

Efficacy and Safety of a Ceramide Containing Moisturizer Followed by Fixed-dose Clindamycin Phosphate 1.2%/Benzoyl Peroxide 2.5% Gel in the Morning in Combination With a Ceramide Containing Moisturizer Followed by Tretinoin 0.05% Gel in the Evening for the Treatment of Facial Acne Vulgaris

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ABSTRACT

Combination therapy addressing multiple pathogenic factors should be used to achieve optimal outcomes in treating acne. The following study demonstrated both safety and efficacy of fixed-dose clindamycin phosphate 1.2%/benzoyl peroxide 2.5% in the morning with micronized tretinoin 0.05% gel in the evening. Both products were applied to the skin following the use of a ceramide containing moisturizing lotion.

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INTRODUCTION

The pathophysiology of acne vulgaris is multifactorial. Follicular hyperkeratinization, *Propionibacterium acnes* (*P. acnes*) proliferation, sebum production, and inflammation all contribute to the development of acne lesions.¹ Therefore, the ideal acne treatment is combination therapy using medications with complimentary mechanisms of actions addressing these multiple pathogenic factors.² Consensus guidelines recommend the use of a topical retinoid plus an antimicrobial agent with or without benzoyl peroxide (BPO) as first-line therapy for most patients with mild to moderate acne.¹

Combination therapy with a topical retinoid in conjunction with a fixed dose topical BPO/clindamycin gel addresses three of the four major pathogenic factors in acne. Topical retinoids normalize abnormal follicular hyperkeratinization which prevents the formation of microcomedones.^{3,4} Retinoids also reduce inflammation in acne by down-regulating toll-like receptors,⁵ cytokines,⁶ and nitric oxide.⁷ Antimicrobial agents such as clindamycin reduce *P. Acnes* colonization on the skin and its subsequent pro-inflammatory effects.¹ BPO is at the same time keratolytic, anti-inflammatory, and bactericidal.⁸ It is commonly used in combination with topical antibiotics to reduce the risk of antibiotic resistance.⁹⁻¹¹ Moreover, the addition of BPO has been shown to give improvements even in patients with previously known bacterial resistance.¹²

The most common side of effects of topical acne medications are local cutaneous adverse events including erythema, dryness, and burning/stinging.^{1,2} For topical retinoids, the side effects are most

common in the first two weeks, when the skin undergoes a period of "retinization," acclimating to the drug.¹³ Several strategies exist to minimize this irritation, including initiating therapy with a low strength drug and titrating up as tolerated, as well as attempts at improving skin barrier function.¹³⁻¹⁵ Unlike that of topical retinoids, the irritation potential of BPO is independent of this type of adjustment period and has been linked to concentration of the drug itself.¹⁶ It is important to minimize these side effects as they can interfere with patient adherence to applying their medications.¹⁷

In this report, we review the results of an open-label investigation to evaluate the safety and efficacy of combination therapy using a fixed-dose combination antimicrobial/BPO gel in the morning and a topical retinoid in the evening. The medications evaluated were clindamycin phosphate 1.2%/BPO 2.5% (CP/BPO) in an aqueous gel free of preservatives, surfactants, parabens, or alcohol (Acanya® Gel, Valeant Dermatology) in the morning and micronized tretinoin 0.05% in an aqueous gel containing hydrating ingredients (Atralin® Gel, Valeant Dermatology) in the evening. A ceramide containing moisturizer (CeraVe® Lotion, Valeant Dermatology) was applied to the skin prior to application of the medications in the morning and in the evening.

METHODS

Treatment Regimen

This open-label investigation was performed at a single center for a 12-week treatment period. In the morning, all patients were instructed to wash their faces with a non-soap cleanser (CeraVe® Hydrating Cleanser, Valeant Dermatology) then pat dry. They then

applied a ceramide containing moisturizer (CeraVe® Lotion, Valeant Dermatology) to the entire face, followed by application of a fingertip amount of CP 1.2%/BPO 2.5% gel (Acanya® Gel, Valeant Dermatology) divided to cover the entire face. Patients were allowed to use a sunscreen of their choice, to be applied after moisturizing, but before application of the CP 1.2%/BPO 2.5% gel. In the evening, all patients were instructed to wash and moisturize their faces as they did in the morning. Subjects then applied a pea-sized amount of tretinoin 0.05% gel (Atralin® Gel, Valeant Dermatology) divided to cover the entire face, every other night for two weeks followed by every night thereafter. Patients were instructed to apply the study medications over the entire face using a 6-dot method to ensure complete and even coverage. They were also advised to avoid application of medications close to the mouth, lips, eyes, angles of the nose.

