Fixed-Combination Therapy for Moderate to Severe Acne: A Review of Clindamycin Phosphate 1.2%–Benzoyl Peroxide 2.5% Gel

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Fixed-combination products are commonly used in the treatment of acne, particularly the combination of clindamycin and benzoyl peroxide (BPO). Benzoyl peroxide is known to cause dryness and irritation, often limiting its use. The potential discomfort that can result from the concentration-dependent tolerability of BPO has only recently been elucidated and is particularly noteworthy. An optimized formulation of clindamycin phosphate 1.2%–BPO 2.5% is highly effective and well-tolerated in the treatment of moderate to severe acne and in adolescent acne. Objective clinical assessments such as lesion counts and physician grading classifications alone do not adequately capture the impact of acne severity from a patient's perspective; therefore, assessment of patient satisfaction and improvement in quality of life (QOL) are essential. This review provides an analysis of some of the most recent studies on clindamycin phosphate 1.2%–BPO 2.5% gel for the treatment of moderate to severe acne.

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Fixed-combination products containing clindamycin and benzoyl peroxide (BPO) are widely used in the treatment of acne vulgaris.[1,2] Products containing BPO are highly bactericidal and reduce the development of antibiotic-resistant bacteria.[3] A potential limitation of BPO, however, is concentration-dependent dryness and irritation that may impact patient compliance and limit product use.[4] The extent to which patients are bothered by these side effects and what they do to manage them has only recently been elucidated.[5] Some degree of dryness and irritation occurred in nearly all of the patients who participated in an online survey after using a fixed-combination clindamycin–BPO 5% product in the last 6 months (Table). These side effects were bothersome for the majority of participants, with one-third (67/200) reporting severe dryness. Subsequent self-adjusted treatment was common, with many participants switching

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Degree of Bother From Local Adverse Events (N=200)

Degree of Bother[a]	Participants Reporting Side Effect, %				
	Dry Skin	Redness	Flaking/ Peeling	Itching	Irritation
None	7	14	10	12	12
Mild (score of 1–3)	26	30	29	32	26
Moderate (score of 4–7)	34	36	34	34	42
Severe (score of 8–10)	34	20	27	22	22

[a]Participants were asked to rate the degree of bother for each side effect while using clindamycin 1%–benzoyl peroxide 5% gel (BenzaClin [sanofi-aventis US LLC] or Duac [Stiefel, a GSK company]). Side effects were scored on a 10-point scale (1=not at all bothersome; 10=extremely bothersome).

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products, reducing frequency of application, or even stopping use altogether.[5] With overall adherence to topical therapies generally being poor, particularly among adolescent acne patients, it is important to avoid or better manage side effects that reduce adherence. The selection of less irritating therapies or treatment regimens specifically aimed at minimizing side effects as well as development of formulations that contain lower concentrations of BPO are desirable alternatives.

Historically, one notable suggestion was to formulate a fixed-combination clindamycin-BPO product with a lower BPO concentration. Even before the patient survey mentioned above was conducted, patients reported greater frequency and severity of burning, erythema, and peeling from BPO 10% than from BPO 2.5%.[6] More recently, fixed-combination products containing even a 5% concentration of BPO were reported to be moderately irritating in a cumulative irritation study.[4] Although advances in formulation technology have facilitated the reduction of irritation levels, the most substantial reductions have been achieved through application of lower concentrations of BPO (2.5%).[7]

CLINICAL EXPERIENCE WITH CLINDAMYCIN PHOSPHATE 1.2%–BENZOYL PEROXIDE 2.5% GEL

One concern associated with reduced concentrations of BPO is the potential for reduced efficacy in the treatment of acne. The development of a lower-strength formulation with equal efficacy and greater tolerability as compared to the higher strengths is what is desired. In 1986, Mills et al[6] reported that BPO 2.5% may be as effective as the 5% or 10% concentrations of BPO in reducing the number of inflammatory acne lesions. The study also revealed that BPO 2.5% led to a substantial reduction of *Propionibacterium acnes* counts after 1 week of topical application to the face.[6]

More recently, in an in vitro percutaneous penetration study, Bucks et al[7] achieved skin penetration results with clindamycin phosphate 1.2%–BPO 2.5% that were comparable to fixed combinations containing BPO 5%; however, the clinical significance was to be determined.

