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CUTANEOUS MEDICINE FOR THE PRACTITIONER

VOL. 84 NO. 5S

NOVEMBER 2009

Fixed-Combination Monotherapy With Clindamycin 1%–Benzoyl Peroxide 5% Gel:

FOCUS ON ACNE PATIENT BENEFITS AND CLINICAL USE

Funding for the peer-reviewed publication was provided by Stiefel, a GSK company.

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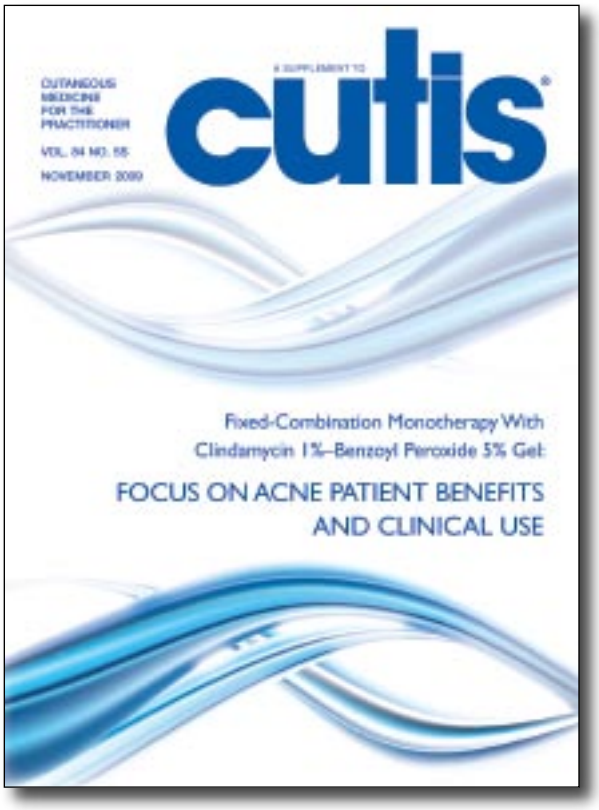

Fixed-Combination Monotherapy With Clindamycin 1%–Benzoyl Peroxide 5% Gel: FOCUS ON ACNE PATIENT BENEFITS AND CLINICAL USE

Funding for the peer-reviewed publication was provided by Stiefel, a GSK company.

Introduction

Lawrence Eichenfield, MD

Acne has an enormous impact on healthcare in the United States, causing substantial morbidity and imposing emotional and social limitations on patients' quality of life.[1] Although the pathogenesis of acne has not been completely characterized, it is viewed as a chronic inflammatory disease arising from a combination of factors including sebaceous gland hyperplasia, follicular hyperkeratinization, bacterial proliferation, and immune and inflammatory reactions.[2] Both the 2003 and 2009 acne treatment consensus guidelines recommend the use of topical combination therapy for mild to moderate disease presentation to address as many pathogenetic aspects as possible.[3,4] Therapeutic benefits supporting the use of combination therapies include more rapid and sustained efficacy and improved tolerability. However, the efficacy and tolerability of a therapeutic regimen hinges on the patient's adherence to treatment, which can be heavily influenced by treatment factors, including excipients contained in the medication vehicle, the ease of use, and the speed with which the patient can visualize improvement.

The efficacy and tolerability of a therapeutic regimen hinges on the patient's adherence to treatment, which can be heavily influenced by treatment factors, including excipients contained in the medication vehicle, the ease of use, and the speed with which the patient can visualize improvement.

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Dr. Eichenfield is an investigator for and has received grant and research support (not personal) from Galderma Laboratories, LP; Ortho Dermatologics; and Stiefel, a GSK company. He also is an advisory board member and consultant for Coria Laboratories, Ltd; Galderma Laboratories, LP; Ortho Dermatologics; Stiefel, a GSK company; and Valeant Pharmaceuticals International.

Patients may be disinclined to use topical medications because they are irritating or require multiple applications, and they may stop therapy altogether if they believe that treatment is not producing the desired response.

Poor adherence to treatment represents a major challenge for healthcare professionals. Patients may be disinclined to use topical medications because they are irritating or require multiple applications, and they may stop therapy altogether if they believe that treatment is not producing the desired response. It should be noted that clinicians and patients with acne often characterize therapeutic success differently. During drug development and postmarketing analyses, therapeutic efficacy of an acne medication is defined in terms of lesion count reduction success often determined through analyses of inflammatory and noninflammatory lesion reduction as well as investigator and patient global assessments, and recommendations for treatment regimens are based on these findings.[5] However, clinical experience holds that patients are most concerned with the overall appearance of their skin, the tolerability and ease of use of the medication, and the rapidity with which they see results, which suggests a disconnect between the efficacy end points we depend on to rate our treatment options and the patient's experience and treatment goals.[5]

It is intuitive that a patient's adherence to treatment improves with a simple regimen, strong and rapid efficacy, tolerability, and convenience. A fixed-combination gel monotherapy containing clindamycin 1% and benzoyl peroxide 5% (C/BPO) is eminently useful in addressing factors leading to poor adherence to a topical regimen. This combination formulation is an aqueous gel containing glycerin 4% and dimethicone 1% and is available in a tube. Glycerin is a humectant that draws water from the viable layers of the dermis to maintain

hydration at the surface, and dimethicone is an occlusive moisturizer that helps prevent epidermal water loss.[6] The cosmetic elegance and tolerability benefits from the addition of these hydrating agents may obviate the need for additional moisturizers.[7] This fixed-combination C/BPO gel has demonstrated efficacy against both inflammatory and noninflammatory lesions[8] and provides excellent tolerability in a simplified once-daily regimen that can be used with other classes of agents; these features work in concert to better ensure a patient's compliance with his/her treatment regimen.

This supplement reviews the literature supporting the use of the fixed-combination C/BPO hydrating gel for the treatment of acne both as monotherapy and in combination with other antiacne agents. We review efficacy and tolerability data of C/BPO as well as its unique vehicle features, and explore how these product attributes improve tolerability and better ensure patient adherence to therapy. Kircik[9] reviews acne pathogenesis, including new aspects of our understanding of inflammation in acne and the importance of these findings on treatment choice. He also reviews the efficacy of the fixed-combination C/BPO hydrating gel on both inflammatory and noninflammatory lesions including its rapid onset of effect.[9] The vehicle science and tolerability data supporting C/BPO for the treatment of mild to moderate acne and how these characteristics enhance patient compliance also are discussed.[10] Tanghetti[11] provides an overview of data supporting the various regimens utilizing C/BPO and compares efficacy and tolerability data for each of them.

These articles further establish the fixed-combination C/BPO hydrating gel as a rapidly efficacious and well-tolerated treatment that has the potential to improve a patient's adherence to therapy, the cornerstone of successful treatment outcomes for all of our patients with acne.

Acknowledgment—This supplement was prepared with clinical trial data contributions provided by Lou Barbato, MD, of Stiefel, a GSK company.

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Rapid and Efficacious Fixed-Combination Monotherapy: Desired Results for the Patient and Improved Adherence for the Clinician

Leon Kircik, MD

Ideally, acne therapy should treat multiple causative disease factors and improve clinical symptoms while considering patient tolerability and expectations as well as other factors that could negatively impact patient adherence to therapy. This article reviews data describing the role of inflammation in disease pathogenesis and how it impacts treatment choice. Pivotal efficacy data supporting use of a fixed-combination monotherapy gel containing clindamycin 1% and benzoyl peroxide 5% (C/BPO) also are reviewed. This fixed-combination monotherapy demonstrates efficacy for the treatment of both inflammatory and noninflammatory acne lesions, both alone and in combination with a retinoid, which may favorably influence a patient's adherence to therapy.

Cutis. 2009;84(suppl 5):5-11.

New Findings in Acne Pathogenesis Influence Selection of Therapy

Since the publication of the 2003 acne consensus guidelines, new findings on disease pathogenesis could impact how therapies are designed and prescribed in the future as well as provide additional information on how existing therapies function.[1] It is known that sebum production rates correlate with disease as well as severity.[2] The traditional view is that excessive sebum production causes abnormal keratinization and follicular plugging, which lead to the proliferation of *Propionibacterium acnes*, a resident anaerobic organism in the pilosebaceous unit. Ultimately, this process leads to inflammation following chemotaxis and the release of various proinflammatory mediators.[3]

Activation of intracellular signaling cascades have been shown to be associated with 2 important transcription factors involved in inflammation and matrix destruction: nuclear factor κB and activator protein 1 (AP-1). Both are activated in acne lesions with consequent elevated expression of their target gene products, inflammatory cytokines and matrix-degrading metalloproteinases, respectively.[4] These findings suggest that inflammation and matrix remodeling occur in the earliest stages of lesion development, supporting the recommendation that agents with anti-inflammatory activity should be used at the initiation of treatment and to prevent scarring in patients with severe acne.[4,5]

Combining Therapies: A Rational Approach

The rational approach to acne treatment is combination therapy, which has the potential to target multiple pathogenetic processes; establish synergy among the individual agents; and overcome limitations associated with traditional monotherapy, such as poor response and poor tolerability. These signs and symptoms can reduce adherence to therapy and negatively impact treatment outcomes.