The study was an open-label investigation, so investigators, participants, and study coordinators were not blinded. All study procedures were reviewed and approved by the Mt. Sinai Medical Center institutional review board. Fully informed and written consent was obtained from all participants or the parent/guardian of those younger than 18 years.

Participants were treated for 12 weeks with study visits at baseline and at weeks 2, 4, 8, and 12. At the baseline visit, patient demographic information and medical histories were collected. In addition, investigator static global assessments, local tolerability assessments, and urine pregnancy tests were performed. At each subsequent visit, efficacy was evaluated by the investigators using a 6-point physician's global assessment (PGA) score. Investigators also assessed participant erythema, dryness and peeling on a 3-point scale (0=none, 3=severe). Patients reported presences of burning/stinging on a 3-point scale (0=none, 3=severe). Investigators also monitored other adverse events (AE's). Finally, patient drug diaries were monitored at each visit.

Patients

A total of 20 patients were enrolled into the study. Eligible patients were males and females at least 12 years old with stable, mild to moderate facial acne vulgaris, graded as a 2 or 3 on a 6-point Physician's Global Assessment (grade 0=normal, clear skin; grade 5=highly inflammatory lesions predominate). Participants were required to understand and sign consent forms and follow study procedures. Exclusion criteria included female patients known to be pregnant, attempting to conceive, breastfeeding, or of child-bearing potential not using a reliable contraception. In addition, the following washout periods were required: 1 week for topical acne medications and 2 weeks for systemic antibiotics. Female patients who were stable on birth control pills used for contraception for at least the 6 months prior were allowed to participate.

Study End Points

The primary end point of the study was treatment success, a static

end point defined as a score of 0 (clear) or 1 (almost clear) on a 6-point Physician's Global Assessment scale. The secondary end point of the study was to determine local tolerability and irritation potential based on investigator assessments of dryness, scaling, and erythema and participant assessments of burning/stinging at each study visit. Investigators assessed dryness, scaling, and erythema using a 3-point scale from 0 (none) to 3 (severe). Safety was assessed by recording the frequency of adverse events throughout the study. If a local tolerability reaction or skin irritation required medical treatment or an interruption/change in study regimen, the event was recorded as an AE.

Data Analysis and Statistical Methods

No sample size calculation was undertaken; rather the sample size was determined to be sufficient to descriptively assess the tolerability in patients with acne. Local tolerability and irritation potential assessments were analyzed using summary statistics and frequency tabulations, and AE's were analyzed using frequency tabulations. Analysis was performed using the intention-to-treat population (ITT), which consisted of all participants who received at least 1 application of either study medication.

STUDY RESULTS

Participants

The study was conducted between June and October 2011. A total of 20 patients were enrolled, and 16 patients completed the study. Four participants withdrew consent throughout the course of the study. All participants were healthy males and females from the ages of 13 and 49 years, with mild to moderate facial acne. Patient

TABLE 1.

Patient Demographic Data

Parameter	N=20
Age	
year (mean [SD])	29.50 (11.57)
Range	13-49
Gender	
Male (n [%])	5 (25%)
Female (n [%])	15 (75%)
Race	
Caucasian (n [%])	7 (35%)
Black (n [%])	6 (30%)
Asian (n [%])	3 (15%)
Hispanic (n [%])	4 (20%)
Baseline PGA Score	
Clear (n [%])	0
Almost Clear (n [%])	0
Mild (n [%])	13 (65%)
Moderate (n [%])	7 (35%)
Severe (n [%])	0
Very Severe (n [%])	0

demographic information is summarized in Table 1.

Efficacy

60% (12 of 20) of patients were considered to be a treatment success at week 12. Treatment success was defined as having a PGA score of 0 or 1 ("Clear" or "Almost Clear"). This calculation was performed using the ITT population with the last observation carried forward (LOCF). 1 patient who was considered a treatment success withdrew consent before completing 12 weeks of therapy.

Tolerability

The number of subjects and their respective scores for erythema, dryness, scaling, and burning/stinging at each study visit are summarized in Figures 1 through 4. The majority of patients reported scores of none to mild for all tolerability parameters throughout the study. As the skin accommodates to topical retinoid application during an initial period of retinization, erythema, dryness, scaling, and burning/stinging are common. At week 2, 65% (13 of 20) and 35% (7 of 20) of patients experienced none or mild burning/stinging, respectively. 55% (11 of 20) and 45% (9 of 20) of patients experienced none or mild dryness, respectively. 55% (11 of 20) and 40% (8 of 20) of patients experienced none or mild erythema, respectively. 75% (15 of 20) and 25% (5 of 20) of patients experienced none or mild scaling, respectively.