The clinical efficacy of clindamycin phosphate 1.2%–BPO 2.5% gel has now been reported extensively in the literature.[8-14]

Gold[10] reported a 64.1% reduction in inflammatory lesion counts and a 48.7% reduction in noninflammatory lesion counts in patients treated with clindamycin phosphate 1.2%–BPO 2.5% gel for 12 weeks. Results were compared with treatment with clindamycin phosphate gel 1.2% (54% and 40.3%, respectively; $P<.001$ for both), BPO gel 2.5% (55.2% and 43.8%, respectively; $P<.001$ and $P=.001$, respectively), and vehicle gel (34.4% and 26.0%, respectively; $P<.001$ for both)(Figure 1).[10]

Seidler and Kimball[15] recently conducted a meta-analysis comparing the efficacy of fixed-combination

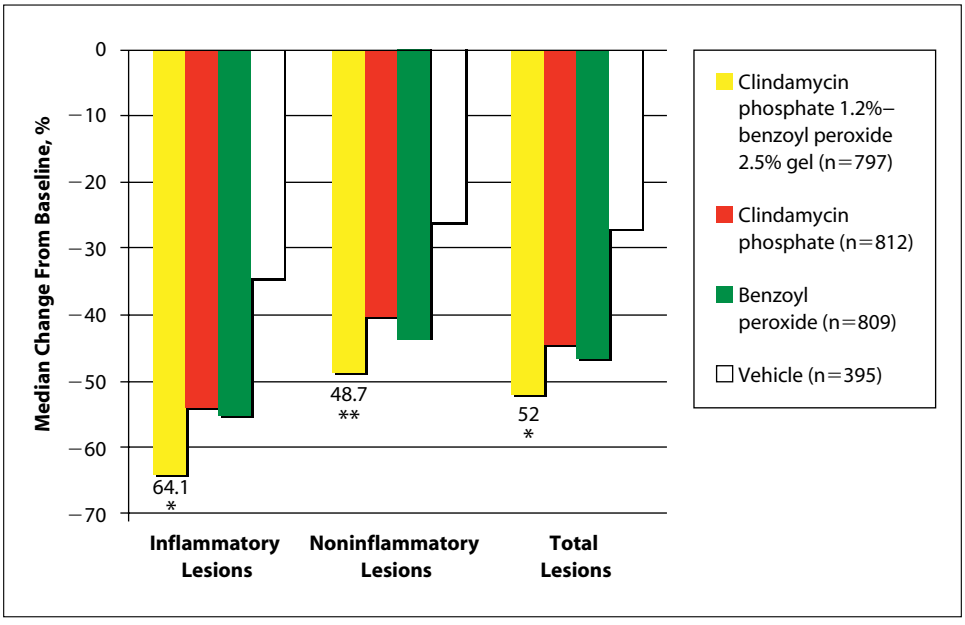

Figure 1. Reduction in inflammatory and noninflammatory lesions. Asterisk indicates $P<.001$ vs clindamycin phosphate 1.2%, benzoyl peroxide 2.5%, and vehicle; double asterisk, $P<.001$ vs clindamycin phosphate 1.2% and vehicle and $P=.001$ vs benzoyl peroxide 2.5%. Reprinted with permission from Valeant Pharmaceuticals North America LLC.

products containing clindamycin–BPO 5% to clindamycin phosphate 1.2%–BPO 2.5% gel. The authors concluded that clindamycin phosphate 1.2%–BPO 2.5% gel was comparable to other topical products containing clindamycin–BPO 5% in reducing lesion counts and may have an advantage in treating noninflammatory lesions. It also was observed that combination formulas performed better than the single agents alone in treating inflammatory lesions over 10 to 12 weeks.[15]

EFFICACY IN SPECIAL POPULATIONS

Investigators have conducted post hoc analyses of pivotal clinical studies in the literature to evaluate the efficacy of clindamycin phosphate 1.2%–BPO 2.5% gel in the treatment of 2 special populations of patients: patients with moderate to severe acne and adolescent acne patients.

Patients With Moderate to Severe Acne

Patients with moderate to severe acne continue to challenge physicians in clinical practice. In 2 pivotal studies of clindamycin phosphate 1.2%–BPO 2.5% gel, almost 20% of the 2813 patients had severe acne.[8] More than 45% (70/154) of the participants with severe acne met the criteria for treatment success (a 2-grade improvement in the evaluator's global severity score) at week 12 with clindamycin phosphate 1.2%–BPO 2.5% gel.[12]

