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[ORIGINAL RESEARCH]

Efficacy and Safety of Clindamycin Phosphate 1.2% and Tretinoin 0.025% Gel for the Treatment of Acne and Acne-induced Post-inflammatory Hyperpigmentation in Patients with Skin of Color

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ABSTRACT

Objective: To assess the efficacy and safety of a topical gel containing clindamycin 1.2% and tretinoin 0.025% for the treatment of acne and acne-induced postinflammatory hyperpigmentation (PIH) in darker skinned patients. **Design:** Randomized, double-blind, placebo-controlled study. **Setting:** Two United States clinical sites. **Participants:** Thirty-three patients 12 years of age or older with skin types IV to VI, mild-to-moderate facial acne, and PIH were enrolled. **Measurements:** Patients applied clindamycin phosphate/tretinoin gel or a nonmedicated vehicle each evening and a sun protection factor 30 sunscreen daily. Changes in skin erythema and hyperpigmentation were measured using a chromameter and photographic images. Efficacy was assessed using the Evaluators Global Acne Severity Scale, lesion counts, Post-inflammatory Hyperpigmentation Severity Scales and Patient's Global Assessment Scale. Safety and tolerability were assessed by adverse event reports and a Safety Assessment Scale. **Results:** The mean (SD) baseline inflammatory lesion count was 11.9 (11.1) in clindamycin/tretinoin-treated patients, decreasing by 5.5 (6.56) after 12 weeks while the mean baseline inflammatory lesion count was 13.6 (11.15) in placebo-treated patients, decreasing by 4.1 (11.36) (p=0.05 for change from baseline, clindamycin/tretinoin vs. placebo). Clindamycin/tretinoin-treated patients generally demonstrated superior efficacy versus placebo treatment. The clindamycin/tretinoin topical gel was well tolerated, causing little or no irritation, although one patient withdrew due to periorbital edema of moderate severity possibly related to clindamycin/tretinoin gel. **Conclusion:** Although limited by small sample size, the results of this pilot study suggest clindamycin phosphate 1.2% and tretinoin 0.025% topical gel is a safe and effective option for treating mild-to-moderate acne in patients with skin of color. (*J Clin Aesthet Dermatol.* 2012;5(7):25–32.)

Acne is a chronic disorder of the pilosebaceous unit characterized by inflammatory papules, pustules, open and closed comedones, cysts and nodules affecting both adolescents and adults. The pathophysiology of acne is complex, but includes increased sebum production, follicular hyperkeratosis, proliferation of *Propionibacterium acnes*, and reactive inflammation.[1,2] It affects people without regard to race or ethnicity and is therefore one of the most common conditions treated by dermatologists.[3]

Of special concern among darker skinned patients with acne is the occurrence of postinflammatory hyperpigmentation (PIH).[4–7] Inflammatory acne lesions disrupt the epidermal basal layer causing melanocytes to increase

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TABLE 1. Evaluator's global acne severity scale

GRADE	VALUE	DEFINITION
Clear	0	Normal, clear skin with no evidence of acne vulgaris
Almost clear	1	Rare noninflammatory lesions present, with rare noninflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
Mild	2	Some noninflammatory lesions are present, with few inflammatory lesions (papules/pustules only, no nodulocystic lesions)
Moderate	3	Noninflammatory lesions predominate, with multiple inflammatory lesions evident; several to many comedones and papules/pustules; there may or may not be one small nodulocystic lesion
Severe	4	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be a few nodulocystic lesions
Very severe	5	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules, and many nodulocystic lesions

From: Schlessinger J, Menter A, Gold M, et al. Clinical safety and efficacy studies of a novel formulation combining 1.2% clindamycin phosphate and 0.025% tretinoin for the treatment of acne vulgaris. *J Drugs Dermatol.* 2007;6: 607–615.[11]

melanin production.[8] PIH is common in patients with skin of color and can persist for months or years. The psychological and emotional distress caused by dyschromias, such as PIH, can have a significant impact on the health-related quality of life of affected individuals.[8,9] While PIH may respond to treatments, such as chemical peels and laser therapy,[7] the preferred approach is to prevent or minimize the occurrence of PIH.

