has shown significantly superior efficacy in the treatment of noninflammatory lesions versus other retinoid formulations ($P\leq.04$).[13-15] The median reduction in noninflammatory lesions was 60% with tazarotene gel 0.1% versus only 38% with tretinoin gel microsphere 0.1%,[13] 55% with tazarotene gel 0.1% versus 42% with tretinoin gel 0.025%,[14] and 71% with tazarotene gel 0.1% versus 48% with adapalene gel 0.1%.[15] Skin irritation with tazarotene gel 0.1% appears to be similar to that encountered with standard tretinoin formulations, but the cream formulation is reported to be the least irritating form of tazarotene.[7]

Antimicrobial Agents

Topical Antibiotics—Generally slower acting and less effective than oral antibiotics, topical antibiotics are indicated in the treatment of mild to moderate inflammatory acne.[1,5] Like oral antibiotics, topical antibiotics reduce the number of *P acnes* and suppress the inflammatory responses triggered by these bacteria. Because of the probability of bacterial resistance in extended use, antibiotics should never be used as monotherapy but rather in combination with the potent antimicrobial agent, benzoyl peroxide (BP).[5]

Topical antibiotics commonly prescribed for acne include clindamycin, erythromycin, and tetracycline. A landmark review of the literature 15 years ago found that the paucity of well-designed, randomized, controlled trials made it impossible to rank the efficacy of topical antibiotics.[16] This is even more difficult today because monotherapy with a topical antibiotic is no longer a recommended course of action. Based on past clinical reports, however, clindamycin and erythromycin appear to have greater efficacy in reducing inflammatory lesions than topical tetracycline.[4,16] Common AEs attributed to the vehicle include peeling, burning, erythema, itching, and dryness.[5]

Topical Antimicrobials—BP, the most potent antimicrobial agent available for acne,[16] rapidly destroys *P acnes* by generating reactive oxygen species in the sebaceous follicle that physically interact with constituents of the bacteria.[1] BP can reduce *P acnes* by 90% after a few days of therapy,

an effect that is greater and more rapid than that of antibiotics.[5] Furthermore, there is no evidence that *P acnes* develops resistance to BP. BP has antimicrobial and anti-inflammatory activity, direct comedolytic activity, and, like antibiotics, indirect comedolytic activity through its effects on *P acnes*.[5,17] The comedolytic effect is reflected in the greater efficacy of BP over a topical antibiotic in the resolution of noninflammatory lesions: a 30% reduction with BP 5% versus only a 9% reduction with clindamycin 1%.[18]

BP is available in a wide variety of formulations and concentrations, ranging from 1% to 10%.[5] Gels tend to be more stable and allow more consistent release of the active ingredient compared with creams and lotions. Water-based gels are less drying than alcohol-based gels.[10] Wash formulations are useful for covering large areas of skin, such as the chest and back, and may improve compliance because they can be applied in the shower.

The most common AE of BP is local irritation, which is usually transient and most troublesome during the first few days of treatment.[1,5] In addition, BP can cause erythema, dryness, and allergic contact dermatitis in approximately 1% to 3% of patients.[1] These AEs can be minimized with the use of combination clindamycin 1%-BP 5% (Duac® Topical Gel), with its unique emollient formulation.[19] Patients should be aware that BP can bleach hair, clothes, and bed linens.

Another topical antimicrobial, azelaic acid, is a dicarboxylic acid first developed for use in treating benign hyperpigmentation disorders.[1] Although structurally unrelated to other acne therapies, azelaic acid has bacteriostatic activity against various aerobic and anaerobic bacteria, including *P acnes*, and anti-inflammatory activity, possibly because of its ability to decrease superoxide anion and hydroxyl radical generation by neutrophils.[1,5] In clinical studies, azelaic acid has shown mild comedolytic, antibacterial, and anti-inflammatory activity.[1,5] Because it can lighten the skin, azelaic acid may be useful for reducing postinflammatory hyperpigmentation in susceptible patients.[5]

Oral Antibiotics—The primary indication for oral antibiotics is moderate to severe inflammatory acne.[5] Systemic antibiotics also are useful for areas difficult to reach with topical agents (eg, the back) and for acne with high scarring potential.[1] Like topical antibiotics, oral antibiotics target both the bacterial and inflammatory pathogenic factors of acne. These agents reduce the number of *P acnes* within follicles by interfering with their growth, metabolism, or both.[5] As a result, oral antibiotics suppress the production of inflammatory cytokines by *P acnes*, as well.

