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.

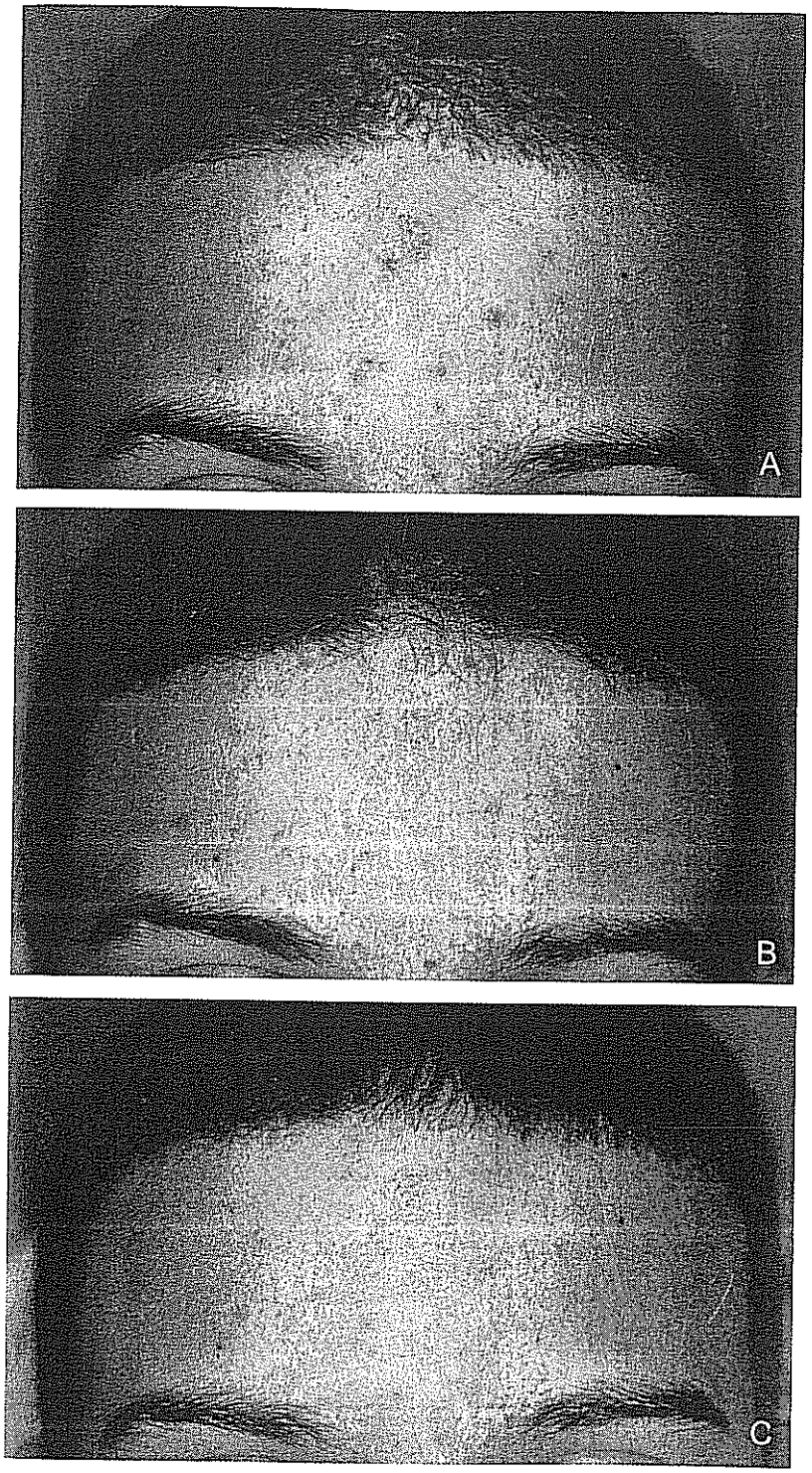

Figure 1. A 17-year-old adolescent boy presented for follow-up with unsatisfactory response to monotherapy with adapalene gel 0.1% applied once daily at night (A). Marked improvement was seen in inflammatory lesion counts after 4 weeks of treatment with clindamycin 1%–benzoyl peroxide 5% (C/BPO) hydrating 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.

