

Compared Efficacy and Safety of Tretinoin 0.1% Microsphere Gel Alone and in Combination With Benzoyl Peroxide 6% Cleanser for the Treatment of Acne Vulgaris

Alan R. Shalita, MD; Elyse S. Rafal, MD; Dina N. Anderson, MD; Regina Yavel, MD; Shoshana Landow, MD; Wei-Li S. Lee, PhD

Our purpose was to evaluate the efficacy and safety of a combination of benzoyl peroxide 6% cleanser and tretinoin 0.1% microsphere gel versus monotherapy with tretinoin 0.1% microsphere gel. Eighty-seven healthy males and nonpregnant nonlactating females between the ages of 12 and 30 years with moderate inflammatory acne vulgaris were enrolled in this randomized controlled, investigator-blind, parallel group clinical trial. Subjects were evaluated over 12 weeks for a total of 4 visits. The investigators and subjects completed questionnaires about the test medications. Data from the 56 subjects completing the protocol were considered in the analyses of efficacy and tolerability. The reduction in inflammatory lesions from baseline was significant for both treatment groups at the end of the study. However, there was a significantly greater reduction in the group receiving the combination regimen. Both treatment groups had significant reductions from baseline in noninflammatory lesions at week 12, but no differences were observed between treatment groups. With the exception of skin tightness,

which was significantly greater at week 12 in the subjects who received the monotherapy, there were no significant differences between the 2 treatment groups with respect to localized irritation. Adverse events were rare in all subjects. Not only did the combination regimen result in a greater reduction of inflammatory acne lesions than use of the monotherapy but also it did not result in an increase in local irritation.

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Tretinoin has long been considered a first-line topical treatment for noninflammatory acne. The adverse events that sometimes accompany the use of tretinoin include erythema and scaling, which can increase with higher concentration of the drug and frequency of use. The tretinoin 0.1% microsphere gel formulation has been demonstrated to limit these side effects through controlled release of the tretinoin.¹⁻⁴

Benzoyl peroxide in a formulation containing glycerin and zinc lactate as adjuvant ingredients fosters gentle cleansing and deposition of an effective residual level of benzoyl peroxide and has been demonstrated to produce an effective reliable reduction in *Propionibacterium acnes* after 20 seconds of washing.⁵

The purpose of the study was to evaluate the efficacy and safety of this benzoyl peroxide 6% cleanser used in combination with tretinoin 0.1% microsphere gel versus tretinoin 0.1% microsphere gel alone for the treatment of moderate inflammatory acne vulgaris.

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Drs. Shalita, Anderson, Yavel, Landow, and Lee are from the Department of Dermatology, State University of New York, Health Science Center at Brooklyn. Dr. Rafal is from the DermResearchCenter of New York, Inc., Stony Brook. This study was funded by Medicis Pharmaceutical Corporation. The authors report no conflict of interest. Reprints: Heather M. Vander Ploeg, Medicis Pharmaceutical Corporation, 8125 N Hayden Rd, Scottsdale, AZ 85258 (e-mail: hvanderploeg@medicis.com).