Several treatments are currently available alone or in combination for the treatment of acne including benzoyl peroxide, topical or oral antibiotics, and topical retinoids. Some of these combinations may be more beneficial for the treatment of acne and PIH than others. For example, a trial comparing different topical therapeutic regimens in patients of color with acne treated with a clindamycin 1% + benzoyl peroxide 5% topical gel in combination with tretinoin 0.04% topical gel showed greater resolution of hyperpigmentation than patients treated with the same clindamycin/benzoyl peroxide topical gel in combination with tretinoin 0.01% or adapalene 0.1% topical gels.[10]

Combined therapy with a topical retinoid and clindamycin has been shown to be more effective than monotherapy in addressing all the pathogenic factors of acne[11] and the safety and efficacy of this combination has become well established.[12–17] A commercially available product containing clindamycin phosphate 1.2% combined with tretinoin 0.025% gel is approved for the treatment of acne vulgaris in patients 12 years of age and older. The primary objective of the following placebo-controlled, double-blind study was to assess the efficacy and safety of clindamycin 1.2%/tretinoin 0.025% gel for the treatment of mild-to-moderate acne and acne-induced PIH.

METHODS

Study subjects. Patients were eligible for enrollment if they were 12 years of age or older with skin types IV to VI and exhibited mild-to-moderate facial acne and mild-to-moderate PIH. Patients were excluded from participation if they had seborrheic dermatitis, PIH of solely dermal origin, acne vulgaris known to be resistant to oral antibiotics or had a history of Crohn's disease, regional enteritis, or ulcerative or antibiotic-related colitis. Patients taking erythromycin, neuromuscular blocking agents, hormone replacement or oral/transdermal contraceptive therapy, hydroquinone or other depigmenting medication within 14 days of the study, tetracycline or any other photosensitizing medication within 30 days of the study, isotretinoin, chemical peels, microdermabrasion or laser treatment within six months of the study, and patients with a known allergy or sensitivity to the study medication or its components were also excluded. Women who were pregnant or breastfeeding were not allowed to participate in the study. Women of childbearing age agreed to use a reliable form of contraception other than oral contraceptives for the duration of the study and were required to provide a negative pregnancy test before starting the study.

Study drugs. The active treatment contained clindamycin phosphate 1.2% and tretinoin 0.025% in an aqueous base of purified water, glycerin, carbomer 981, methylparaben, polysorbate 80, edetate sodium, citric acid,

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TABLE 2. Postinflammatory hyperpigmentation severity scale

GRADE	OVERALL DISEASE SEVERITY	PIGMENTARY INTENSITY OF HYPERPIGMENTED LESIONS	AREA OF HYPERPIGMENTED LESIONS (% FACIAL AREA)	DEGREE OF HYPOPIGMENTATION	ERYTHEMA, BURNING, PEELING, DRYNESS
0	Normal	None	None	None	None
1	Present, but <mild	Trace (mild and localized)	Trace (1–10%)	Trace (slight and localized)	Trace
2	Mild (slightly noticeable)	Mild (mild and diffuse)	Mild (1–25%)	Mild (slight and diffuse)	Mild
3	Between mild and moderate	Moderate (moderate and diffuse)	Moderate (26–40%)	Moderate (noticeable and diffuse)	Moderate
4	Moderate (noticeable)	Marked (moderate and dense)	Marked (41–50%)	Marked (noticeable and dense)	Marked
5	Between moderate and marked	Severe (prominent and dense)	Severe (>50%)	Severe (complete lack of melanin pigmentation)	Severe
6	Marked (distinctive)	—	—	—	—
7	Between marked and severe	—	—	—	—
8	Severe (very distinctive)	—	—	—	—

propylparaben, butylated hydroxytoluene and tromethamine (Ziana® Gel, Medicis Pharmaceutical Corporation, Inc., Scottsdale, Arizona). The placebo consisted of the nonmedicated gel vehicle. Other products used in the study included a cleansing bar (Vanicream™ Cleansing Bar, Pharmaceutical Specialties, Inc., Rochester, Minnesota) and sunscreen containing titanium dioxide 5%, zinc oxide 5% (Vanicream™ Sunscreen SPF 30, Pharmaceutical Specialties, Inc.). This brand of sunscreen was specifically chosen because it lacks fragrances, parabens, and other potentially irritating ingredients.

Study procedures. This 12-week, double-blind, randomized, placebo-controlled study was performed at two clinical trial sites. Following a 30-day washout period for oral corticosteroids, antibiotics, and contraceptives and a 14-day washout period for topical acne medications, medicated cosmetics, and bleaching products, eligible patients underwent a baseline medical history and physical examination including assessment of acne and PIH severity and photographic and chromameter measures. Patients were instructed to wash their face with the cleansing bar each morning, rinse, pat dry, and then apply the sunscreen. The use of a sunscreen was important because of the risk of photosensitivity and sunburn due to the retinoid in the study medication. Each evening, patients were to wash their face with the cleansing bar, rinse, and pat dry. Patients were randomized to then apply a thin layer of either the clindamycin/tretinoin gel or the placebo gel. Each patient returned to the center after 2, 4, 8, and 12 weeks of treatment for safety and efficacy assessments. Treatment compliance was established by weighing the study drug or placebo at each return visit.