Synergy of Clindamycin and Benzoyl Peroxide as a Fixed-Combination Agent

Synergy results when there is substantial overlap in the mechanistic actions of agents that are used in

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combination. Table 1 describes the different points of potential synergism of topical acne treatment.[1,6,7] For example, this overlap can be observed with the combination of a topical antibiotic, retinoid, and benzoyl peroxide (BPO) because both antibiotics and BPO decrease *P acnes*, and both retinoids and BPO normalize keratinization.[1,6] Furthermore, each of these agents has varying levels of anti-inflammatory activity. Because of the multifactorial nature of the disease and the potential for synergy with the use of combination therapy, consensus guidelines for acne treatment recommend the utilization of classes of medications that target as many pathogenetic factors as possible.[1,6] For treatment of mild to moderate acne, topical agents can decrease *P acnes* population and inflammation and normalize keratinization, but only oral agents can decrease sebum production.[1] Although combination therapy has obvious advantages, the use of multiple medications complicates the treatment regimen for the patient, increases the risk for adverse events, and may threaten adherence to therapy.

Clindamycin 1%–BPO 5% Gel Fixed-Combination Monotherapy: Flexible as Initial or Add-on Therapy

Because of the role of inflammation in acne disease pathogenesis, the clindamycin 1%–BPO 5% (C/BPO) fixed-combination monotherapy is a flexible treatment that can be used in a variety of ways. It can be used as initial treatment because both the antibiotic and BPO provide anti-inflammatory effects to attack the earliest inflammatory response and decrease *P acnes* colonization. Furthermore, C/BPO can be used in combination with a topical retinoid to enhance the anti-inflammatory and antibacterial effects of the C/BPO fixed-combination monotherapy while providing the added benefit of normalizing keratinization. Monotherapy with a topical retinoid may be considered for the treatment of mild or moderate acne[1]; however, the addition of BPO alone or in combination with an antibiotic can greatly accelerate the onset of action of the retinoid.[1,8] As we learn more about acne pathophysiology (eg, the inflammatory changes at the earliest stages of acne lesion development), we are learning new ways of using and combining existing therapies to treat inflammation, even in mild and primarily comedonal acne.

Efficacy of C/BPO Gel in Inflammatory and Noninflammatory Lesions

There is much data from clinical studies and experience reported in the literature on the safety and efficacy of C/BPO. In 5 randomized, double-blind, pivotal trials in 1319 participants with moderate to severe facial acne vulgaris, once-daily use of C/BPO for 11 weeks was significantly more effective than clindamycin or BPO monotherapy or vehicle in 3 of 5 studies ($P<.05$)(Table 2).[9,10] In all studies,

Table 1.

Various Effects of Topical Acne Therapies[1,6,7,a]

Topical Therapy	Normalize Keratinization	Decrease *Propionibacterium acnes*	Decrease Inflammation
Antibiotics	No	Yes	Yes
Retinoids	Yes	No	Yes
Benzoyl peroxide	Yes	Yes	Yes

[a]The mechanistic actions of topical acne agents and how each agent can overlap and enhance efficacy when utilized in combination.

Table 2.

Mean Improvement in Investigators' Global Assessment at Week 11[10,a]

	Study 1 (n=120)	Study 2 (n=273)	Study 3 (n=280)	Study 4 (n=288)	Study 5 (n=358)
C/BPO fixed combination	2.9	2.5	2.0	2.7	2.3
Benzoyl peroxide 5%	1.9	2.0	1.8	2.5	2.0
Clindamycin 1%	2.0	1.8	2.0	2.3	1.6
Vehicle	1.3	1.1	1.8		1.4

Abbreviation: C/BPO, clindamycin 1%–benzoyl peroxide 5% gel.

[a]The C/BPO fixed-combination gel group showed greater overall improvement in the investigators' global assessment than the benzoyl peroxide, clindamycin, and vehicle groups in studies 1, 2, and 5. Study 4 did not assess performance versus vehicle.

there was a trend for improved efficacy with the C/BPO fixed-combination gel, and in 3 studies, the combination significantly outperformed the other treatment arms ($P<.05$)(Table 2).[8] The overall mean percentage reduction in inflammatory lesion counts at week 11 for the C/BPO fixed-combination therapy ranged from −42% to −65%.[9-11]

Lookingbill and colleagues[11] reported on noninflammatory lesion counts from 2 of 5 pivotal trials in a total of 334 participants, showing that all 3 active treatments demonstrated statistically significant superiority in reduction of noninflammatory lesion counts from baseline compared with vehicle ($P<.05$), and both the fixed-combination therapy and BPO monotherapy were significantly superior to clindamycin monotherapy ($P\leq.01$). The positive results of these studies also were evident in the investigators' mean global assessment scores, which were good or excellent with the C/BPO gel in 66% of participants versus 41% with BPO monotherapy, 36% with clindamycin monotherapy, and 10% with vehicle.[11]

Rapid Efficacy: Improved Adherence to Therapy

Perceptions of Efficacy—Patients with acne often have unrealistic expectations of the length of treatment necessary to achieve response, which may occur because the clinician may not set proper expectations about the disease course and treatment and because patients, especially teenagers, are not well practiced in delayed gratification.[12] In a study assessing various beliefs and perceptions of 78 patients with acne, it was found that 31% (24/78) of young patients expected their acne to be cured after 4 weeks of therapy.[13] Although impatience among teenaged patients is to be expected, women with acne also have clear goals and expect rapid results, especially if they work outside the home.[12]

Rapid Results With C/BPO for Inflammatory and Noninflammatory Acne—Although there is no cure for acne, treatment with C/BPO fixed-combination monotherapy can work relatively quickly on 1 or more pathogenetic factors, which may serve to enhance patient compliance and treatment regimen adherence. In an in vivo open-label study assessing C/BPO gel versus 3 different clindamycin 1% preparations (gel, solution, lotion), there was a 99.8% (>2 logs) reduction in propionibacteria counts with the C/BPO gel compared with 30% to 62% with the clindamycin preparations. No statistically significant difference in activity was noted between any of the clindamycin preparations at either 1 or 2 weeks, but the combination C/BPO gel demonstrated statistically significant differences ($P<.01$).[14]

In the pivotal trials, C/BPO gel was significantly superior to vehicle in inflammatory lesion count reduction as early as week 2 ($P \leq .002$) and remained evident throughout the study.[9,11] Regarding noninflammatory lesions, the C/BPO hydrating gel also outperformed the vehicle by week 2 ($P \leq .004$) and by weeks 5 and 11 for the BPO and clindamycin monotherapy arms, respectively. Both the C/BPO and BPO monotherapy groups were significantly superior to the clindamycin monotherapy group ($P \leq .01$), which was apparent by week 2 for the C/BPO group and by week 5 for the BPO monotherapy group. Finally, global assessment scores demonstrated rapid results. Each of the 3 active preparations was statistically superior to vehicle from week 2 onward ($P < .01$), and C/BPO was significantly better than clindamycin monotherapy by week 2 and BPO monotherapy by week 5 ($P < .02$).[11]

The rapid onset of action also was demonstrated in a single-blind, parallel-group, multicenter, comparative study of the efficacy of C/BPO gel and adapalene gel 0.1% in mild to moderate acne. The C/BPO gel significantly reduced inflammatory and total lesion counts compared with adapalene monotherapy beginning at week 1 and consistently until study end at week 12 ($P = .001$).[8]

Additionally, it has been demonstrated that time to response can be further improved with the addition of a topical retinoid. Del Rosso[15] assessed the comparative efficacy of initiating therapy with C/BPO gel monotherapy and in combination with adapalene gel 0.1% compared with adapalene monotherapy in 109 participants with acne vulgaris. In group 1, participants initiated therapy in the morning with C/BPO monotherapy once daily for 4 weeks and then received a combination regimen of C/BPO in the morning and adapalene in the evening for 8 weeks, while group 2 participants were treated with adapalene monotherapy for 12 weeks. In group 3, participants initiated combination therapy with C/BPO in the morning and adapalene in the evening for 12 weeks. Overall results showed superior and more rapid benefit in inflammatory lesion counts, and marked and rapid effect as early as week 2 for noninflammatory lesion counts in the treatment groups using C/BPO in combination with adapalene compared with adapalene monotherapy. The mean percentage change from baseline in inflammatory lesion counts at week 2 was 20% in group 1 and 30% in group 3 compared with 17% in group 2 (the adapalene monotherapy group). This benefit was maintained by the 12-week combination group (group 3) throughout the study (Figure 1A). Noninflammatory lesion count reduction produced similar results as early as week 2 (Figure 1B). At week 12, there was a statistically greater percentage reduction in noninflammatory lesion counts in group 3 versus group 2 ($P < .05$).[15]