At week 4, 95% of patients experienced none or mild erythema, dryness, scaling, or burning/stinging. Scores of moderate (2, on a 4-point scale) were given to a total of 3 patients at week 4. One patient was given a score of 2 for erythema, which resolved at week 8. One patient was given scores of 2 for both dryness and scaling. Dryness improved at week 8, and scaling persisted as moderate at week 8, but resolved at week 12. One patient was given a score of 2 for burning/stinging, which improved at week 8.

Adverse Events

A total of 3 AE's were reported in 3 participants over the course of the study, all of which occurred from 2 to 4 weeks of treatment. All AE's were considered to be mild and treatment related. Mild application site irritation occurred in 2 patients, resulting in interruption of application of study of medications. One of the patients missed one application of the study medications, and the other patient missed 3 applications of the study medications. One patient reported an increase number of acne lesions, and as a result skipped several study-drug application doses; that patient ultimately withdrew consent at week 8.

DISCUSSION

Current expert guidelines for acne treatment stress the importance of combination therapy. Combining medications with complementary mechanisms of action can effectively treat acne by addressing multiple pathophysiologic factors that cause acne.¹The current regimen combining CP/BPO with tretinoin offers a favorable tolerability profile and excellent efficacy. These

FIGURE 1. Burning/Stinging Scores

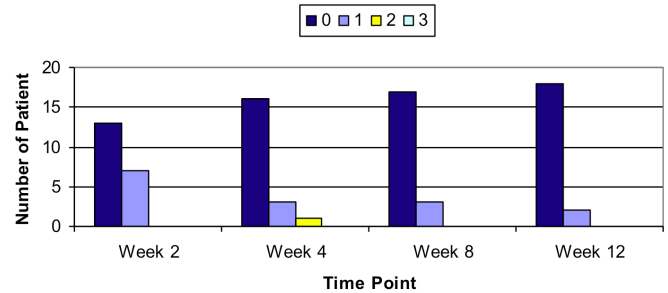


FIGURE 2. Dryness Scores

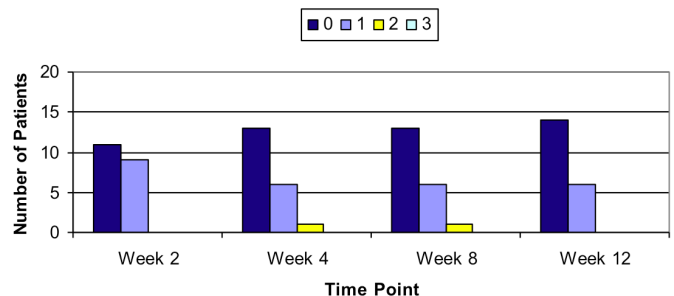


FIGURE 3. Erythema Scores

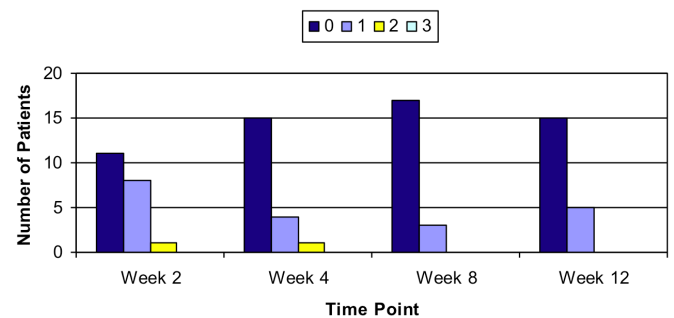
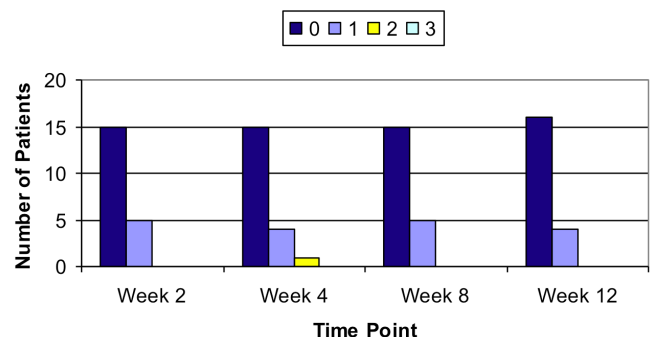


FIGURE 4. Scaling Scores



results are consistent with previous studies evaluating combination therapy with other fixed dose combinations of CP/BPO with topical retinoids such as adapalene¹⁸ and tazarotene.¹⁹

