Randomized Tolerability Analysis of Clindamycin Phosphate 1.2%–Tretinoin 0.025% Gel Used With Benzoyl Peroxide Wash 4% for Acne Vulgaris

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The multiple etiologic factors involved in acne vulgaris make the use of several medications necessary to treat the condition. Use of a fixed combination of clindamycin phosphate 1.2% and tretinoin 0.025% in conjunction with a benzoyl peroxide (BPO) wash 4% targets several pathologic factors simultaneously and mitigates the potential for clindamycin-induced Propionibacterium acnes*–resistant strains. New formulations may allow such regimens to be effectively used without overly reduced tolerability resulting from the irritation potential of tretinoin and BPO.*

This randomized, single-blind study investigated the local tolerability, irritation potential, and safety of an aqueous-based gel (clindamycin phosphate 1.2%–tretinoin 0.025% [CT gel]) when used in conjunction with a BPO wash 4% in participants with mild to moderate acne vulgaris. Participants applied the CT gel once daily in the evening for 4 weeks in conjunction with once-daily morning use of either BPO wash 4% or nonmedicated soap-free cleanser lotion (SFC). Local tolerability and irritation potential were assessed by participants and investigators using separate 6-point scales. The frequency and severity of dryness, scaling, erythema, burning/stinging, and itching increased during the first week of treatment in both treatment arms but decreased thereafter. Local tolerability reactions were slightly more frequent in the CT gel + BPO wash group versus the CT gel + SFC group at week 1 but were generally mild and improved within 1 to 2 weeks. In conclusion, therapy with CT gel + BPO wash appears safe and well-tolerated in participants with mild to moderate acne vulgaris.

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Acne affects 80% of individuals aged 11 to 30 years and has a substantial economic and social impact.[1] According to the American Academy of Dermatology, the condition affects approximately 40 to 50 million individuals in the United States and is associated with a direct treatment cost of more than $2.2 billion.[2] However, despite the psychological burden of acne, adherence to treatment remains poor due to insufficient efficacy or tolerability.[3] Acne treatment can be individualized to each patient's needs using monotherapy or combination therapy, but of primary importance in tailoring any therapeutic approach is the availability of highly effective and well-tolerated treatment options.

As a disease, acne has 4 primary pathogenic features: stimulation of sebum gland activity, *Propionibacterium acnes* proliferation, abnormal

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follicular hyperkeratosis and obstruction of the follicle, and release of inflammatory mediators.[4] Because of the complexity of these mechanisms, currently there is no single topical pharmaceutical agent that is able to simultaneously target all 4 mechanisms. Therefore, consensus guidelines recommend utilizing combination therapy.[4] In particular, the guidelines advocate use of a retinoid and an antibiotic as first-line therapy in patients with both inflammatory and noninflammatory lesions.[4,5] This approach addresses 3 of 4 pathogenic processes.[6] Retinoids inhibit microcomedone formation and reduce the number of precursor lesions as well as reduce comedones and inflammatory lesions,[7] whereas antimicrobials (eg, antibiotics and other agents with bacteriostatic or bactericidal properties) primarily affect inflammatory lesions.[6] Combining a retinoid with an antimicrobial agent also enables synergistic and more complete results than treatment based on either agent used alone.[4] Retinoid monotherapy is slow to clear inflammatory lesions. When combined with an antimicrobial, a retinoid has the potential to enhance the skin penetration of the antimicrobial, resulting in faster lesion clearance.[8] Indeed, fixed-combination products are reported to be more effective, well-tolerated, and convenient for patients than multiple individual agents. By reducing the number of medications and applications, fixed-combination products may improve patient adherence and successful treatment outcomes.[5]

Another important component of acne therapy is benzoyl peroxide (BPO), which has keratolytic, anti-inflammatory, and additional bactericidal properties.[9] The drug's antibacterial properties are of particular significance when considering adjunctive therapy. Monotherapy with topical antibiotics is no longer recommended because of the tendency to increase the emergence of resistant *P acnes* strains.[6] In contrast, evidence suggests that BPO can mitigate the potential risk for *P acnes* resistance in addition to actively reducing *P acnes* counts.[10,11] For example, a study by Leyden et al[11] showed that BPO cleanser 6% prevented and reduced *P acnes* counts to control acne lesions, even when the strains were resistant to common tetracycline and macrolide antibiotics. Therefore, benzoyl peroxide wash often is prescribed in conjunction with antibiotic-containing products, but as with retinoids, it has the potential to increase local irritation when used with other topical products, which has important implications because lack of adherence to treatment regimens is the chief cause of treatment failure among patients with acne.[1]