Rapid efficacy also was demonstrated in a 12-week, multicenter, randomized study in 147 participants with facial acne characterized by 20 to 60 inflammatory lesions, 20 to 60 noninflammatory lesions, and 2 or fewer facial nodules and/or cysts.[16] Participants were randomized to treatment with either C/BPO gel in the morning plus tretinoin microsphere gel (TMG) 0.04% in the evening (n=73), or BPO wash 5% in the morning followed by a fixed-combination gel containing clindamycin phosphate 1.2% and tretinoin 0.025% in the evening (n=74). There were significantly more participants in the C/BPO plus TMG group with percentage decreases in inflammatory lesion counts of 50% or more and 75% or more from baseline to week 4 ($P = .0429$ and $P = .0063$, respectively); at week 8, more participants achieved a 75% or more decrease in inflammatory lesion counts in the C/BPO plus TMG group ($P = .0266$)(Figure 2A). This trend continued throughout the study, though the results were not significant at week 12.[16]

Similarly positive results were found for noninflammatory lesion counts (Figure 2B).[16] There was a significantly greater mean percentage change in open comedones with C/BPO plus TMG (44.35%) compared with BPO plus clindamycin phosphate–tretinoin (23.5%)($P = .0104$). This trend continued throughout the study, though without significant differences between groups. Changes in closed comedones were similar for both treatment regimens from baseline to week 12.[16]

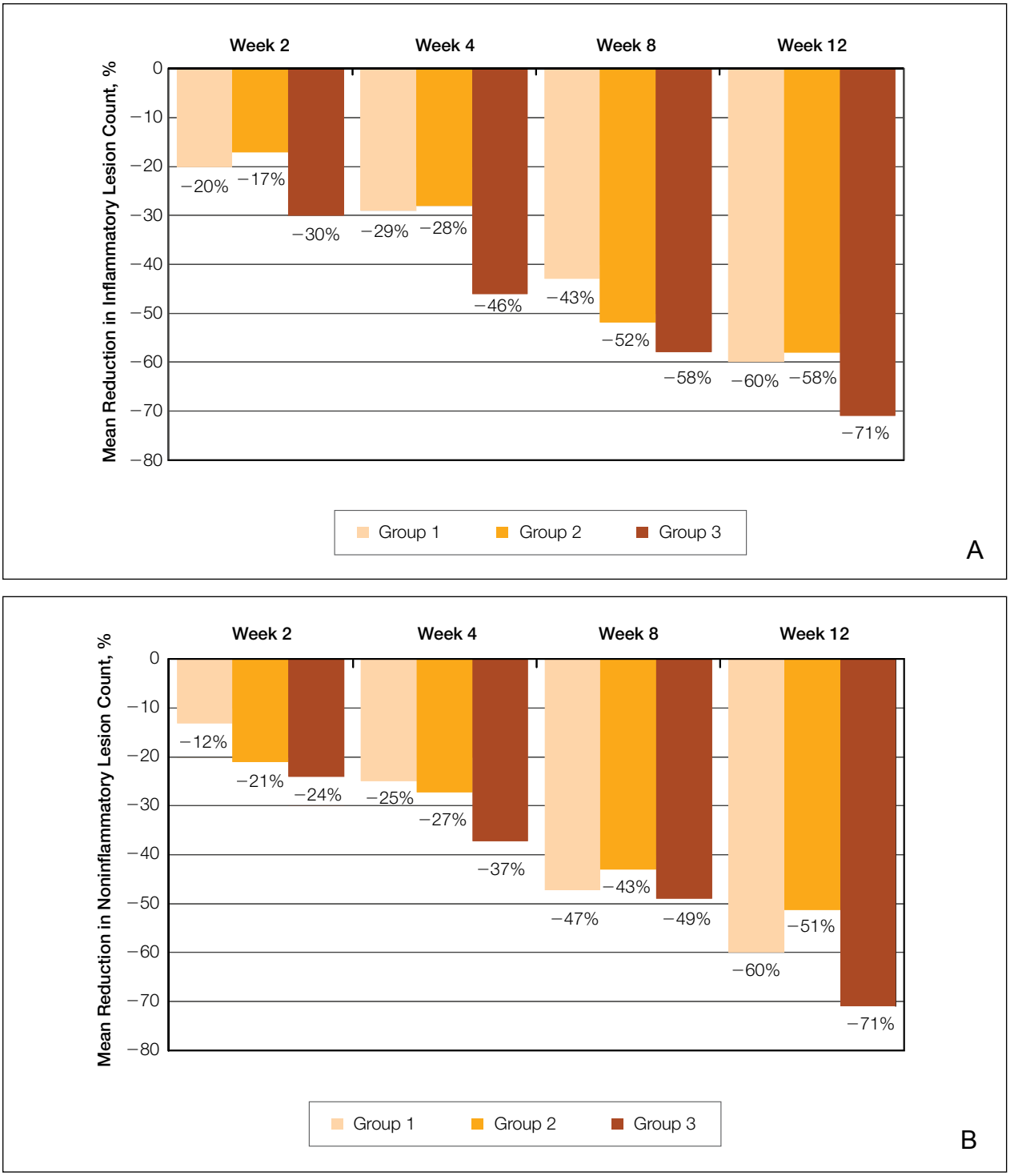
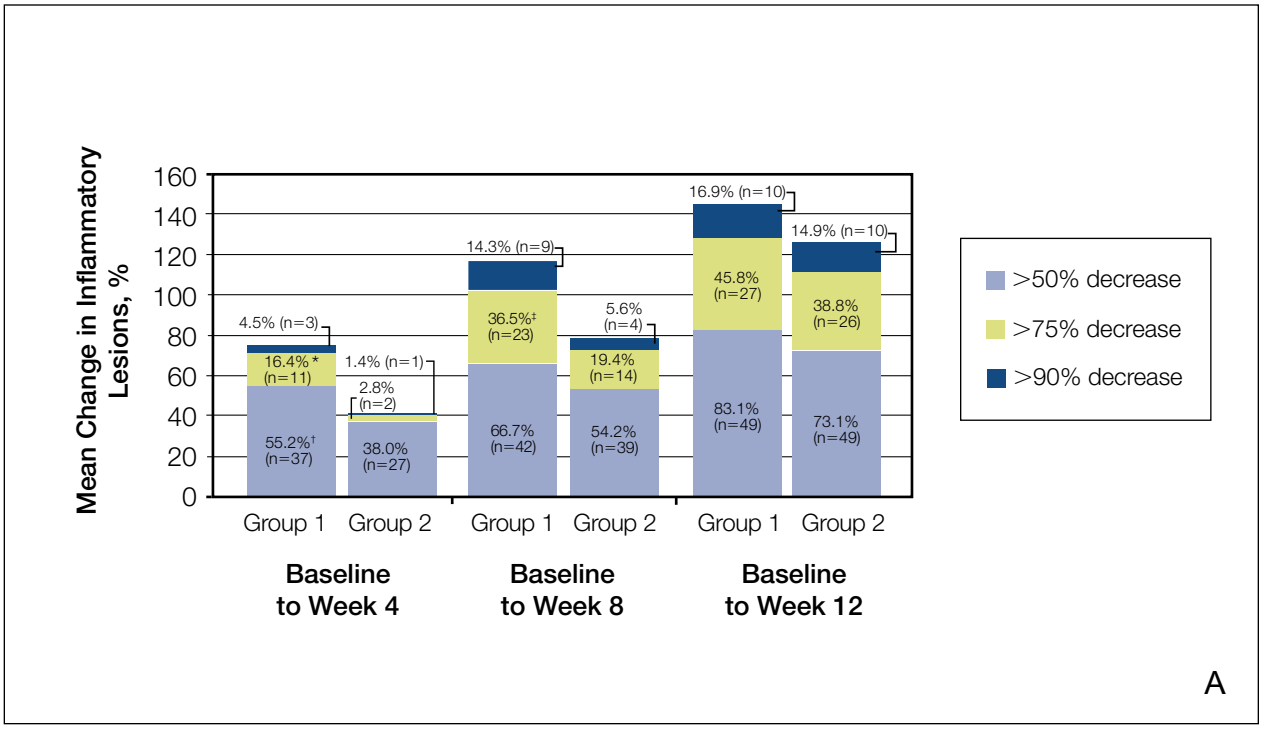


Figure 1. Mean percentage reduction from baseline in inflammatory (A) and noninflammatory lesion counts (B). Group 1 received initial therapy with clindamycin 1%–benzoyl peroxide 5% (C/BPO) hydrating gel for 4 weeks and combination therapy with C/BPO in the morning and adapalene gel 0.1% in the evening for 8 weeks; group 2 received adapalene monotherapy for 12 weeks; and group 3 received combination therapy with C/BPO in the morning and adapalene in the evening for 12 weeks. Adapted with permission from Del Rosso.[15]