Adolescents With Acne

Adolescent acne patients experience more self-esteem issues, social isolation, depression, and self-consciousness than their peers without acne.[16,17] Despite the psychosocial impact, many adolescents with acne do not seek treatment; those who do often have unrealistic expectations for therapy outcomes or experience poor tolerability, which can lead to low adherence to the treatment regimen.[17,18] Effective therapies demonstrating early signs of improvement that are well-tolerated may provide improved adherence and yield substantially improved clinical outcomes.[19] In addition, adolescent patients often prefer a once-daily treatment because of its convenience.[20,21]

In a post hoc analysis of 1755 adolescent patients with moderate to severe acne (age range, 12 to <18 years), a once-daily formulation of clindamycin phosphate 1.2%–BPO 2.5% gel was found to be superior to treatment with the individual active ingredients and vehicle at week 12 for all primary and supportive end points.[13,22] More than 31% of participants observed at least marked improvement in their acne with clindamycin phosphate 1.2%–BPO 2.5% gel as early as 2 weeks after starting treatment (Figure 2). Satisfaction with clindamycin phosphate 1.2%–BPO 2.5% gel was much greater than prior therapies, and overall participant satisfaction at the end of the study was 81%.[13,22]

PATIENT EXPECTATIONS AND TREATMENT SATISFACTION

Objective clinical assessments such as lesion counts and physician grading classifications alone do not adequately capture the impact of acne severity from a patient's perspective.[23] In clinical practice, patient expectations of and satisfaction with acne therapies are important aspects of

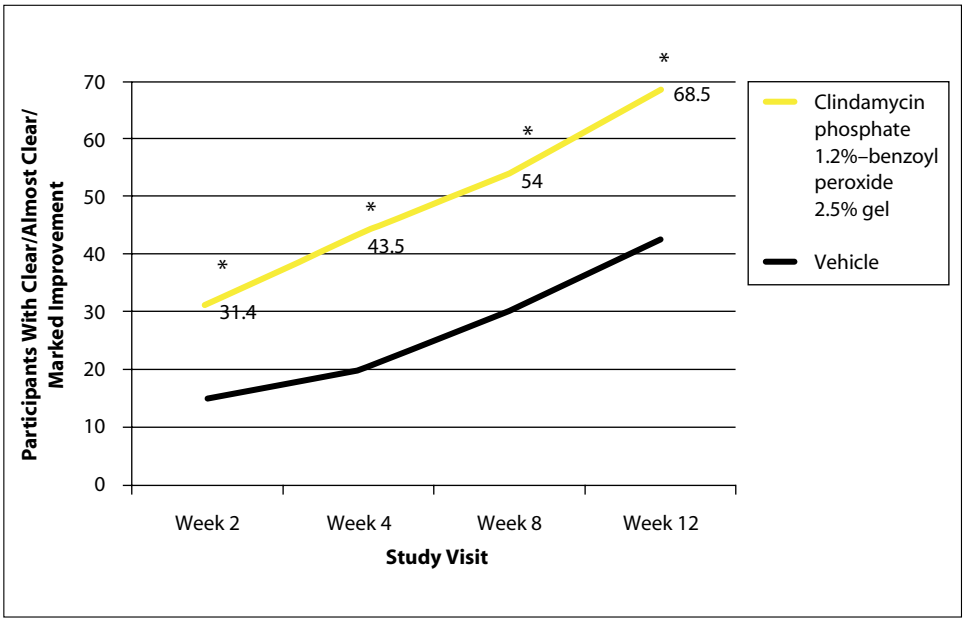

Figure 2. Participant self-assessment of adolescent acne subpopulation. Asterisk indicates $P=.001$ vs vehicle. Reprinted with permission from Gold.[22] ©2012 Matrix Medical Communications. All rights reserved.

acne management. Improved adherence and patient outcomes, including quality of life (QOL) benefits, often are associated with once-daily medications that are perceived by patients to be as safe and effective as treatments with more frequent dosing regimens.[24,25]

Higher levels of patient satisfaction have been associated with clindamycin phosphate 1.2%–BPO 2.5% gel compared with prior therapies.[8,10,11] More than 80% of participants (608/749) were satisfied with treatment outcomes at week 12 compared to 26% (206/791) at baseline. Participant self-assessment of acne improvement was higher than investigator evaluations.[8]

Assessing the impact of facial acne on health-related quality of life (HRQL) also is important when analyzing the effectiveness of acne treatment. Participant self-assessment of overall acne severity has been found to correlate with patient-reported HRQL better than with physician-based assessments.[26]