A common antibiotic-containing regimen is the retinoid and antibacterial pairing of clindamycin and tretinoin. One such fixed-combination product, clindamycin phosphate 1.2%–tretinoin 0.025% gel (CT gel), has proven to be well-tolerated and more effective than its individual components in 3 large randomized trials comprising 3868 participants with mild to moderate acne.[12,13] Tretinoin and BPO traditionally have been sequentially administered to enhance both tolerability and efficacy,[14] thus the current trial was designed to evaluate the local tolerability, irritation potential, and safety of CT gel in a solubilized aqueous-based gel formulation (Veltin™) when used in conjunction with BPO wash 4% in a hydrophase base formulation (Brevoxyl®-4) in participants with mild to moderate acne vulgaris. (Physicians may wish to consult the National Institutes of Health Clinical Trials Registry [http://clinicaltrials.gov; Identifier: NCT00891982].)

Methods and Participants

Study Design—This single-blind, parallel-group study was performed at 5 centers (dermatology clinics) in the United States. Participants were randomized (1:1 ratio) using a computer-generated random assignment schedule from the study sponsor to treatment with either BPO wash 4% or nonmedicated soap-free cleanser lotion (SFC)(Impruv®) once daily in the morning. Additionally, all participants washed the face in the evening with SFC and then applied the CT gel (Table 1). Participants were treated for 4 weeks with study visits at baseline and at weeks 1, 2, and 4. Investigators were blinded to treatment assignment but participants, study nurses, and coordinators were not.

All study procedures were reviewed and approved by an institutional review board, and the International Conference on Harmonisation guidelines of good clinical practice were followed. Fully informed and written consent was obtained from all participants or the parent/guardian of those younger than 18 years.

Participants—To be eligible for the study, participants were required to have mild to moderate acne based on an investigator static global assessment score of 2 or more (grade 0=normal, clear skin; grade 5=highly inflammatory lesions predominate) as well as 17 to 40 inflammatory facial lesions (papules and pustules, including nasal lesions) and 20 to 150 non-inflammatory lesions (open and closed comedones, excluding the nose). Participants also were required to use adequate contraception (if female), understand and sign consent forms, and follow study procedures. Participants were excluded if they met any of the

Table 1.

Treatment Regimen

	Morning	Evening
Treatment 1 (CT gel + BPO wash group)	BPO wash 4%	SFC + CT gel
Treatment 2 (CT gel + SFC group)	SFC	SFC + CT gel

Abbreviations: CT, clindamycin phosphate 1.2%–tretinoin 0.025% gel; BPO, benzoyl peroxide; SFC, soap-free cleanser lotion.

following criteria: presence of any nodulocystic lesions or facial dermatitis; history or presence of regional enteritis, photosensitivity, or inflammatory bowel disease (eg, ulcerative colitis, pseudomembranous colitis, chronic diarrhea, antibiotic-associated colitis); receipt of any investigational product in the preceding 4 weeks or during the study; recent use of antibiotics, corticosteroids, or topical treatment of acne or postinflammatory hyperpigmentation (topical agents, within preceding 2 weeks; systemic agents, within preceding 4 weeks); use of systemic retinoids within the last 6 months; facial procedure (peel, dermabrasion, or UV light therapy) within the last 4 weeks; current use of photosensitizers, neuromuscular blockers, or any medication that may affect evaluation of the study products or put the participant at risk; prior participation in a CT gel study; pregnant and/or breastfeeding; hypersensitivity to study medication or excipients; significant medical history or substance abuse; unable or unlikely to attend study visits; and sharing a household with another study participant.

Procedures and Study End Points—At baseline, information was collected regarding demographics and medical histories; investigator static global assessments, local tolerability assessments, and pregnancy tests were performed. Participants were instructed to wash the face in the morning with either BPO wash 4% or SFC and then apply an oil-free, noncomedogenic, hypoallergenic facial emollient with sunscreen prior to any other skin products. This moisturizer with sunscreen could be reapplied throughout the day as needed. All participants also were instructed to wash the face each evening with SFC and pat their skin dry before applying the CT gel (pea-sized amount, 0.2−0.4 g). The CT gel was applied over the entire face using a 9-dot method to ensure complete and even coverage. Participants were advised to avoid close contact between the product and the mouth, lips, eyes, angles of the nose, and mucous membranes, and to avoid washing the face for at least 4 hours (preferably 8 hours) following application. Participants were asked to complete a diary documenting each application as well as any missed applications.