Minocycline appears to have greater in vivo activity against *P acnes* than doxycycline or tetracycline.[20] Oral antibiotics have various other anti-inflammatory properties, such as the ability of tetracycline and erythromycin to inhibit leukocyte chemotaxis and bacterial lipase activity.[21,22] Tetracyclines also decrease prostaglandin production and inhibit cytokines and matrix metalloproteinases involved in inflammation and tissue breakdown.[23]

The primary oral antibiotics used for acne are the second-generation tetracyclines (minocycline and doxycycline) and erythromycin.[4] Less commonly used alternatives include trimethoprim and sulfamethoxazole/trimethoprim.[5] Although few randomized controlled trials have studied the efficacy of oral antibiotics in acne,[4] tetracycline and erythromycin have been shown to reduce inflammatory lesions by 64% and 67%, respectively.[24] Other comparative studies typically have shown little or no important differences in efficacy among the oral antibiotics.[5] Results of a recent Cochrane meta-analysis concluded that minocycline is effective for moderate acne, but data are insufficient to compare its efficacy to that of other acne therapies.[25]

Given the limited controlled comparative clinical data for oral antibiotics in the treatment of acne, factors other than efficacy often are used for selecting one agent versus another. Because of the increasing antimicrobial resistance to erythromycin, second-generation tetracyclines are generally preferred over erythromycin, except in patients in whom the tetracyclines are contraindicated (eg, pregnant or breast-feeding women, young children) or poorly tolerated.[5]

Gastrointestinal AEs are common with all oral antibiotics, particularly erythromycin, but tend to be mild and transient. These gastrointestinal AEs may be minimized without altering absorption by taking erythromycin, doxycycline, or minocycline with food; tetracycline, however, should be taken on an empty stomach. Another consideration when choosing an antibiotic is photosensitivity. The antibiotics listed from the most likely to the least likely to cause photosensitivity are doxycycline, tetracycline, and minocycline.

Minocycline has been associated with discoloration that localizes to scars and traumatized areas. Also, it is associated with rare occurrences of benign intracranial hypertension and drug-induced lupus.[5] In addition, minocycline appears to cause a higher incidence of dizziness than other tetracyclines.

Trimethoprim alone or sulfamethoxazole/trimethoprim generally are considered third-line therapy and reserved for patients who have failed therapy with either tetracycline or erythromycin.[5] Although generally well tolerated, these agents can

cause skin rash and severe allergic reactions, including erythema multiforme, Stevens-Johnson syndrome, and rare aplastic anemia.

Drug Resistance

Resistance of *P acnes* to topical and oral antibiotics is a growing problem, with resistant strains and multidrug resistance now found in a large percentage of patients.[5] Antibiotic resistance has been associated with treatment failures[26] and should be suspected in patients who fail to improve.[5] With oral antibiotic therapy, resistance is more common with erythromycin than with tetracycline and least common with minocycline.[27,28] Similarly, resistance among topical antibiotics occurs most often with erythromycin, followed by clindamycin, tetracycline, and doxycycline; resistance to minocycline is less common.[29] Recommendations for preventing antibiotic resistance include refraining from antibiotic monotherapy, avoiding long-term antibiotic use, and combining antibiotics with BP therapy.[5]

Combination Regimens

Combination regimens using agents that target different areas of acne pathophysiology are increasingly recognized as an effective strategy in the management of acne. For example, one common strategy is to prescribe a product that combines a topical antibiotic with BP.