TABLE 3. Patient's Global Assessment Scale

How would you rate your acne and postinflammatory hyperpigmentation now?

SCORE	GRADE	DEFINITION
0	Clear	No signs of dark areas
1	Almost Clear	Minor evidence of dark areas
2	Significant	Significant evidence of dark areas

Efficacy endpoints. During the initial baseline visit, the investigator selected and photographed a target skin area for evaluation. Objective changes in skin erythema and

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TABLE 4. Safety assessment scale

SCALING

SCORE	GRADE	DESCRIPTION
0	None	No scaling
1	Mild	Barely perceptible, fine scales present to limited areas of the face
2	Moderate	Fine scale generalized to all areas of the face
3	Severe	Scaling and peeling of skin over all areas of the face

ERYTHEMA

SCORE	GRADE	DESCRIPTION
0	None	No evidence of erythema present
1	Mild	Slight pink discoloration
2	Moderate	Definite redness
3	Severe	Marked erythema, bright red to dusky dark red in color

ITCHING

SCORE	GRADE	DESCRIPTION
0	None	No itching
1	Mild	Slight itching, not really bothersome
2	Moderate	Definite itching that is somewhat bothersome
3	Severe	Intense itching that may interrupt daily activities and/or sleep

BURNING

SCORE	GRADE	DESCRIPTION
0	None	No burning
1	Mild	Slight burning sensation, not really bothersome
2	Moderate	Definite warm, burning sensation that is somewhat bothersome
3	Severe	Hot burning sensation that causes definite discomfort and may interrupt daily activities and/or sleep

STINGING

SCORE	GRADE	DESCRIPTION
0	None	No stinging
1	Mild	Slight stinging sensation, not really bothersome
2	Moderate	Definite stinging sensation that is somewhat bothersome
3	Severe	Stinging sensation that causes definite discomfort and may interrupt daily activities and/or sleep

From: Leyden J, Wortzman M, Baldwin EK. Tolerability of clindamycin/tretinoin gel vs. tretinoin microsphere gel and adapalene gel. *J Drugs Dermatol.* 2009;8:383–388.[13]

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TABLE 5. Lesion counts

	BASELINE		CHANGE, WEEK 12	
Endpoint, Mean (SD)	Clindamycin phosphate/ tretinoin gel (N=17)	Placebo (N=15)	Clindamycin phosphate/ tretinoin gel (N=16)	Placebo (N=15)
Lesion Counts				
Inflammatory Lesions	11.9 (11.10)	13.6 (11.15)	-5.5 (6.56)*	-4.1 (11.36)
Noninflammatory Lesions	48.6 (46.10)	64.7 (73.08)	-21.3 (22.60)	-12.8 (40.08)

* p=0.05 vs. placebo

hyperpigmentation were measured using a chromameter (Mexameter MX 18; Courage+Khazaka Electronic GmbH, Köln, Germany) and photographic images of the front, left, and right sides of the faces of each patient were recorded (Canfield Imaging Systems, Fairfield, New Jersey). Efficacy assessments consisted of improvements in acne and PIH severity based on changes in Evaluator's Global Acne Severity Scale scores (Table 1) and PIH Severity Scale scores (Table 2). At Week 12, each study participant provided his or her opinion of the tolerability and effectiveness of the treatment and the overall clinical results he or she achieved by completing the Patient's Global Assessment Scale (Table 3).

Safety. Safety measures included the Safety Assessment Scale (Table 4) at each visit and reports of adverse events (AEs) since the previous visit. Although rare, pseudomembranous colitis has been reported following the application of topical clindamycin,[18,19] and patients were specifically questioned by the investigators about any episodes of diarrhea.

Ethics. The protocol, informed consent document, and relevant supporting information were approved by a local institutional review board (IRB). The study was conducted in accordance with the regulations of the United States Food and Drug Administration as described in 21 CFR 50 and 56, the ethical principles that have their origin in the Declaration of Helsinki, and was consistent with Good Clinical Practice and applicable regulatory requirements. Each enrolled patient provided written informed consent prior to participating in any study-related procedures.