At each visit following treatment initiation, participants returned their diaries along with any dispensed product tubes for weighing and provided updated information on concomitant medication or nutritional supplements. Both participants and investigators also completed local tolerability and irritation potential reports (on the frequency of each event and change from baseline), and adverse events (AEs) were monitored.

The primary end point of the study was to determine local tolerability and irritation potential based on participant assessments of burning/stinging and itching, and investigator assessments of dryness, scaling, and erythema. Participants assessed burning/stinging and itching using a 6-point scale from 0 (normal, no discomfort) to 5 (definite continuous discomfort that interferes with normal daily activities). Investigators assessed dryness, scaling, and erythema using a 6-point scale from 0 (normal) to 5 (prominent and dense).

Safety was assessed by recording the frequency of treatment-emergent events, treatment-related events, events leading to discontinuation, and serious events. 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 AEs were analyzed using frequency tabulations. Analysis was performed using the intention-to-treat population, which consisted of all participants who received at least 1 application of either study medication.

Results

Participants—The study was conducted between April and June 2009. Of the 61 participants who were enrolled (30 participants in the CT gel + BPO wash group; 31 participants in the CT gel + SFC group) and comprised the intention-to-treat population, 58 participants completed the study (28 [93%] and 30 [97%], respectively). Two participants (1 in each treatment group) withdrew consent and 1 participant (CT gel + BPO wash group) discontinued because of noncompliance. All participants were aged 12 to 37 years and were healthy males or females with mild to moderate facial acne. Demographic characteristics were similar in both treatment groups at baseline (Table 2) and exposure to the study products was comparable between the groups throughout the study.

Local Tolerability and Irritation Potential—In general, most of the changes in tolerability parameters during the study were small. The combination of CT gel + BPO wash led to a slightly higher rate of local tolerability reactions versus CT gel + SFC within the first week of treatment, but these reactions were generally mild in severity and improved within 1 to 2 weeks. The overall severity of the changes decreased by weeks 2 or 4 in almost all cases, except 1 participant in the CT gel + BPO wash group who developed grade 3 erythema at week 1 that persisted at this severity through weeks 2 and 4, and another participant in the CT gel + SFC group who had grade 3 erythema at baseline that improved at week 1 and then returned to grade 3 at weeks 2 and 4. Grade 4 or grade 5 ratings were only seen at week 1: grade 4 erythema in 2 participants in the CT gel + BPO wash group, grade 4 scaling and grade 5 dryness in 1 participant in the CT gel + BPO wash group, and grade 4 dryness and scaling in 1 participant in the CT gel + SFC group.

Mean scores over time for each tolerability parameter are shown in Figures 1 and 2. With the exception of erythema, all mean investigator-rated scores improved over time in both treatment groups. A similar trend of improvement occurred for the participant-rated parameter of itching. Scores for burning/stinging improved in both treatment arms from their peak at week 1, though scores remained slightly higher at week 4 in the CT gel + SFC group versus the CT gel + BPO wash group.

Additional use of moisturizer during the study was considered an indirect indicator of tolerability. Application of the moisturizer was similar across the 2 treatment groups throughout the study and generally occurred once daily, thus suggesting that increased irritation was not a problem.

Adverse Events—A total of 14 AEs were reported in 9 participants over the course of the study: 1 participant (3%) in the CT gel + BPO wash group and 8 participants (26%) in the CT gel + SFC group. Specific events are outlined in Table 3. Four participants experienced events that were considered treatment related, all in the CT gel + SFC group (3 mild application-site reactions of dryness with or without erythema or irritation, and 1 case of mild sunburn); 3 participants in this group interrupted or reduced their use of the study product. All AEs were of mild (12 events) or moderate (2 events considered unrelated to treatment) intensity, and there were no serious or severe AEs and no AEs leading to discontinuation.