The 60% success rate in this study is statistically higher than the success rates of those achieved in the pivotal studies evaluating the individual medications, supporting the recommendation for combination therapy. Head-to-head comparisons, however, are limited by differences in study design, patient entry criteria, and investigators' assessment biases. Two, phase-III clinical trials were performed evaluating monotherapy with micronized tretinoin 0.05% for mild to moderate acne vulgaris. Pooled data from both studies demonstrated a 17% success rate compared to vehicle.²⁰ In addition, the two pivotal studies comparing CP/BPO 2.5% to its monads and vehicle resulted in a 32.3% treatment success in a post-hoc analysis of patients with baseline moderate acne.²¹ In these studies, treatment success was defined as achieving a 2-grade improvement in evaluators' global severity score compared to baseline.²² The success rate in the current study is comparable to data in other combination therapy acne studies, but again, direct comparisons are limited for the same reasons previously stated. Concurrent use of CP/BPO 5% with tazarotene 0.1% cream resulted in success in 57% of patients after 12 weeks. In this study, success was defined as 50% or greater global improvement from baseline.¹⁹ Success rate was not reported in the trial evaluating CP/BPO 5% with adapalene 1% gel.¹⁸

Several factors explain the excellent tolerability profile of combination therapy with CP/BPO with micronized tretinoin 0.05% gel in this study. First, 2.5% BPO carries a lower rate of cutaneous adverse events compared products with higher concentrations. In one comparative study, 2.5% BPO gel demonstrated equal efficacy to 5% and 10% BPO, but with lower cutaneous adverse events compared to 10% BPO.¹⁶ Even 5% BPO has been shown to be a source of significant irritation for acne patients.²³

Excipients in the topical medications likely helped minimize local skin adverse events. CP/BPO 2.5% used in the current study is contained in a moisturizing hydrogel vehicle, which is also free of potentially irritating surfactants and preservatives.²⁴ This helps minimize irritation potential of the CP/BPO product itself²⁵ and can help prevent potential irritation from concurrent use of a topical retinoid. In a previous trial evaluating combination therapy with CP/BPO 5% with adapalene 0.1% gel, week 4 skin irritation was statistically less in patients using both medications as compared to those applying adapalene 0.1% gel monotherapy. Excipients in the CP/BPO 5% product were thought to mitigate the dryness and peeling that patients commonly develop during the first several weeks of treatment, during which patients underwent a period of retinization.¹⁸ While statistical significance was not achieved, a similar trend was observed in another study evaluating the combination of CP/BPO 5% with tazarotene 0.1% cream.¹⁹

Similar to the effects of excipients in topical medications, moisturizers themselves may help lower the risk of skin irritation

from topical acne medications. In a head to head study comparing tazarotene 0.1% cream alone to tazarotene cream applied 20 minutes after application of a skin moisturizer, there was no statistical significance in efficacy between the two groups. However, there was consistently less dryness during all study points in moisturizing arm, with statistical significance at week 2 (at the peak of the retinization period). There was also a trend of less skin peeling and erythema in the group using the moisturizer.¹⁵

There is evidence suggesting that skin barrier defects contribute to the pathogenesis of acne, and ceramide levels have been shown to be deficient in acne patients. In one study, the mean percentage of total ceramides in the polar lipid fraction from the stratum corneum of acne patients was demonstrated to be significantly lower than that of matched control subjects without acne. Ceramide deficiency and the resulting impaired skin barrier were hypothesized to promote follicular hyperkeratosis, which in turn led to comedone formation.²⁶ Moreover, there is data to suggest that phytosphingosine, a ceramide sphingolipid ingredient in the moisturizer, is both antimicrobial against *P. acnes* and directly anti-inflammatory.²⁷ Selecting a moisturizer containing ceramides not only helps moisturize the skin, but may also help restore ceramides, improve skin barrier function, and reduce inflammation. In this study, all patients applied the moisturizer prior to their medications, and there was no comparator arm without moisturizer use. However, given the high success rate and minimal cutaneous adverse events, we conclude that prior use of the ceramide-based moisturizer did not interfere with efficacy, but helped improve tolerability of the regimen.

CONCLUSION

Combination therapy CP/BPO and tretinoin addresses multiple pathogenic factors involved in acne pathogenesis. This triple therapy, along with prior application of a ceramide-based moisturizer, is an effective and well-tolerated treatment for acne vulgaris.

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DISCLOSURES

Dr. Zeichner has served as an advisory board member, consultant, or investigator for Beiersdorf, Galderma, Medicis, Onset Dermatology, Ortho Dermatology, Pharmaderm, Procter and Gamble, Promius Pharma, and Valeant Dermatology. Drs. Patel and Haddican and Ms. Wong have no disclosures.

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