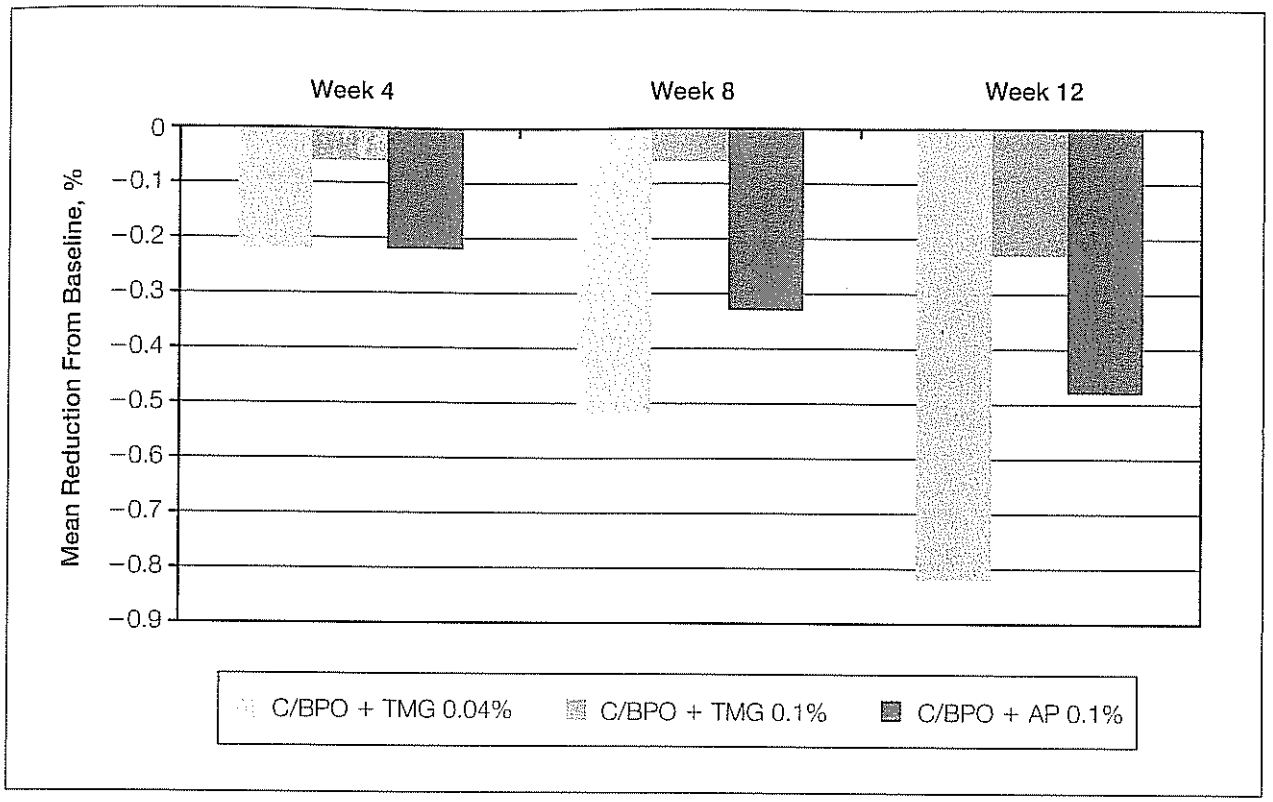

Figure 2. Mean percentage reduction from baseline of hyperpigmentation in participants with skin of color (n=167). Hyperpigmentation was assessed using a 5-point scale (0=absent; 1=slight; 2=mild; 3=moderate; 4=severe). C/BPO indicates clindamycin 1%–benzoyl peroxide 5% hydrating gel; TMG, tretinoin 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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