Comment

The use of a topical retinoid plus an antimicrobial agent has become the standard of care for acne, and the addition of BPO-containing products is recommended to limit the emergence of *P acnes*–resistant strains.[4] However, because BPO has the potential to irritate the skin,[9] it is important to determine if it can be used compatibly with other topical preparations, particularly those containing retinoids, which also have the potential to cause local irritation.[7]

This relatively small study demonstrates that CT gel can be safely used with BPO wash 4% for the treatment of acne vulgaris. Although CT gel in conjunction with BPO wash led to a slightly higher rate of local tolerability reactions during the first week of treatment, they were generally mild in severity and improved over the subsequent 1 to 2 weeks. Erythema and itching are to be expected at the onset of treatment and patients should be counseled to use moisturizer and sunscreen.

Our results are consistent with preclinical assessments showing no increase in irritation when CT gel was used with this BPO wash in an ex vivo human skin model.[15] Our tolerability data also are consistent with 2 earlier clinical studies in which clindamycin phosphate 1.2%–tretinoin 0.025% (Ziana®) was used in conjunction with BPO wash. Kircik[16] reported small increases in tolerability scores over 4 weeks when clindamycin phosphate 1.2%−tretinoin 0.025% gel was used in conjunction with once daily BPO wash 5% and scores decreased with continued treatment. In the second study, which had a similar

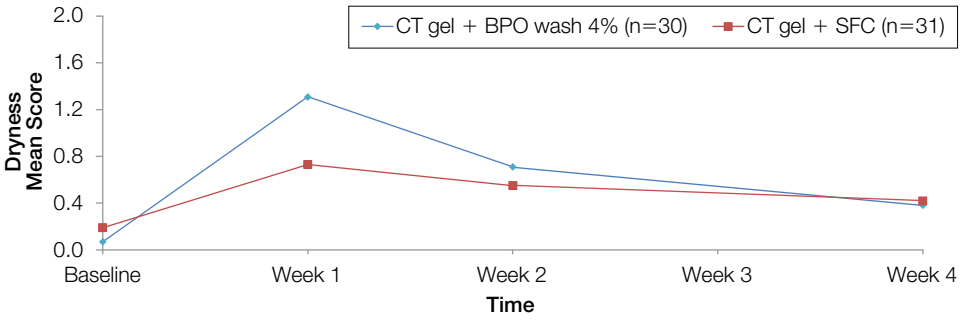
Table 2.

Demographics and Baseline ISGA

	CT Gel + BPO Wash 4% (n=30)	CT Gel + SFC (n=31)
Age, y		
Mean (SD)	17.9 (5.0)	19.2 (5.3)
Minimum, maximum	13, 37	12, 31
Age category, n (%)		
12 to <18 y	16 (53)	14 (45)
18 to 37 y	14 (47)	17 (55)
Gender, n (%)		
Male	12 (40)	11 (35)
Female	18 (60)	20 (65)
Race, n (%)		
Black	2 (7)	3 (10)
Multiracial	4 (13)	0 (0)
White	24 (80)	28 (90)
Ethnicity, n (%)		
Hispanic or Latino	6 (20)	5 (16)
Not Hispanic or Latino	24 (80)	26 (84)
ISGA, n (%)[a]		
Grade 2	9 (30)	11 (35)
Grade 3	18 (60)	15 (48)
Grade 4	3 (10)	5 (16)

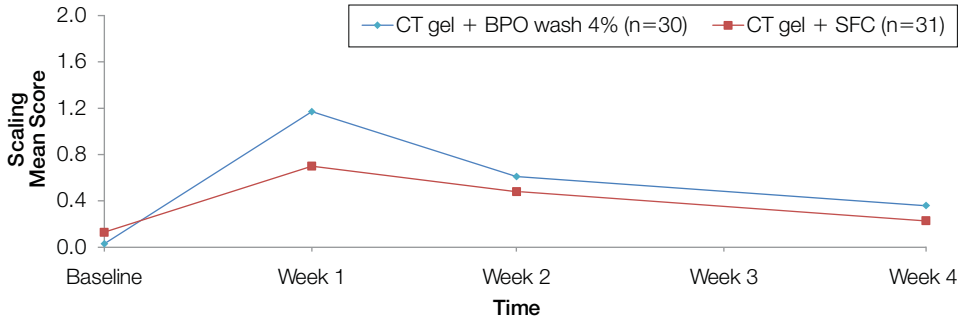
Abbreviations: CT, clindamycin phosphate 1.2%−tretinoin 0.025%; BPO, benzoyl peroxide; SFC, soap-free cleanser lotion; SD, standard deviation; ISGA, investigator static global assessment.