RESULTS

The 33 enrolled subjects included 26 women and seven men with a mean age of 28.3 years (range, 13–51 years). Patients described themselves as Black or African American (N=32) or African American/Caucasian (N=1) and exhibited skin types IV (N=2), V (N=23), or VI (N=8). One patient was of Hispanic ethnicity. Patients were randomized to undergo treatment with clindamycin/tretinoin gel (N=17) or placebo (N=16); 15 patients in each group completed the 12-week trial. Reasons for not completing the trial included being lost to follow up (N=2) and withdrawal of consent (N=1).

Efficacy. At baseline, the mean scores/frequency counts for all efficacy measures were not significantly different between treatment groups. Although patients treated with clindamycin/tretinoin gel consistently demonstrated numerically superior efficacy results in acne improvement compared to placebo treatment, the study was not sufficiently powered to achieve statistical significance for all efficacy measures. The chromameter assessments for melanin and erythema were highly variable and could not be interpreted.

Among patients treated with clindamycin/tretinoin gel, the mean (SD) baseline noninflammatory lesion count was 48.6 (46.10), decreasing by 21.3 (22.60) after 12 weeks while the mean baseline noninflammatory lesion count of 64.7 (73.08) for placebo-treated patients decreased by 12.8 (40.08) (Table 5). Among clindamycin/tretinoin gel-treated patients, the mean (SD) baseline inflammatory lesion count was 11.9 (11.1), decreasing by 5.5 (6.56) after 12 weeks while the mean baseline inflammatory lesion count of 13.6 (11.15) for placebo-treated patients decreased by 4.1 (11.36); (p=0.05, change from baseline to 12 weeks; clindamycin/tretinoin vs. placebo) (Table 5).

Evaluator's Global Acne Severity Scale scores ≥2 were demonstrated by all patients at baseline, which decreased to 0 or 1 (clear or almost clear) at 12 weeks for 47 and 27 percent of patients treated with clindamycin/tretinoin gel and placebo, respectively (Table 6).

All patients had baseline PIH Severity Scale scores ≥2 and a substantial proportion had scores of 3 or 4 in the clindamycin/tretinoin gel (70%) and placebo groups (69%) (Table 6). The improvement in mean PIH score from Baseline to Week 12 was greater for clindamycin/tretinoin gel vs. placebo (-1.2 vs. -0.9) and this small improvement was consistent throughout the trial. The number of patients with ≥2-point improvements in PIH scores was similar between clindamycin/tretinoin gel and placebo treatment groups (N=5; 33%).

At baseline, more than 80 percent of patients had Patient's Global Assessment scores of 2 (Table 7). The proportion of clindamycin/tretinoin gel- and placebo-treated patients with ≥1-point improvement in Patient's Global Assessment at Week 12 was 67 and 40 percent, respectively. The proportion of patients treated with clindamycin/tretinoin gel and placebo

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TABLE 6. Evaluator's Global Acne Severity Scale and Postinflammatory Hyperpigmentation (PIH) Severity Scale Scores

	BASELINE		≥≥2-POINT IMPROVEMENT, WEEK 12		
	Clindamycin phosphate/ tretinoin gel, N=17	Placebo, N=16	Clindamycin phosphate/ tretinoin gel, N=15	Placebo, N=15	Significance
EVALUATOR'S GLOBAL ACNE SEVERITY SCORE, N (%)					
0	—	—	7 (46.7)	4 (26.7)	*p*=0.45
1	—	—			
2	9 (52.9)	7 (43.8)	3 (20.0)	1 (6.7)	
3	7 (41.2)	9 (56.3)			
4	1 (5.9)	—			
PIH SEVERITY SCORE, N (%)					
2	4 (23.5)	3 (18.8)			
3	5 (29.4)	5 (31.1)	5 (33.3)	5 (33.3)	*p*=1.00
4	7 (41.2)	6 (37.5)			
5	1 (5.9)	2 (12.5)			

TABLE 7. Patient's global assessment scores

	BASELINE		≥≥1-POINT IMPROVEMENT, WEEK 12		
	Clindamycin phosphate/ tretinoin gel, N=17	Placebo, N=16	Clindamycin phosphate/ tretinoin gel, N=15	Placebo, N=15	Significance
PATIENT'S GLOBAL ASSESSMENT SCORES, N (%)					
1	3 (17.6)	2 (12.5)	10 (66.7)	6 (40.0)	*p=0.27*
2	14 (82.4)	14 (87.5)			