The combination of either topical erythromycin or clindamycin with BP provides superior results compared with either agent used alone.[18,30] Both agents are mildly comedolytic and have activity against *P acnes*.[3] Furthermore, combining BP with a topical antibiotic in a stable formulation has been proven in clinical trials to rapidly reduce total *P acnes* count by 99.7% after only one week of therapy,[31] eliminating both susceptible and resistant strains of *P acnes*.[32] In a clinical trial, the statistically significant ($P<.02$) difference in reductions of inflammatory lesions between Duac Topical Gel (clindamycin 1%-BP 5%) and either clindamycin 1% or BP 5% alone was evident after 2 weeks of therapy.[18]

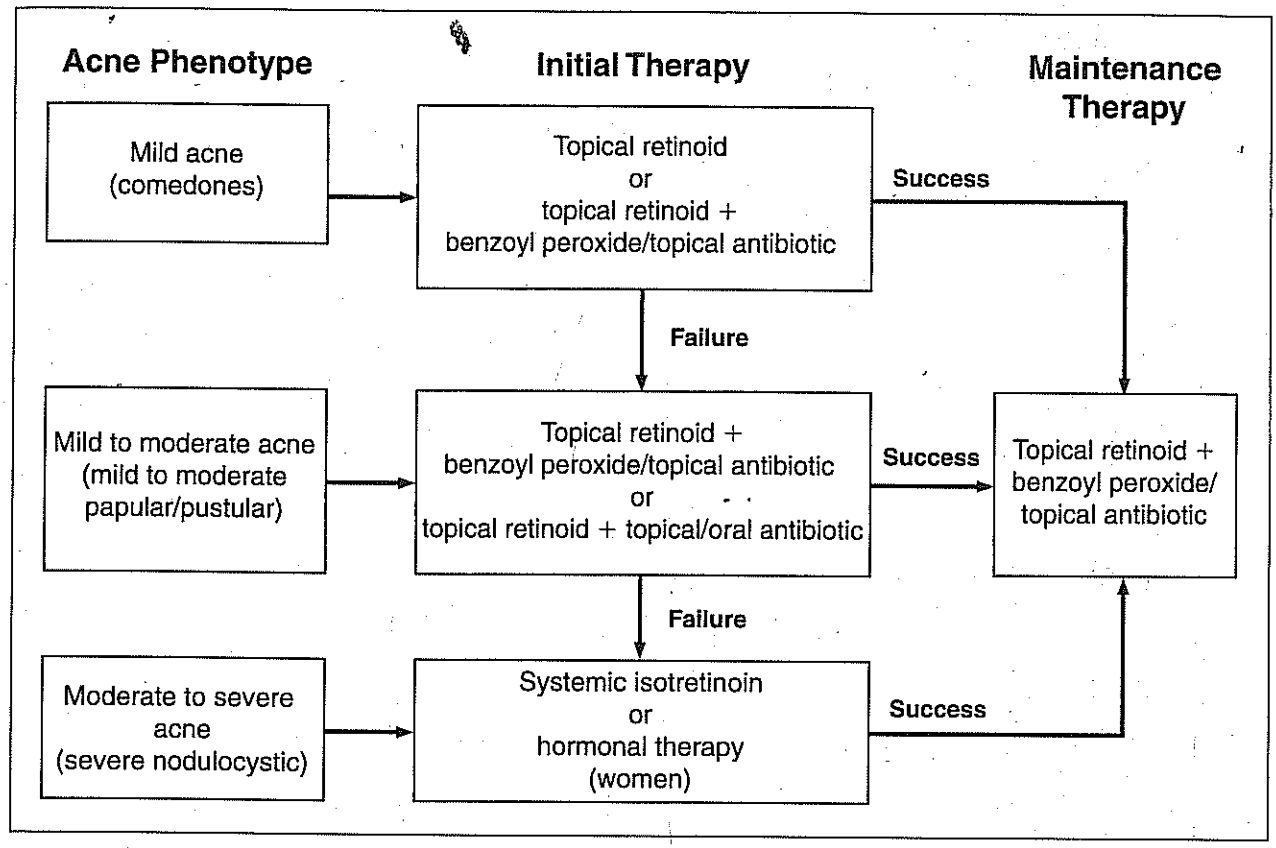
The combination of topical retinoids with topical or oral antibiotics also is recognized as an effective strategy in the treatment of inflammatory acne.[3,5] Retinoids have comedolytic activity, whereas antibiotics reduce *P acnes* and have anti-inflammatory and mild comedolytic activity, as well.[5] Ideally, the combination should not be used as maintenance therapy, as this combination is prone to the development of antibiotic resistance.[33] To minimize the development of antibiotic resistance, the antibiotic component should be discontinued as soon as the inflammatory lesions resolve.[5,18]