[a]ISGA measured on a 6-point scale (grade 2=some noninflammatory lesions are present with few inflammatory lesions [papules/pustules only, no nodulocystic lesions]; grade 3=noninflammatory lesions predominate with multiple inflammatory lesions evident [several to many comedones and papules/pustules, and there may or may not be 1 small nodulocystic lesion]; grade 4=inflammatory lesions are more apparent [many comedones and papules/pustules, there may or may not be a few nodulocystic lesions]).



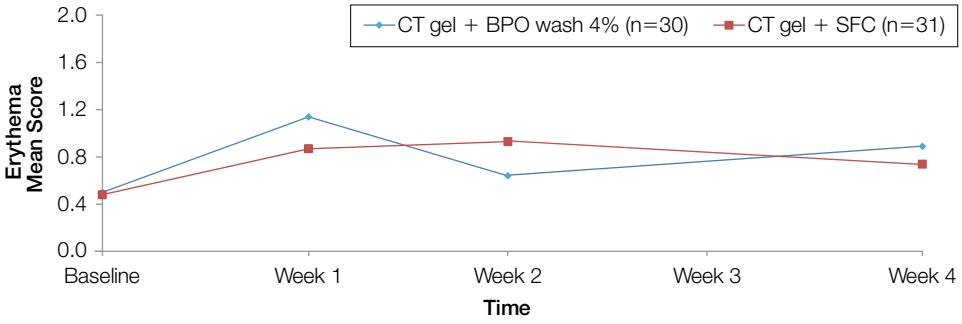
	Baseline		Week 1		Week 2		Week 4	
	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum
CT gel + BPO wash 4%	0	1	0	5	0	3	0	2
CT gel + SFC	0	2	0	4	0	2	0	2

A



	Baseline		Week 1		Week 2		Week 4	
	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum
CT gel + BPO wash 4%	0	1	0	4	0	3	0	2
CT gel + SFC	0	2	0	4	0	2	0	2

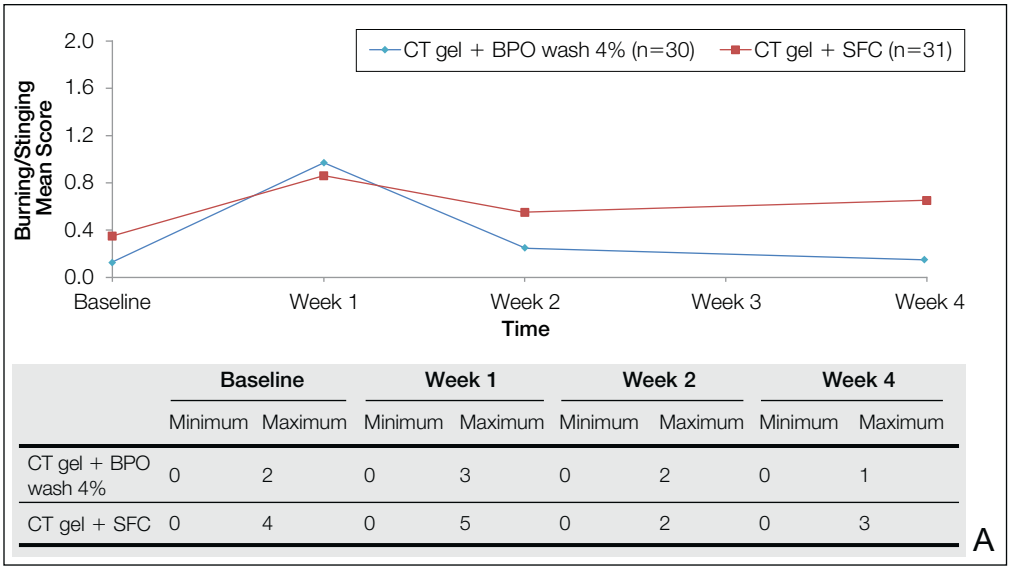
B



	Baseline		Week 1		Week 2		Week 4	
	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum
CT gel + BPO wash 4%	0	3	0	3	0	3	0	3
CT gel + SFC	0	3	0	4	0	3	0	3