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TABLE 8. Safety assessments

	BASELINE		≥≥2-POINT IMPROVEMENT, WEEK 12	
	Clindamycin phosphate/ tretinoin gel, N=17	Placebo, N=16	Clindamycin phosphate/ tretinoin gel, N=15	Placebo, N=15
SCALING SCORE, N (%)				
0	11 (64.7)	10 (62.5)		
1	3 (17.6)	4 (25.0)	2 (100.0)	2 (66.7)
2	2 (11.8)	—		
3	1 (5.9)	2 (12.5)		
ERYTHEMA SCORE, N (%)				
0	11 (64.7)	11 (68.8)		
1	3 (17.6)	4 (25.0)	3 (100.0)	1 (100.0)
2	3 (17.6)	—		
3	—	1 (6.3)		
ITCHING SCORE, N (%)				
0	11 (64.7)	12 (75.0)		
1	4 (23.5)	4 (24.0)	2 (100.0)	—
2	1 (5.9)	—		—
3	1 (5.9)	—		
BURNING SCORE, N (%)				
0	14 (82.4)	14 (87.5)		
1	2 (11.8)	2 (12.5)	1 (100.0)	—
2	1 (5.9)	—		—
3	—	—		
STINGING SCORE, N (%)				
0	15 (88.2)	12 (75.0)		
1	1 (5.9)	2 (12.5)	1 (100.0)	2 (100.0)
2	1 (5.9)	2 (12.5)		
3	—	—		

* For each assessment, there was no significant difference between groups

with Patient's Global Assessment scores of 0 or 1 at Week 12 was 80 and 53 percent, respectively.

Safety. For the majority of patients, the severity of scaling, erythema, burning, stinging, and itching was very low. Baseline scores of 0 or 1 were reported by more than 80 percent of patients for scaling and more than 90 percent of patients for itching and burning (Table 8). The severity of scaling, erythema, burning, stinging, and itching remained low for both treatment groups throughout the trial, and severity scores remained 0 or 1 for 85 to 100 percent of patients at the end of the 12-week trial.

Two additional AEs were reported by two patients. One patient reported mild crusting of the cheek, which was determined to be probably related to clindamycin/tretinoin gel, but did not lead to discontinuation of treatment. The other was described as periorbital edema of moderate severity, which was believed to be possibly related to clindamycin/tretinoin gel and lead to withdrawal from the study. There were no AEs suggestive of pseudomembranous colitis.

DISCUSSION

The clindamycin phosphate 1.2% and tretinoin 0.025% gel used in this study is known to be an effective treatment for acne vulgaris[11] without causing the inflammatory flare[16] associated with the use of retinoids alone.[20,21] During two Phase III clinical trials, 845 patients, including 105 Black patients (12%), were randomized to undergo treatment with

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clindamycin/tretinoin gel for 12 weeks.[11] Based on the Evaluator's Global Severity Scale, a significant number of patients were rated as "clear" or "almost clear" at Week 12 compared to treatment with clindamycin or tretinoin alone or placebo; however, efficacy and safety results were not stratified by race or skin type.

This pilot study clearly demonstrated a strong trend toward clinical improvement among the clindamycin/tretinoin-treated patients, but the study was not sufficiently powered to achieve statistical significance for all measures of efficacy. For example, patients in both groups were found to have baseline Evaluator's Global Acne Severity Scale scores ≥2, which decreased to 0 or 1 at 12 weeks for 47 and 27 percent of patients treated with clindamycin/tretinoin gel and placebo, respectively. Demonstrating statistically significant 2-point improvements would have been difficult to achieve since the approximately 50 percent of patients with baseline scores of 2 would have needed to achieve scores of 0. Nevertheless, a greater proportion of clindamycin/tretinoin-treated patients did demonstrate a 2-point improvement at the end of the study. Similar results were observed for inflammatory and noninflammatory lesion counts and Patient Global Assessment scores.

Chromameter scores did not show a significant decrease in melanin or erythema during the 12-week study. A greater or more consistent change in chromameter readings may have become more apparent if a larger group of patients were treated or if the changes were observed for a longer time period. Importantly, the results of the Patient Global Assessment indicate that the clindamycin/tretinoin gel used in this study did not stimulate an inflammatory response that might lead to a significant increase in PIH. This suggests clindamycin/tretinoin gel is relatively nonirritating and well tolerated by patients with sensitive skin. This is further supported by safety data indicating clindamycin/tretinoin gel acne treatment is well tolerated in this patient population, as the severity of scaling, erythema, burning, stinging, and itching remained low for both treatment groups.