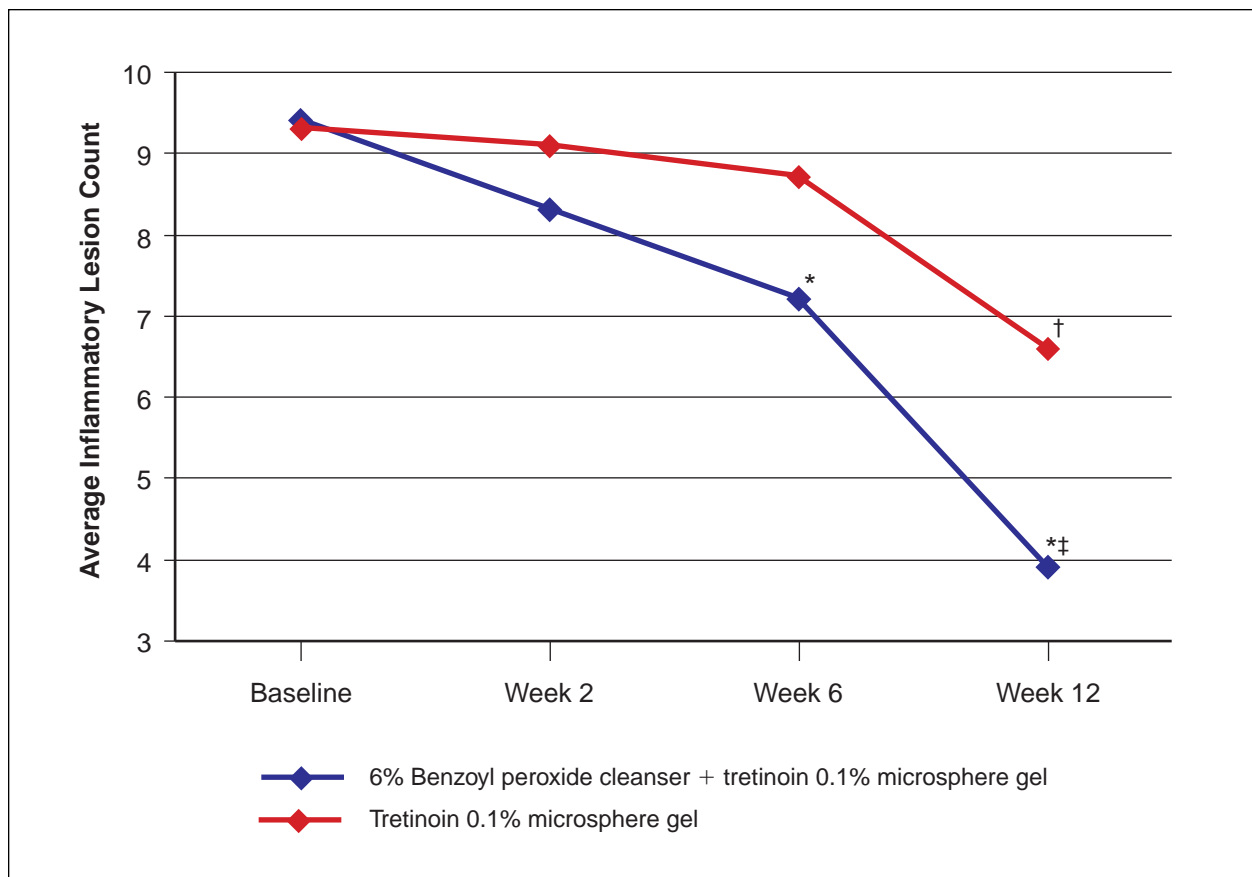


Figure 1. Average inflammatory lesion counts in the combination group (benzoyl peroxide 6% cleanser and tretinoin 0.1% microsphere gel) vs the monotherapy group (tretinoin 0.1% microsphere gel). Asterisk indicates $P < .01$ vs combination group baseline value; dagger, $P < .001$ vs monotherapy group baseline value; double dagger, $P < .01$ combination group vs monotherapy at week 12.

METHODS

This 12-week study, conducted at 2 investigational sites, was a randomized controlled, investigator-blind, parallel group study. The study included institutional review board approval, and all subjects gave signed informed consent.

Subjects were males or nonpregnant nonlactating females between the ages of 12 and 30 years who were in good general health and were not using any other treatments for their acne. Use of systemic retinoids and/or anabolic steroids was not allowed within 6 months prior to enrollment. Use of systemic antimicrobials, topical retinoids, or systemic steroids other than anabolic steroids was not allowed within 4 weeks of the study's initiation. Use of topical antibiotics, benzoyl peroxide, salicylic acid, medicated or antibacterial washes, α -hydroxy acids, and/or β -hydroxy acids was not allowed within 2 weeks of the study's initiation. No active tanning was allowed within 12 weeks of the start of the study, and participation in the study required that a subject

commit to abstaining from excessive exposure to the sun or to artificial UV light radiation sources during the course of the study.

A subject was eligible for admission into the study if, at the prescreening visit, he or she had moderate inflammatory acne vulgaris, defined as having a minimum of 8 papules.

Subjects were evaluated over the course of 12 weeks for a total of 4 visits: a pretreatment baseline visit, follow-up visits at weeks 2 and 6, and a final visit at week 12. The investigators conducted the following clinical evaluations: acne lesion counts; overall rating of the severity of the acne; and assessments of skin irritation including dryness, erythema, edema, peeling, scaling, and tightness. The severity and irritation assessments were rated on an 11-point scale. At the final visit, each investigator gave an overall opinion of the test medication and each subject's tolerability to it, as well as how well the medication cleared each subject's acne. All opinions were rated on a 5-point scale.