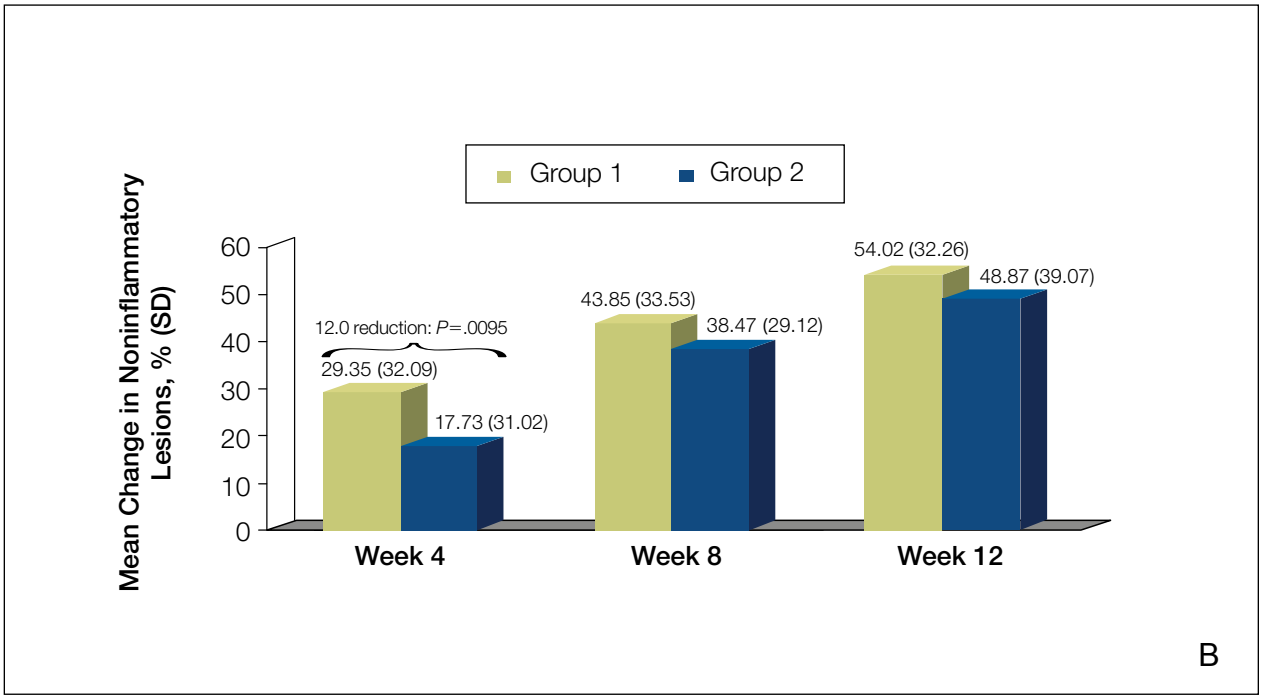


Figure 2. Mean percentage change from baseline in inflammatory (A) and noninflammatory lesions (B). Participants in group 1 received clindamycin 1%–benzoyl peroxide 5% hydrating gel in the morning plus tretinoin microsphere gel 0.04% in the evening (n=73); group 2 received benzoyl peroxide wash 5% in the morning and clindamycin phosphate 1.2%–tretinoin 0.025% gel in the evening (n=74). Asterisk indicates 13.60 reduction (*P*=.0429); dagger, 17.20 reduction (*P*=.0429); double dagger, 17.10 reduction (*P*=.0266); SD, standard deviation. Reprinted with permission from Kircik.[16]

Comment

New findings in acne pathogenesis and treatment support the use of combination treatment initiated with anti-inflammatory agents, which could rapidly improve clinical symptoms and increase patient adherence and tolerability. The patient's adherence to a therapeutic regimen is of paramount importance in ensuring the best treatment outcome, but several factors, including inadequate and/or slow response to therapy, local intolerability, or a complicated treatment regimen, can lead to poor adherence to therapy. To ensure adherence to a prescribed treatment regimen, optimal therapy should target as many pathogenetic factors as possible; have a rapid onset of efficacy and favorable tolerability profile; and be used in a simple, easy-to-follow regimen.

As proven in multiple studies and through nearly a decade of substantial community-based clinical experience, the fixed-combination monotherapy agent C/BPO is an especially efficacious and flexible treatment option that can be used with success as monotherapy or in combination with any topical retinoid. This product allows the clinician to treat the patient with one fixed-dose medication that simultaneously provides anti-inflammatory action while decreasing the population of *P acnes* on the skin. It is a flexible and simple once-daily regimen that demonstrates substantial efficacy against noninflammatory lesions and, more importantly, the inflammatory lesions that would eventually lead to scarring; therefore, the early and effective treatment of inflammatory lesions is of paramount importance in the prevention of scarring.

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Improving Treatment Outcomes: Tolerability of a Fixed-Combination Clindamycin 1%–Benzoyl Peroxide 5% Hydrating Gel as Monotherapy or in Combination With a Retinoid

Lawrence Eichenfield, MD

Patient adherence to acne therapy is a fundamental element of successful treatment outcomes, which can be increased by the selection of rapidly acting, well-tolerated medications used in simplified regimens. A fixed-combination monotherapy gel containing clindamycin 1% and benzoyl peroxide 5% (C/BPO) has an established safety and efficacy profile through almost a decade of published literature and clinician experience. This unique product may improve a patient's adherence to therapy by providing a well-tolerated and efficacious once-daily monotherapy with multiple mechanisms of action. This article reviews data outlining the enhanced tolerability of the fixed-combination C/BPO gel both alone and when used with a retinoid. The favorable tolerability profile of C/BPO hydrating gel may impart additional benefit to the patient in helping to maintain adherence to treatment.

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It is the consensus of the dermatology community that a patient's adherence to therapy maximizes treatment success; in fact, poor adherence to treatment regimens is one of the most important causal factors of unsuccessful acne therapy.[1,2] Failure to adhere to a therapeutic regimen can arise from any number of factors relating to patient satisfaction including inefficacy, slow treatment response, and/or poor tolerability, which ultimately result in less than satisfactory therapeutic outcomes.

Pharmionics (ie, the study of how patients utilize prescribed medications) is gaining increased attention in medicine, especially in dermatology. In a review of the pharmionics of topical and oral drugs used for acne, several barriers unique to adherence with topical regimens were identified, including time-consuming application, cosmetic unacceptability, and irritation.[3] These observations are supported by data from a recent study of adherence to a 6-week regimen of benzoyl peroxide (BPO) 5% monotherapy. Results showed that mean adherence to treatment in 11 participants ranged from 14% to 79% and declined over time, with 82% of participants applying their medication on day 1 compared with 45% on day 43 ($P<.001$) (Figure 1).[4] Adherence is best with simple regimens that are rapidly efficacious, well tolerated, and easy to incorporate into the patient's lifestyle.[1,5]

This article describes different tolerability factors that can impact a patient's adherence to a

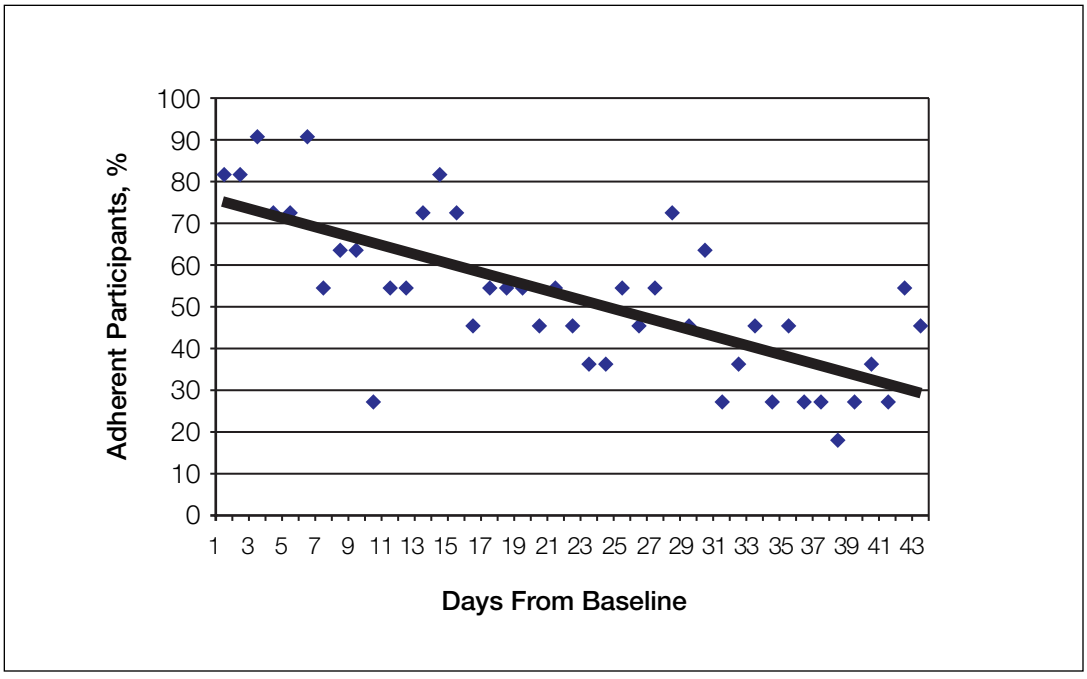

Figure 1. Mean adherence to once-daily treatment with benzoyl peroxide gel 5% declined over the 6-week study at a rate of approximately 1% per day (N=11)($P<.001$; $R^2=0.52$). Reprinted from Yentzer et al,[4] with permission from the American Academy of Dermatology.

therapeutic regimen and reviews data supporting the enhanced tolerability profile of a fixed-combination monotherapy agent in a hydrating gel containing clindamycin 1% and BPO 5% (C/BPO) that likely could optimize treatment outcomes.