CONCLUSION

This randomized, placebo-controlled, double-blind trial revealed that clindamycin phosphate 1.2% and tretinoin 0.025% combination gel is an effective and safe treatment option for patients with skin of color with mild-to-moderate acne. There was a statistically significant decrease in inflammatory lesions, and the medication causes little to no irritation. Although the study was not sufficiently powered to demonstrate statistically significant acne improvement, the data consistently favored clindamycin/tretinoin gel over time across all endpoints except PIH.

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REFERENCES

1. Purdy S, de Berker D. Acne. *BMJ.* 2006;333:949–953.
2. Zaenglein AL, Thiboutot DM. Expert committee recommendations for acne management. *Pediatrics.* 2006;118:1188–1199.
3. Davis EC, Callender VD. A review of acne in ethnic skin: pathogenesis, clinical manifestations, and management strategies. *J Clin Aesthet Dermatol.* 2010;3:24–38.
4. Callender VD. Acne in ethnic skin: special considerations for therapy. *Dermatol Ther.* 2004;17:184–195.
5. Callender VD. Considerations for treating acne in ethnic skin. *Cutis.* 2005;76(2 Suppl):19–23.
6. Taylor S, Grimes P, Lim J, et al. Postinflammatory hyperpigmentation. *J Cutan Med Surg.* 2009;13:183–191.
7. Davis EC, Callender VD. Postinflammatory hyper-pigmentation: a review of the epidemiology, clinical features, and treatment options in skin of color. *J Clin Aesthet Dermatol.* 2010;3:20–31.
8. Callender VD, St Surin-Lord S, Davis EC, Maclin M. Postinflammatory hyperpigmentation: etiologic and therapeutic considerations. *Am J Clin Dermatol.* 2011;12: 87–99.
9. Grimes PE. Management of hyperpigmentation in darker racial ethnic groups. *Semin Cutan Med Surg.* 2009;28: 77–85.
10. Taylor SC. Utilizing combination therapy for ethnic skin. *Cutis.* 2007;80(1 Suppl):15–20.
11. Schlessinger J, Menter A, Gold M, et al. Clinical safety and efficacy studies of a novel formulation combining 1.2% clindamycin phosphate and 0.025% tretinoin for the treatment of acne vulgaris. *J Drugs Dermatol.* 2007;6: 607–615.
12. Eichenfield LF, Wortzman M. A novel gel formulation of 0.25% tretinoin and 1.2% clindamycin phosphate: efficacy in acne vulgaris patients aged 12 to 18 years. *Pediatr Dermatol.* 2009;26:257–261.
13. Leyden J, Wortzman M, Baldwin EK. Tolerability of clindamycin/tretinoin gel vs. tretinoin microsphere gel and adapalene gel. *J Drugs Dermatol.* 2009;8:383–388.
14. Kircik LH, Peredo MI, Bucko AD, et al. Safety of a novel gel formulation of clindamycin phosphate 1.2%-tretinoin 0.025%: results from a 52-week open-label study. *Cutis.* 2008;82:358–366.
15. Abdel-Naser MB, Zouboulis CC. Clindamycin phosphate/tretinoin gel formulation in the treatment of acne vulgaris. *Expert Opin Pharmacother.* 2008;9:2931–2937.
16. Leyden JJ, Wortzman M. A novel gel formulation of clindamycin phosphate-tretinoin is not associated with acne flaring. *Cutis.* 2008;82:151–156.
17. Del Rosso JQ, Jitpraphai W, Bhambri S, Momin S. Clindamycin phosphate 1.2%- tretinoin 0.025% gel: vehicle characteristics, stability, and tolerability. *Cutis.* 2008;81: 405–408.
18. Milstone EB, McDonald AJ, Scholhamer CF Jr. Pseudomembranous colitis after topical application of clindamycin. *Arch Dermatol.* 1981;117:154–155.
19. Parry MF, Rha CK. Pseudomembranous colitis caused by topical clindamycin phosphate. *Arch Dermatol.* 1986;122: 583–584.
20. Leyden JJ. A review of the use of combination therapies for the treatment of acne vulgaris. *J Am Acad Dermatol.* 2003;49(Suppl 3):S200–S210.
21. Kligman AM, Fulton JE Jr, Plewig G. Topical vitamin A acid in acne vulgaris. *Arch Dermatol.* 1969;99:469–476.