Acne treatments can differentially impact HRQL. Consequently, HRQL is an important end point in comparative clinical trials, complementing the clinical objective assessments of efficacy and tolerability; however, prior studies of the impact of acne treatments on HRQL included small numbers of patients,[27-29] did not fully examine changes in HRQL,[27-31] included only patients with mild to moderate facial acne,[31,32] and were unblinded observational studies.[32,33]

Improvement in HRQL with clindamycin phosphate 1.2%–BPO 2.5% gel was assessed in 2 pooled, large QOL studies in acne patients.[34] The acne QOL analyses in this study population demonstrated that treatment with clindamycin phosphate 1.2%–BPO 2.5% gel significantly improved participant self-perception of facial acne compared with the individual active ingredients and vehicle in moderate to severe acne across all 4 domains of the acne QOL questionnaire ($P<.001$) (Figure 3). Moreover, the changes in HRQL also were clinically meaningful, and a significantly greater proportion of participants treated with clindamycin phosphate 1.2%–BPO 2.5% gel had a clinically meaningful change in HRQL than in the individual active treatment arms ($P<.001$).[34]

CONCLUSION

The pivotal clinical data on clindamycin phosphate 1.2%–BPO 2.5% gel were published more than 3 years ago.[8] At the time, the 2 pooled, phase 3 studies represented the largest study of moderate to severe acne and the database continues to provide a wealth of information for us to better understand the management of this common condition. Feedback from acne patients has led to increased awareness of how bothersome the concentration-dependent dryness and irritation caused by BPO can be as well as patient response to these adverse affects. Clindamycin phosphate 1.2%–BPO 2.5% gel has demonstrated excellent tolerability.[8] We now have independent evidence to suggest that efficacy is not compromised by a lower BPO concentration and clindamycin phosphate 1.2%–BPO 2.5% gel also may be more efficacious in reducing

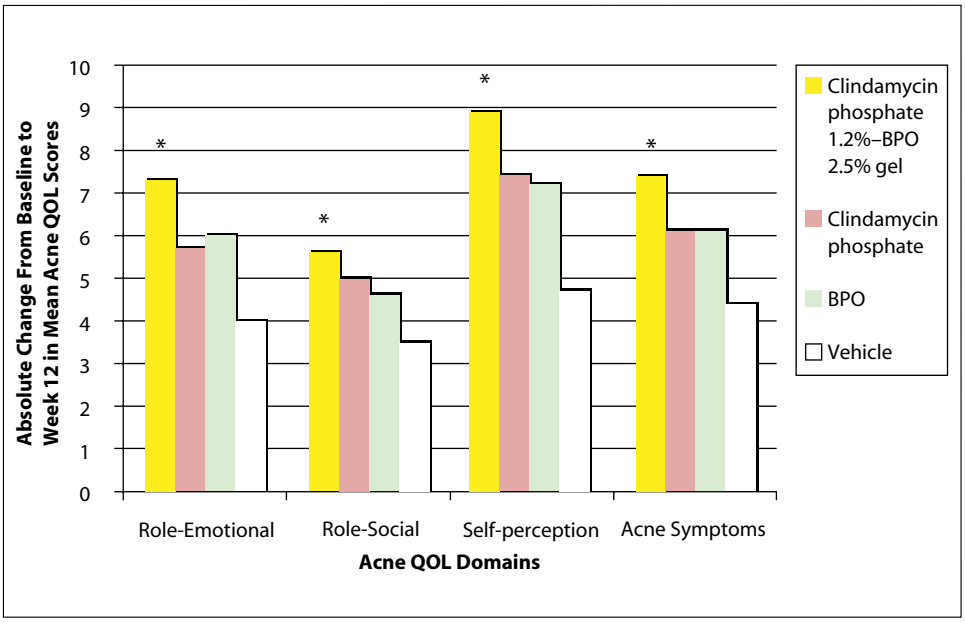

Figure 3. Change in acne quality of life (QOL) domains. BPO indicates benzoyl peroxide; asterisk, $P<.001$ vs active ingredients and vehicle. Reprinted with permission from *Cutis*. 2010;86:263-267. ©2010, Quadrant HealthCom Inc.[34]

noninflammatory lesions.[15] Post hoc analyses in 2 important populations—moderate to severe acne and adolescent acne—in which treatment can be particularly challenging have shown good results, with more than 45% (70/154) of severe acne patients being judged as treatment successes[12] and more than 31% of adolescent patients demonstrating at least marked improvement in their acne at 12 weeks.[13] Most importantly, we are able to gain additional insights of patient perception for product satisfaction, treatment success, and improved QOL that will be important to successfully manage acne in the future.

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