The Role of Excipients in Modulating Irritation

Skin irritation associated with acne arises from within and without the skin barrier. The disease itself directly affects barrier function of the stratum corneum (SC) via inflammation and its impact on epidermal growth and maturation, which is evidenced by high transepidermal water loss, dryness, and peeling.[6] Barrier disruption also may lead to increased absorption of topical medications and skin care products, which may be beneficial because increased penetration of active agents may be allowed; however, further barrier damage could result by allowing increased penetration of irritating excipients.[7]

Barrier perturbation also can be externally caused by drying and/or irritation arising from topical acne treatments, namely retinoids and BPO.[8] Topical retinoids are first-line treatments for mild to moderate acne, and another commonly utilized treatment approach includes BPO in combination with a topical antibiotic. This combination is beneficial because the antibiotic kills *Propionibacterium acnes*, while BPO provides comedolytic activity[9] and prevents the development of resistance to the antibiotic.[10] The efficacy of BPO and a topical antibiotic can be enhanced when combined with a retinoid[8] but at the cost of decreased tolerability and complication of the regimen, both of which could impact a patient's adherence to therapy.

Fortunately some topical medications contain excipients that are capable of initiating barrier repair via rehydration of the SC. Humectants and emollients/occlusives are ingredients used in topical skin care products that can directly affect skin biomechanics.[7] Humectants (eg, glycerin) are hydroscopic, which means they increase hydration by drawing moisture up through the SC. Emollients/occlusives (eg, dimethicone) are lipid-based substances that enhance hydration and make the skin softer and more pliable. These agents form a lipid barrier on the skin, which

allows humectants to absorb water from the deeper epidermis while simultaneously preventing water evaporation from the skin barrier.[7] An ideal formulation contains both humectant and occlusive excipients to provide optimal rehydration of the SC because it has been shown that products containing only humectants actually increase transepidermal water loss when applied to skin with a defective skin barrier.[11]

The hydrating gel containing C/BPO is the only available formulation of its kind with a vehicle that functions as an occlusive moisturizer by forming a thin, water-impermeable film over damaged skin, which optimizes the environment for healing. In addition to creating an artificial barrier to protect the healing skin from external insult, it also increases skin smoothness by filling in gaps caused by damaged corneocytes,[11] which may smooth the skin during the period of retinization when scaling may be apparent and most distressing for the patient.

Proven Tolerability of C/BPO in a Hydrating Gel Vehicle

The tolerability benefits of the hydrating gel C/BPO formulation were demonstrated in a 1-week, randomized, investigator-blinded, split-face study in 61 participants aged 15 to 25 years with mild acne.[12] Two formulations of C/BPO topical gel were compared: one with the humectant glycerin and the occlusive dimethicone (hydrating vehicle), and one without these excipients. Local tolerance was graded by a blinded investigator and by participants at baseline and after 1 week of treatment. Results showed that the formulation with the hydrating vehicle was better tolerated. Based on combined investigator-blinded scores, there was significantly less peeling (P=.045) and less dryness (P=.059) associated with C/BPO with the hydrating vehicle, and improvement in erythema favored C/BPO with the hydrating vehicle (Figure 2). Furthermore, participants' scores showed a significantly lower rate of burning (P=.03) with the C/BPO hydrating formulation.[12]

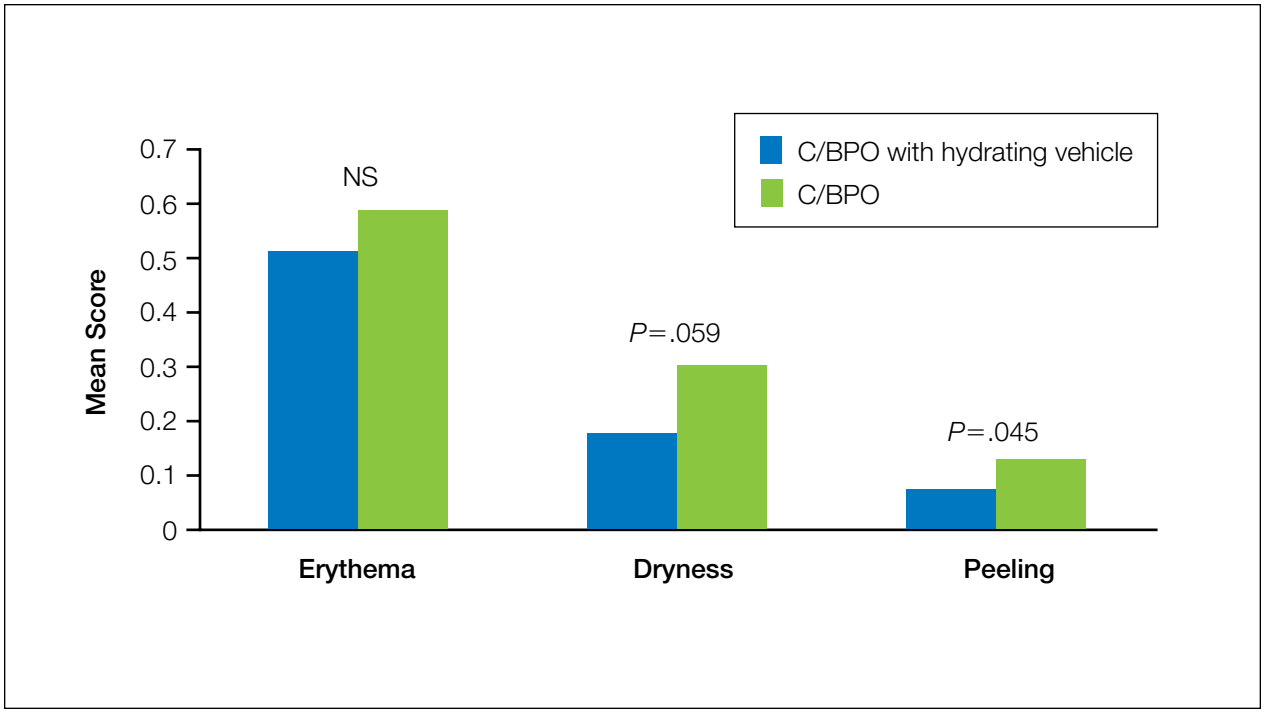

Figure 2. Investigator-blinded scores of local tolerance after 1 week of treatment with clindamycin 1%–benzoyl peroxide 5% (C/BPO) gel with a hydrating vehicle or with a nonhydrating vehicle. Scores for erythema, dryness, and peeling were graded on a 4-point scale (0=absent; 1=mild or slight; 2=moderate; 3=severe). NS indicates not significant. Adapted with permission from Fagundes et al.[12]

Similarly positive results were found in a 6-week, randomized, crossover study assessing C/BPO with the hydrating vehicle (once daily) compared with a nonhydrating vehicle (twice daily).[13] Fifty-two participants with mild to moderate acne (mean age, 21 years) were treated with one formulation for 2 weeks followed by a 2-week washout period, and then participants were switched to the opposite therapy for 2 additional weeks of treatment. Local tolerance was graded by a blinded investigator and by the participants at baseline and after 1 week of each treatment. Results showed that the hydrating formulation (once daily) was superior for local tolerability, with rates of both peeling (Figure 3A) and dryness (Figure 3B) being significantly lower compared with the nonhydrating formulation (twice daily)($P<.05$). Furthermore, significantly more participants (73% [38/52]) thought the C/BPO hydrating formulation had fewer side effects than the nonhydrating formulation ($P<.05$), and significantly more participants (77% [40/52]) preferred once-daily use of medication ($P<.05$).[13]

Fixed-Combination C/BPO Monotherapy Plus Retinoid: Improved Tolerability

The tolerability benefits of the fixed-combination C/BPO hydrating gel also may extend to treatment