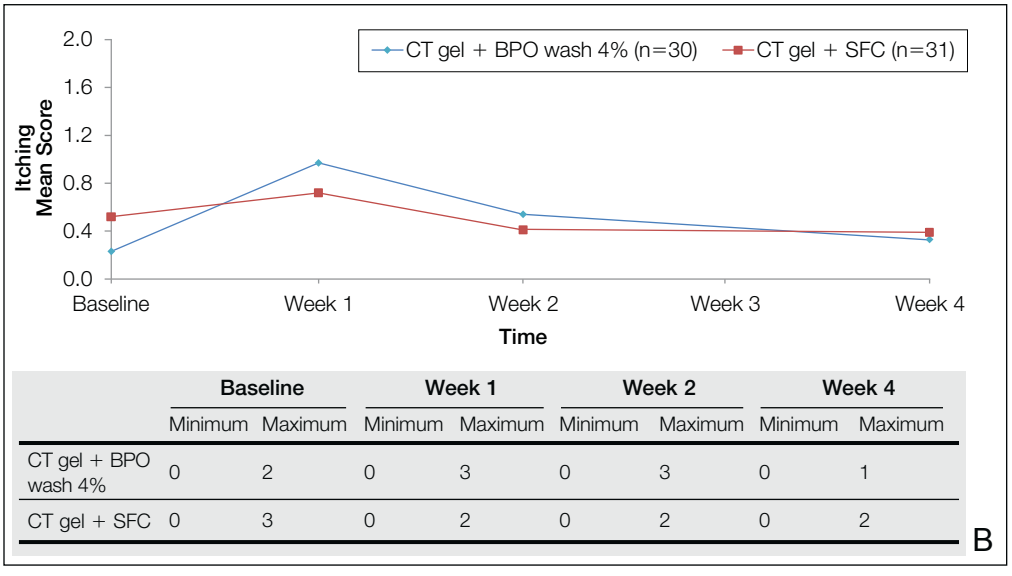
C

Figure 1. Mean scores for investigator-assessed dryness (A), scaling (B), and erythema (C) at each study visit following treatment with clindamycin phosphate 1.2%–tretinoin 0.025% gel (CT gel) plus benzoyl peroxide (BPO) wash 4% or CT gel plus soap-free cleanser lotion (SFC).



	Baseline		Week 1		Week 2		Week 4	
	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum
CT gel + BPO wash 4%	0	2	0	3	0	2	0	1
CT gel + SFC	0	4	0	5	0	2	0	3

A



	Baseline		Week 1		Week 2		Week 4	
	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum
CT gel + BPO wash 4%	0	2	0	3	0	3	0	1
CT gel + SFC	0	3	0	2	0	2	0	2

B

Figure 2. Mean scores for participant-assessed burning/stinging (A) and itching (B) at each study visit following treatment with clindamycin phosphate 1.2%–tretinoin 0.025% gel (CT gel) plus benzoyl peroxide (BPO) wash 4% or CT gel plus soap-free cleanser lotion (SFC).

design to ours, Del Rosso and Kircik[17] randomized participants to BPO microsphere wash 5.5% or gentle cleanser used with a combination gel containing clindamycin phosphate 1.2%–tretinoin 0.025% for 21 days. Tolerability scores for most parameters were greatest at the 14-day assessment and declined thereafter.[17]

Our study has a number of limitations. First, it includes a relatively small number of participants. Second, because of differences in the appearance of the BPO wash and SFC, participants were not blinded to treatment assignment. However, we believe the findings are notable because the investigators who conducted the tolerability assessments were blinded to treatment assignment and our results are consistent with earlier studies in which clindamycin phosphate 1.2%–tretinoin 0.025% gel was used in conjunction with a BPO wash. Lastly, this study was conducted in healthy young participants with mild to moderate acne who were principally white or not Hispanic or Latino. Therefore, the results should not be generalized to other ethnic/racial or age groups or to patients with more severe acne.

Conclusion

The use of a BPO wash 4% in conjunction with CT gel did not appear to increase irritation or cause safety concerns compared to the use of CT gel in conjunction with a nonmedicated cleanser. Therefore, this study demonstrates that CT gel is well-tolerated and is safe to use with this formulation of BPO wash for the treatment of patients with mild to moderate acne vulgaris.