Alternatively, a combination product with BP and a topical antibiotic can be used with a topical retinoid for a maintenance regimen, because the addition of BP has been shown to prevent the development of resistance.[5,18,34] Because combination therapy with BP and a topical antibiotic has been proven to prevent the emergence of resistant strains of *P acnes*,[3] the current clinical recommendation is to include BP in topical antiacne regimens to preclude the development of antibiotic resistance.[29] The addition of BP with clindamycin to topical retinoid therapy adds further antimicrobial, anti-inflammatory, and comedolytic activity but can add further irritation if not formulated with emollients, such as those found in Duac Topical Gel.[5,18,34] A proposed algorithm for using combination therapies in acne is shown in the Figure.[3]

Due to the complementary actions of the individual agents, it is becoming increasingly evident that a triple-agent regimen is indicated for both initial treatment and maintenance therapy. The ideal triple-combination regimen is often a topical antibiotic and BP product plus a retinoid appropriate for the patient's skin type. Several studies have evaluated the therapeutic value of this regimen. In a recent 12-week study, 121 patients with inflammatory acne were treated with tazarotene cream 0.1% alone or in combination with clindamycin 1%-BP 5%.[35] The combination regimen resulted in faster clinical improvement, with a greater reduction in both comedonal lesions (70% vs 60%) and inflammatory lesions (63% vs 58%) at week 12.[35] Among patients with the most severe inflammatory acne at baseline, resolution with the triple combination regimen was significantly greater than with tazarotene alone ($P\leq.01$).[35] In addition, tolerability of the combination was comparable or better than tazarotene alone, probably due to the emollient formulation of the clindamycin 1%-BP 5% combination product.[35] This new data provide added support for the use of triple-combination regimens in the treatment of comedonal and/or inflammatory acne.

A case study of another triple regimen was conducted in patients with inflammatory acne who were treated with clindamycin 1%-BP 5% plus adapalene gel 0.1%. This triple combination resulted in virtual clearing of inflammatory acne lesions after 10 weeks, with faster onset of action and greater efficacy than are normally seen with adapalene gel alone.[36]

The choice of vehicle is important in these combinations due to the potential for additive irritation. In 2 clinical trials, the influence of vehicle on tolerability has shown a significantly more favorable tolerability profile with a combination of clindamycin 1%-BP 5% formulated with 2 emollients (Duac Topical Gel) than with a combination of the



Algorithm for the management of acne vulgaris. Adapted with permission from Leyden.[3] A review of the use of combination therapies for the treatment of acne vulgaris. *J Am Acad Dermatol.* 2003;49(suppl 3):S200-S210. ©2003, American Academy of Dermatology, Inc.

same active ingredients formulated without any emollients (BenzaClin® Topical Gel)($P<.05$).[16,34]

Another issue when adding BP to a combination regimen is the chemical compatibility and stability of all components of the regimen. Because BP is a potent oxidizing agent, there is the potential for it to degrade a topical antibiotic or retinoid when the separate agents are applied at the same time, as opposed to BP-containing products that are formulated together.[31] In a study of retinoid stability when combined with BP lotion 10%, tretinoin gel 0.025% was degraded by 50% in 2 hours when exposed to normal room light and by 95% after 24 hours. Under the same experimental conditions, adapalene gel 0.1% remained stable when combined with BP lotion 10%.[37]

Conclusion

The use of combination therapies targets the major pathogenic factors in acne and can produce greater and faster results than single agents. Combination regimens should be tailored to the individual patient, bearing in mind the number and types of prevailing lesions and the skin type. Care should be taken to choose a formulation designed to maximize tolerability of the combination. For both initial treatment and maintenance therapy, the ideal combination regimen is often a topical antibiotic and BP product plus a retinoid.

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