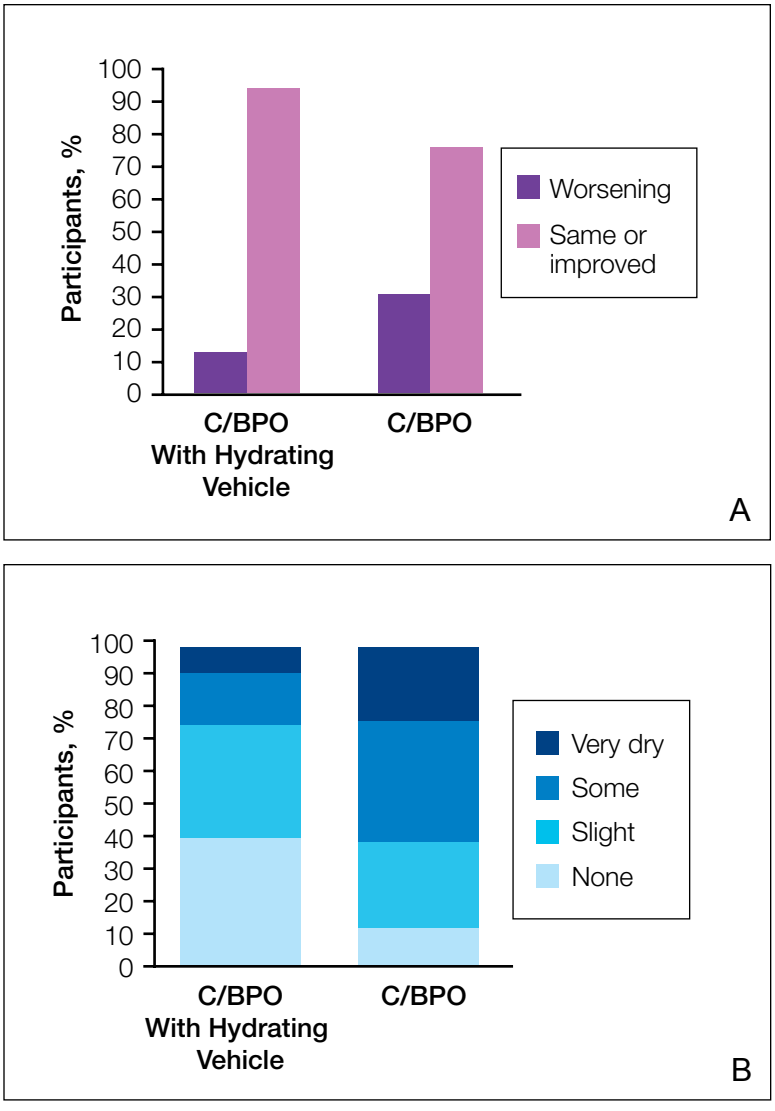

Figure 3. Change in investigator-rated peeling (A) and patient-rated dryness (B) after 2 weeks of treatment with clindamycin 1%–benzoyl peroxide 5% (C/BPO) gel with a hydrating vehicle or with a nonhydrating vehicle (N=52). Adapted with permission from Tanghetti and Gold.[13]

with a topical retinoid. Tanghetti and colleagues[14] assessed the potential benefit of the hydrating vehicle of the fixed-combination C/BPO gel in mitigating poor tolerability of a retinoid. A total of 121 participants with moderate to severe inflammatory facial acne applied tazarotene cream 0.1% every evening for 12 weeks and were randomly assigned to adjunctive treatment with either C/BPO gel or vehicle gel each morning. Tolerability outcome measures consisted of investigator-assessed global response to treatment including pruritus, peeling, erythema, burning, and dryness, and participants rated their overall impression of study medications.[14]

Results showed that the combination of C/BPO plus retinoid was comparable or better than tazarotene alone, with a lower incidence of peeling and dryness in participants using the combination regimen compared with tazarotene monotherapy (10% [6/60] vs 18% [11/61] for peeling, and 8% [5/60] vs 12% [7/61] for dryness). In addition, there was a significant between-group difference in the distribution of grades for peeling at week 4 ($P=.0199$); the combination regimen demonstrated milder grades overall, with 67% of the combination group achieving a grade of none or trace for peeling compared with 57% in the tazarotene monotherapy group.[14]

The tolerability benefits of using C/BPO hydrating gel in combination with topical tretinoin 0.025% extends to greater preference compared with a combination of tretinoin cream 0.025% and C/BPO gel in a nonhydrating vehicle. In a 3-center, 2-week, split-face study, 43 female participants (63% [27/43] white and 37% [16/43] black) with mild to moderate facial acne evaluated their preference for once-daily C/BPO hydrating gel versus twice-daily C/BPO with a nonhydrating gel when using tretinoin cream 0.025%.[15]

Investigator assessment showed significantly less peeling, erythema, and dryness at days 4 and 7 ($P<.05$) and significantly less erythema and dryness at day 14 ($P<.05$) on the side of the face that received the hydrating gel formulation compared with the side of the face that received the nonhydrating gel formulation.[15] Participant assessments showed significantly less dryness at days 4 and 7 ($P<.05$) and significantly less burning at day 4 ($P<.05$) with the hydrating gel compared with the nonhydrating gel, but there were no significant differences in erythema and pruritus between formulations. Overall, 65% (28/43) of participants reported that the hydrating gel was gentler to the skin.[15] Together these findings underscore the importance of ensuring an optimized combination of a humectant and occlusive in the C/BPO gel formulation and that concomitant therapy with a topical retinoid further improves the tolerability outcome measures.

Retinoids are commonly used agents for the treatment of acne but are limited by their irritation profiles. Consensus guidelines recommend the combination of a topical retinoid with the possible addition of BPO and an antibiotic for the treatment of acne because this regimen can treat multiple pathogenetic mechanisms, provide synergy, and minimize the potential for antibiotic resistance.[2,8] However, the data reviewed here demonstrate an additional benefit of tolerability when using the fixed-combination C/BPO hydrating gel both alone or in combination with a retinoid, which could potentially enhance a patient's adherence to a therapeutic regimen.

Comment

The principle that adherence to acne therapy may be improved by the selection of rapidly efficacious and tolerable regimens that will encourage patients to use medications as directed seems simple. Although treatment guidelines recommend the initial use of a topical retinoid for mild to moderate acne,[2,8] topical retinoids are notoriously slow to act compared with oral formulations and are associated with poor tolerability that could negatively impact adherence to therapy in some patients. However, the addition of an antibacterial component (usually BPO and an antibiotic) can hasten visible improvement, which assures the patient that the medication is working and may motivate the patient to adhere to the regimen. Skin comfort and appearance are important in maintaining daily use. Thus, the selection of a medication with a hydrating vehicle and good tolerability profile as shown by vast clinical experience and studies with C/BPO,[9] or even additive therapeutic benefits such as enhanced hydration, is vital to ensuring the best possible treatment outcomes.

However, strengthening patient adherence to a therapeutic regimen does not stop with the careful choice of therapeutic agents. The patient visit is an ideal opportunity for the clinician to educate the patient about the disease and its treatment to further enhance the likelihood of adherence to a therapeutic regimen. For example, it is helpful to explain to the patient that lesions arise from invisible microcomedones that reform and mature into visible lesions after 6 to 8 weeks when left untreated, so it is important to continue treatment even after he/she starts to see improvement.[5] Furthermore, the patient should understand that acne may initially worsen because of the effect of the medication on previously invisible lesions,[16] so it is important to give the patient reasonable expectations regarding the length of therapy as well as ultimate outcomes.

The selection of the fixed-combination C/BPO hydrating gel may improve patient adherence in several ways and limit side effects associated with either agent alone. First, it provides the patient with a simple, once-daily regimen that is easier to adhere to than twice-daily regimens. Furthermore, satisfaction with treatment is improved because the vehicle is enhanced with an optimal combination of glycerin and dimethicone. Finally, the product can be used in combination with a topical retinoid at any time during the treatment course to augment the efficacy of therapy by targeting more pathogenetic factors and to enhance the tolerability of the retinoid, both of which may improve treatment outcomes.

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Fixed-Combination Clindamycin 1%–Benzoyl Peroxide 5% Hydrating Gel: A Flexible Component of Acne Management

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This article reviews various studies supporting the use of a fixed-combination monotherapy hydrating gel containing clindamycin 1% and benzoyl peroxide 5% (C/BPO), which is the only available formulation with a hydrating gel vehicle containing a humectant and an occlusive. The C/BPO hydrating gel provides a flexible and complementary efficacy and/or tolerability profile when used alone or with topical retinoids, which results in rapid response in inflammatory and noninflammatory acne. It also mitigates the irritation associated with disease flare or topical retinoid use, and reduces the postinflammatory hyperpigmentation (PIH) seen in women and in patients with skin of color with acne. These benefits are important because they have the potential to improve patient adherence to therapy and clinical outcomes.

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Acne is a disease with a multifactorial etiology and responds best to a combination of agents that address as many pathogenetic factors as possible. The concomitant use of fixed-combination clindamycin 1%–benzoyl peroxide 5% (C/BPO) hydrating gel and a topical retinoid is complementary. For example, both C/BPO and retinoids have comedolytic and anti-inflammatory effects, and both antibiotics and benzoyl peroxide decrease the *Propionibacterium acnes* population on the skin.[1-3] Ultimately, the effects of these agents overlap because each of them impacts the reduction of microcomedones, comedones, and inflammatory lesions to varying degrees.

Based on an extensive review of the literature focused on the fixed-combination C/BPO hydrating gel in a unique formulation of humectant and occlusive agents, this agent can be used alone or in combination with topical retinoids that have complementary efficacy and/or tolerability profiles for the treatment of mild to moderately severe acne. The safety and efficacy of C/BPO in inflammatory and noninflammatory lesion count reduction compared with its individual components has been proven.[4] In combination with a topical retinoid, time to response and efficacy are enhanced,[5] and the use of 2 agents maintains a relatively simple regimen; both factors impact the potential to improve patient adherence to therapy.

C/BPO Hydrating Gel Plus Topical Retinoid: Broadest Activity, Best Outcomes

The combination of C/BPO hydrating gel and a topical retinoid is advantageous because it treats multiple pathogenetic mechanisms of acne with agents that have different but complementary activity.[1] From the patient's viewpoint, any possible negative impact on adherence arising from the use of multiple agents may be balanced by the potential for more rapid visual results as well as greater skin comfort due to the effects of the optimized C/BPO vehicle.