Table 3.

Adverse Events (AEs)

AE Type	Participants Reporting AEs, n (%)	
	CT Gel + BPO Wash 4% (n=30)	CT Gel + SFC (n=31)
Any AE	1 (3)	8 (26)
Application-site reactions[a]	0 (0)	3 (10)
Influenza	0 (0)	1 (3)
Nasopharyngitis	1 (3)	2 (6)
Sinusitis	0 (0)	1 (3)
Urinary tract infection	0 (0)	1 (3)
Sunburn	0 (0)	1 (3)
Headache	0 (0)	1 (3)
Rhinorrhea	0 (0)	1 (3)

Abbreviations: CT, clindamycin phosphate 1.2%–tretinoin 0.025%; BPO, benzoyl peroxide; SFC, soap-free cleanser lotion.
[a]Dryness, erythema, and/or irritation.

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REFERENCES

1. Berson DS, Chalker DK, Harper JC, et al. Current concepts in the treatment of acne: report from a clinical roundtable. *Cutis*. 2003;72(suppl 1):5-13.
2. Acne Fact Sheet. American Academy of Dermatology Web site. http://www.aad.org/media/background/factsheets/fact_acne.html. Accessed August 25, 2010.
3. Dréno B, Thiboutot D, Gollnick H, et al. Large-scale worldwide observational study of adherence with acne therapy. *Int J Dermatol*. 2010;49:448-456.
4. Thiboutot D, Gollnick H, Bettoli V, et al; Global Alliance to Improve Outcomes in Acne. New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne group. *J Am Acad Dermatol*. 2009;60(suppl 5):S1-S50.
5. Ghali F, Kang S, Leyden J, et al. Changing the face of acne therapy. *Cutis*. 2009;83(suppl 2):4-15.
6. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol*. 2003;49(suppl 1):S1-S37.
7. Thielitz A, Gollnick H. Topical retinoids in acne vulgaris: update on efficacy and safety. *Am J Clin Dermatol*. 2008;9:369-381.
8. Millikan LE. The rationale for using a topical retinoid for inflammatory acne. *Am J Clin Dermatol*. 2003;4:75-80.
9. Tanghetti EA, Popp KF. A current review of topical benzoyl peroxide: new perspectives on formulation and utilization. *Dermatol Clin*. 2009;27:17-24.

10. Cunliffe WJ, Holland KT, Bojar R, et al. A randomized, double-blind comparison of a clindamycin phosphate/benzoyl peroxide gel formulation and a matching clindamycin gel with respect to microbiologic activity and clinical efficacy in the topical treatment of acne vulgaris. *Clin Ther*. 2002;24:1117-1133.
11. Leyden JJ, Wortzman M, Baldwin EK. Antibiotic-resistant *Propionibacterium acnes* suppressed by a benzoyl peroxide cleanser 6%. *Cutis*. 2008;82:417-421.
12. Alexis AF. Clinical considerations on the use of concomitant therapy in the treatment of acne. *J Dermatolog Treat*. 2008;19:199-209.
13. Leyden JJ, Krochmal L, Yaroshinsky A. Two randomized, double-blind, controlled trials of 2219 subjects to compare the combination clindamycin/tretinoin hydrogel with each agent alone and vehicle for the treatment of acne vulgaris [published online ahead of print November 28, 2005]. *J Am Acad Dermatol*. 2006;54:73-81.
14. Jarratt M. Efficacy and safety of a novel clindamycin-tretinoin gel versus clindamycin or tretinoin alone in acne vulgaris: a randomized, double-blind, vehicle-controlled study. Poster presented at: American Academy of Dermatology Summer Academy Meeting; August 4–8, 2010; Chicago, IL. P105.
15. Data on file. Research Triangle Park, NC: Stiefel Laboratories, Inc; 2009.
16. Kircik LH. Comparative efficacy and safety results of two topical combination acne regimens. *J Drugs Dermatol*. 2009;8:624-630.
17. Del Rosso JQ, Kircik L. Comparison of the tolerability of benzoyl peroxide microsphere wash vs a gentle cleanser, when used in combination with a clindamycin and tretinoin gel: a multi-center, investigator-blind, randomized study. Poster presented at: American Academy of Dermatology 67th Annual Meeting; March 6–10, 2009; San Francisco, CA. P719.