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As reported by Mills and Kligman,[6] occlusive moisturizing agents provide rapid repair of the skin barrier by acting as an emollient. Glycerin, a humectant, attracts water from the dermis to the epidermis, and occlusive agents, such as dimethicone, are designed to help prevent transepidermal water loss. It is noteworthy that among the available fixed-combination products approved by the US Food and Drug Administration for the treatment of acne, the synergistic combination of a humectant and an occlusive that promotes rehydration and restoration of the epidermal barrier can only be found with the C/BPO hydrating gel (Table).

The synergistic combination of a humectant and an occlusive that promotes rehydration and restoration of the epidermal barrier can only be found with the fixed-combination C/BPO hydrating gel containing glycerin and dimethicone.

The rapid efficacy of this combination was demonstrated in a study comparing tazarotene cream 0.1% used in the evening with the morning application of either vehicle gel or C/BPO in a hydrating vehicle in 121 participants with moderate to severe acne.[13] The combination of C/BPO and tazarotene achieved a significantly greater and more rapid median reduction in comedone counts from week 4 than tazarotene monotherapy (34% vs 18%) ($P \leq .01$). In those participants with mean baseline papule and pustule counts of 25 or more, a significantly greater median reduction in inflammatory lesion counts was reported at week 12 in participants treated with C/BPO and tazarotene compared with participants treated with tazarotene monotherapy (63% vs 52%)($P \leq .01$). Furthermore, the combination therapy was at least as well tolerated as tazarotene monotherapy.[13]

In addition to speeding visible results, the coadministration of C/BPO hydrating gel and a retinoid may improve the tolerability of the retinoid. In a 12-week study, 109 participants were randomized to treatment with either C/BPO plus adapalene gel 0.1%, adapalene

Vehicle Considerations of Available Fixed-Combination Gels

Fixed-Combination Gels	Water Based	Alcohol Based	Contains a Humectant	Contains an Occlusive
Adapalene 0.1%–BPO 2.5%[7]	Yes	No	Yes	No
CP 1.2%–tretinoin 0.025%[8]	Yes	No	Yes	No
CP 1.2%–BPO 2.5%[9]	Yes	No	No	No
C 1%–BPO 5%[10]	Yes	No	Yes	Yes
C 1%–BPO 5%[11]	Yes	No	No	No
Erythromycin 3%–BPO 5%[12]	No	Yes	No	No

Abbreviations: BPO, benzoyl peroxide; CP, clindamycin phosphate; C, clindamycin.

monotherapy, or C/BPO monotherapy for the first 4 weeks with the addition of adapalene during the last 8 weeks.[5] At week 4, investigator assessment revealed significantly more dryness with adapalene monotherapy ($P<.05$). Additionally, the adapalene monotherapy group required greater moisturizer use during the course of the study compared with the C/BPO group.[5]

It is important to note the utility of the combination of C/BPO gel and a retinoid is not limited to the treatment of mild to moderate acne. A 12-week, investigator-blind, randomized, community-based trial of 353 participants with moderate to severe acne compared C/BPO in a hydrating vehicle in combination with tretinoin microsphere gel (TMG) 0.04% (n=118), TMG 0.1% (n=117), and adapalene gel 0.1% (n=118).[14] Results showed that 44% of the C/BPO plus TMG 0.04% group and 47% of the C/BPO plus TMG 0.1% group had decreased at least 2 grades of global disease severity at week 12, and C/BPO plus TMG 0.04% was significantly superior to C/BPO plus adapalene in mean percentage reduction in inflammatory lesion counts from baseline ($P=.0045$). Adverse events were few and mild in each group and lower than typically observed in retinoid monotherapy studies.[14]

The results of these studies support the improved efficacy and tolerability of treatment with any topical retinoid and fixed-combination C/BPO hydrating gel. This combination provides more rapid efficacy and superior tolerability compared to its individual components, including retinoid monotherapy. Furthermore, therapy can be tailored to the needs of each patient by combining these agents at the initiation of therapy or adding one agent to the other in any sequence.

Fixed-Combination C/BPO Hydrating Gel Monotherapy for Acne Flares

Acne flare is defined as an increase in inflammatory lesion counts that can occur after a period of no treatment or because of topical retinoid therapy.[15] Leyden and Wortzman[15] reported on 3 trials in a total of 4550 participants randomly assigned to treatment with either clindamycin phosphate 1.2%–tretinoin 0.025% gel, clindamycin phosphate monotherapy, tretinoin monotherapy, or vehicle gel. Results showed that participants with mild acne at baseline, but not moderate to severe acne, who were treated with tretinoin monotherapy had significantly higher rates of flare compared with vehicle-treated participants ($P<.001$). Participants treated with the fixed-combination clindamycin phosphate–tretinoin or clindamycin phosphate monotherapy, however, demonstrated significantly lower rates of flare than tretinoin monotherapy or vehicle ($P<.001$ for all).[15]

Bikowski[16] observed similar clinical benefit using C/BPO in an 18-year-old man with disease flare. After 6 weeks of treatment with once-daily C/BPO hydrating gel applied at night, patient-assessed improvement was 70%, with an objective and marked reduction in the number of inflammatory papules and pustules on the forehead. Similar benefit was observed by Bikowski[16] in another case report assessing C/BPO hydrating gel for the treatment of retinoid flare (Figure 1). These patients mimic findings from larger studies of the effect of retinoid-induced flare on the skin and the benefit of C/BPO on mitigating this irritation.[17] It has been suggested that the tolerability benefit of C/BPO hydrating gel is due to the anti-inflammatory effects of the antibiotic and/or potentially the hydrating vehicle.

The benefit of C/BPO for alleviating retinoid-induced irritation is further supported by the tolerability results of the community-based trial previously reviewed.[14] In this trial, Kircik[14] observed a total of 13 adverse events in 353 participants including mild cases of dryness, peeling, erythema, burning, stinging, and irritation. The author noted that this rate was unusually low compared with retinoid monotherapy, which he conjectured was due to the hydrating effects of glycerin and dimethicone contained in the C/BPO gel.[14] Whether the benefit is due to the anti-inflammatory effects of clindamycin, the hydrating excipients, or a combination of both, it would appear that the C/BPO gel has the potential to decrease the level of irritation that one may expect with a topical retinoid.

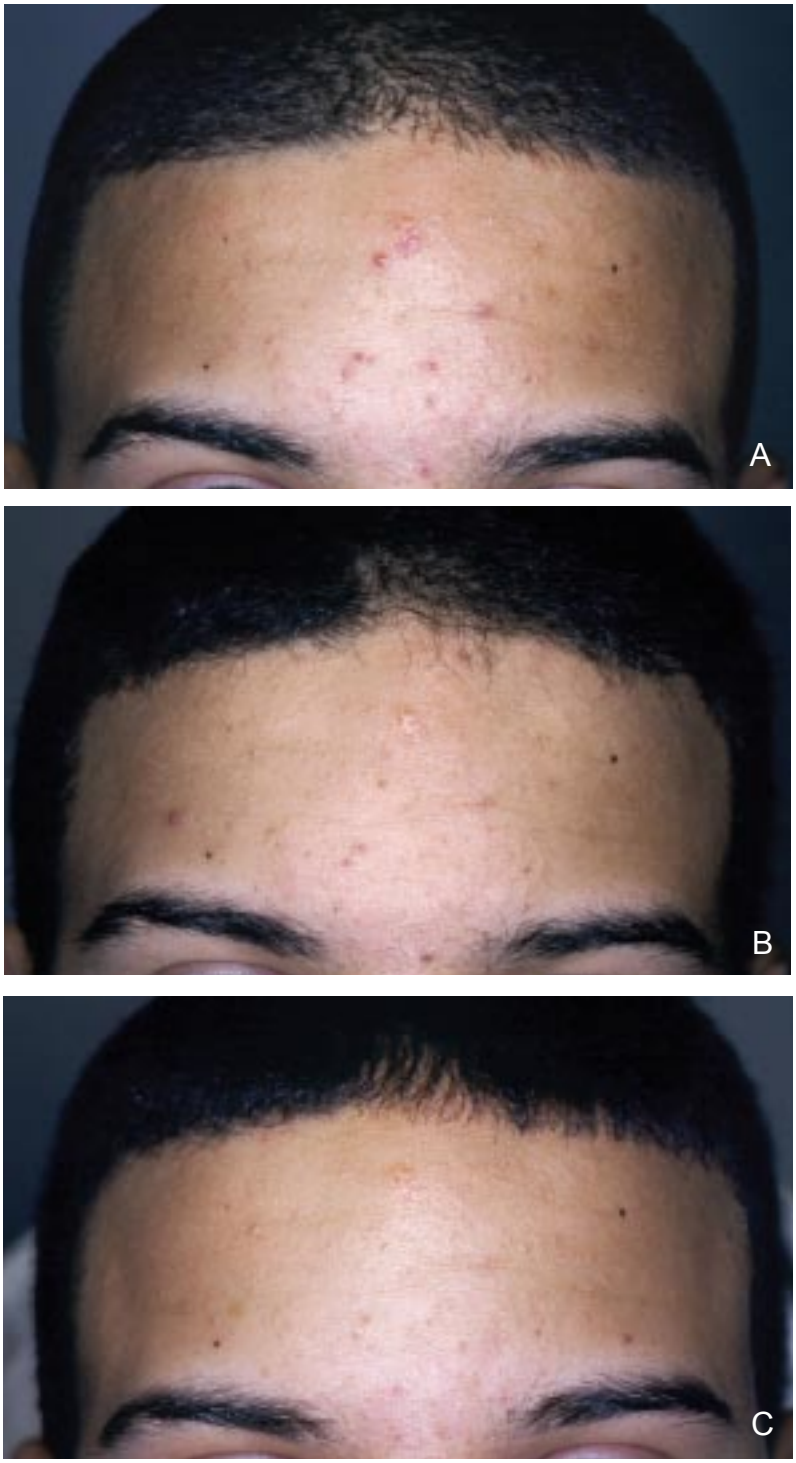

Figure 1. A 17-year-old adolescent boy presented for follow-up with unsatisfactory response to monotherapy with adapalene gel 0.1% applied once daily at night (A). Marked improvement was seen in inflammatory lesion counts after 4 weeks of treatment with clindamycin 1%–benzoyl peroxide 5% (C/BPO) hydrating gel used sparingly on his entire face every morning and adapalene gel 0.1% applied once daily at night (B). Continued improvement was seen after 10 weeks of treatment with C/BPO hydrating gel plus adapalene gel 0.1%, with a decrease in new lesions on the forehead (C). Reprinted with permission from Bikowski.[16]

Utility of C/BPO for Special Populations

The fixed-combination C/BPO hydrating gel also may have value for older patients with acne, especially women. Various diagnostic and treatment factors pertaining to persistent acne in women were discussed by Williams and Layton.[18] They observed that this patient group frequently is ignored in favor of the larger population of teenaged patients,

yet the appearance of acne in this group can result in the same or even more discomfort, inflammation, pigmentary changes, and cosmetic disability than younger patients. Although treatment principles for mature women are largely the same as other patient groups, there are some important differences in this group that can affect the choice of treatment.[18]

Persistent acne in women is notoriously challenging to treat, and therapy often is prolonged in this group. While therapy should consist of a combination of topical and systemic treatments, older skin differs from younger skin in that it is associated with increased irritancy to topical retinoids and antibacterial agents but is resistant to the irritant effects of benzoyl peroxide. Because of the particular needs of this patient group, the potential for irritancy with retinoid use can be offset by using the fixed-combination C/BPO hydrating gel because of its optimized vehicle.[18] Women can benefit from the efficacy and tolerability of the C/BPO formulation, and its once-daily dosing could improve adherence, especially in women who wear makeup or may prefer not to layer multiple products. This observation is supported by data from a preference study comparing C/BPO hydrating gel plus tretinoin cream 0.025% and a fixed-combination C/BPO agent in a jar plus tretinoin cream 0.025% (N=43), which showed that 61% of participants preferred the hydrating gel for ease of use with makeup and significantly more participants (65%) found C/BPO hydrating gel to be more gentle to the skin ($P<.05$).[19]

Individuals with skin of color also may find additional benefit from the fixed-combination C/BPO hydrating gel. Postinflammatory hyperpigmentation (PIH) is a common concern for this group, and the early and aggressive treatment of acne is essential in preventing blemishes that can last for months after acne lesions have resolved. The treatment of PIH and acne in patients with skin of color should strive to be aggressive yet gentle and nonirritating to uninvolved skin.

In a subset of skin of color participants (n=167) with moderate to severe acne from the 12-week community-based trial reviewed above, PIH was assessed in addition to their acne.[20] These participants used the fixed-combination C/BPO hydrating gel in the morning and 1 of 3 topical retinoids (TMG 0.04%, TMG 0.1%, or adapalene gel 0.1%) at night. Each of the 3 retinoid formulations in this study was associated with a decrease in PIH severity. It was surprising to note that the African American (n=60), Hispanic (n=58), and Asian (n=24) participants using C/BPO hydrating gel plus TMG 0.04% demonstrated the largest decreases in hyperpigmentation at all time points. Changes in hyperpigmentation were noted as early as week 4 in participants with skin of color (Figure 2).[20] It is possible that the hydrating properties of the gel formulation mitigated PIH by providing complementary mechanisms of action and allowing for a higher and apparently more effective level of retinoid activity.

Conclusion

Acne is not merely a self-limited affliction of adolescence but is a chronic disease with varying manifestations and changing patient needs over time. Monotherapy with C/BPO hydrating gel or a topical retinoid may be sufficient to treat acne at its earliest stages, but the combination of these agents addresses more pathogenetic processes and provides results more quickly. More importantly, improved tolerability has been proven with C/BPO hydrating gel in multiple clinical studies, perhaps attributable not only to the comedonal effects of the product but also to the use of the unique formulation, which may have positive effects on a patient's adherence to therapy. Furthermore, when inflammation is an important component, it generally is agreed that concomitant use of a fixed-combination agent such as C/BPO hydrating gel and a retinoid is the best approach. In addition to rapid efficacy and improved tolerability, other benefits of the fixed-combination C/BPO gel include flexible, once-daily dosing, and the only available formulation with hydrating excipients, each preserving regimen simplicity and thus improved patient adherence to a therapeutic acne regimen.

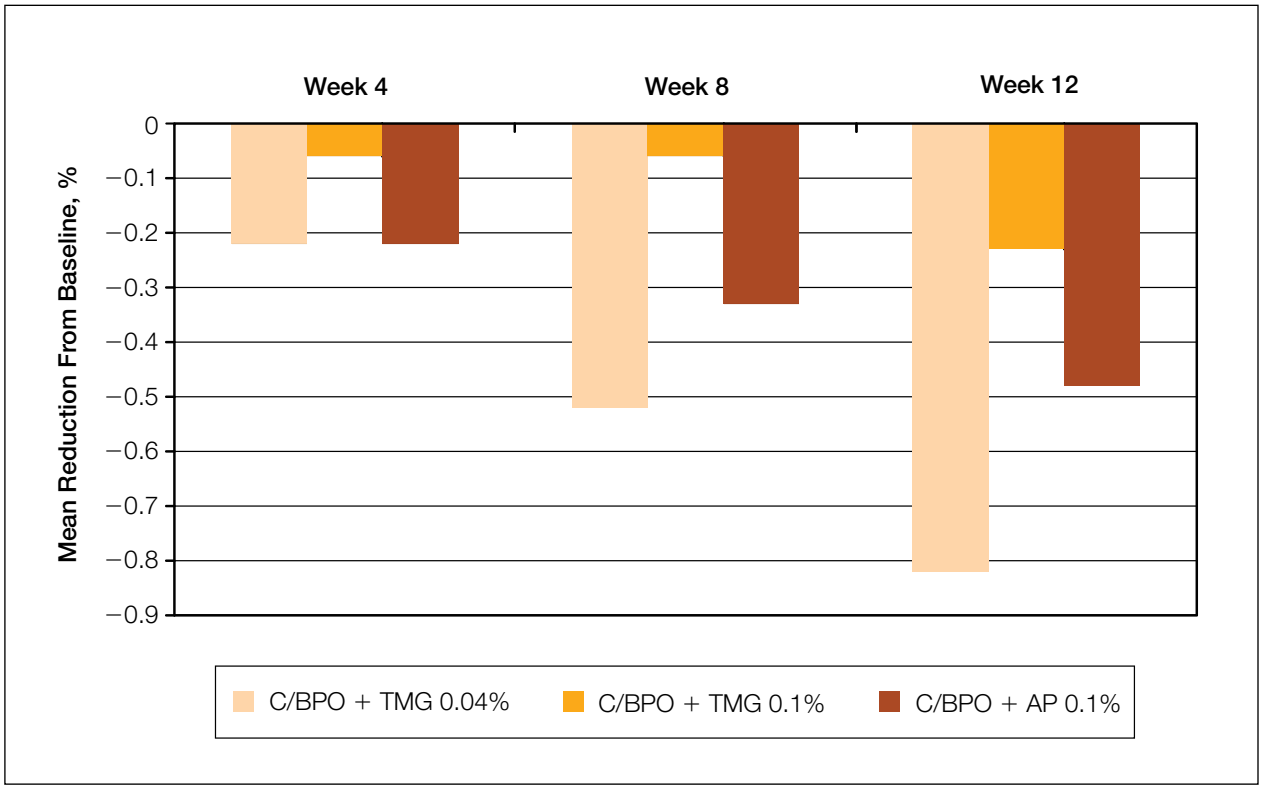

Figure 2. Mean percentage reduction from baseline of hyperpigmentation in participants with skin of color (n=167). Hyperpigmentation was assessed using a 5-point scale (0=absent; 1=slight; 2=mild; 3=moderate; 4=severe). C/BPO indicates clindamycin 1%–benzoyl peroxide 5% hydrating gel; TMG, tretinoin microsphere gel; AP, adapalene gel. Adapted with permission from *Cutis.* 2007;80(suppl 1):15-20. ©2007, Quadrant HealthCom Inc.[20]

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