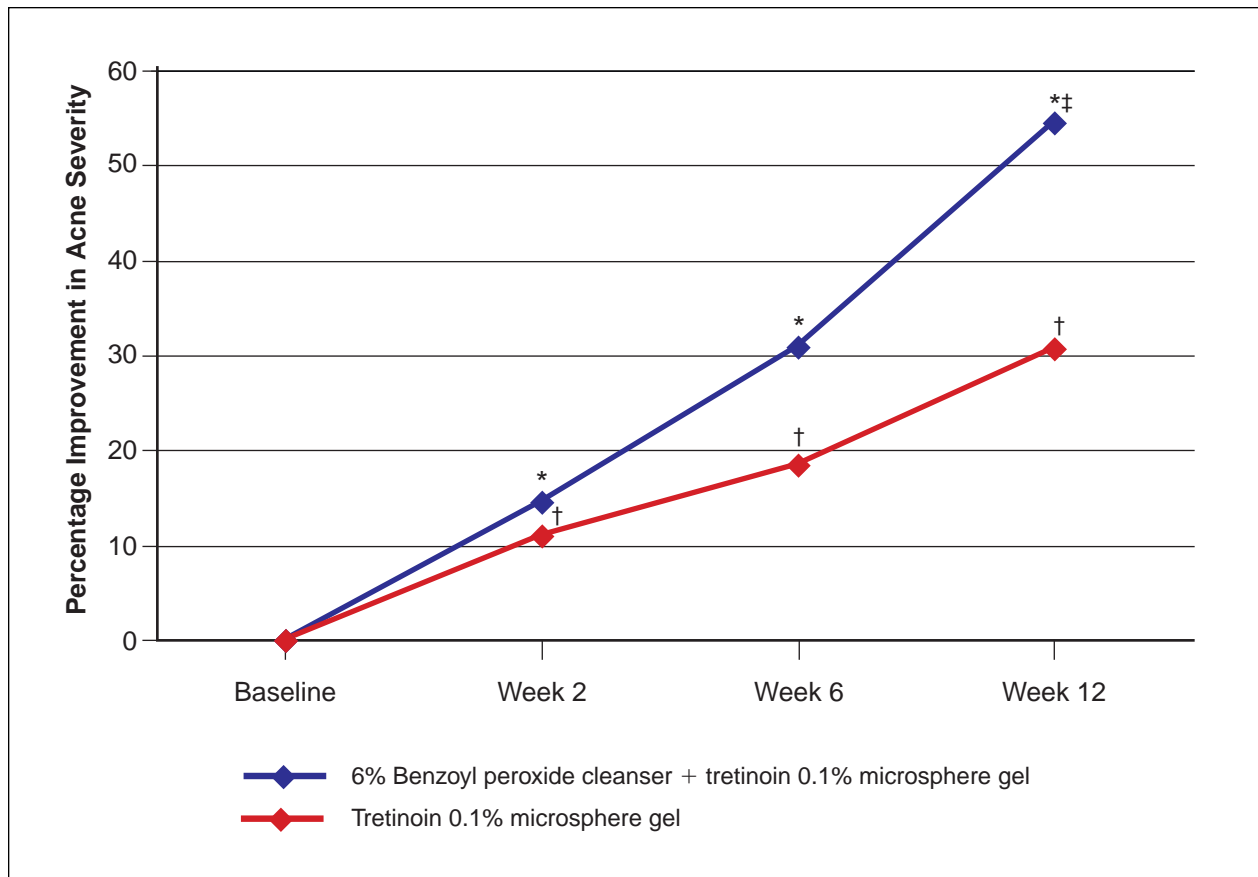


Figure 2. Percentage improvement in severity of acne score in the combination group (benzoyl peroxide 6% cleanser and tretinoin 0.1% microsphere gel) vs the monotherapy group (tretinoin 0.1% microsphere gel). Asterisk indicates $P < .01$ vs combination group baseline value; dagger, $P < .01$ vs monotherapy group baseline value; double dagger, $P < .001$ combination group vs monotherapy.

At each visit, the subjects evaluated the severity of their acne. In addition, they assessed their skin irritation symptoms, including dryness, peeling, redness, and tightness, using the same 11-point rating scale as the investigators. At the first posttreatment visit, the subjects were asked their opinions on product aesthetics such as scent, texture, absorption, and feel. All opinions were rated on a 5-point scale. At the final visit, the subjects also gave their overall opinion of the test medication using the same guidelines and 5-point scale as the investigators.

Photographs documenting each subject's acne were taken at each study visit. Compliance with the treatment regimen, use of concurrent medications, and any adverse events also were recorded at each visit. Urine pregnancy tests were performed on female subjects at the baseline and final visits.

The subjects were randomized to one of 2 treatment groups using a computer-generated randomization schedule. One group of subjects used benzoyl peroxide 6% cleanser in combination with tretinoin

0.1% microsphere gel, while the other group used a nonmedicated cleanser in combination with tretinoin 0.1% microsphere gel. Investigator blinding was maintained through a clinical research coordinator who distributed all test products.

The subjects were instructed to wash their face in the morning with either the benzoyl peroxide 6% cleanser or the nonmedicated cleanser, according to their treatment group assignment. In the evening, all subjects were instructed to wash their face with a nonmedicated cleanser, wait 10 to 15 minutes, and then apply tretinoin 0.1% microsphere gel. Subjects were instructed to wait at least 30 minutes after the product application before going to bed.

The subjects were allowed to use noncomedogenic makeup during the course of the study and were asked to avoid excessive sun exposure. All subjects were provided with a noncomedogenic, broad-spectrum sunscreen and were instructed to wait 5 minutes after washing before applying it.

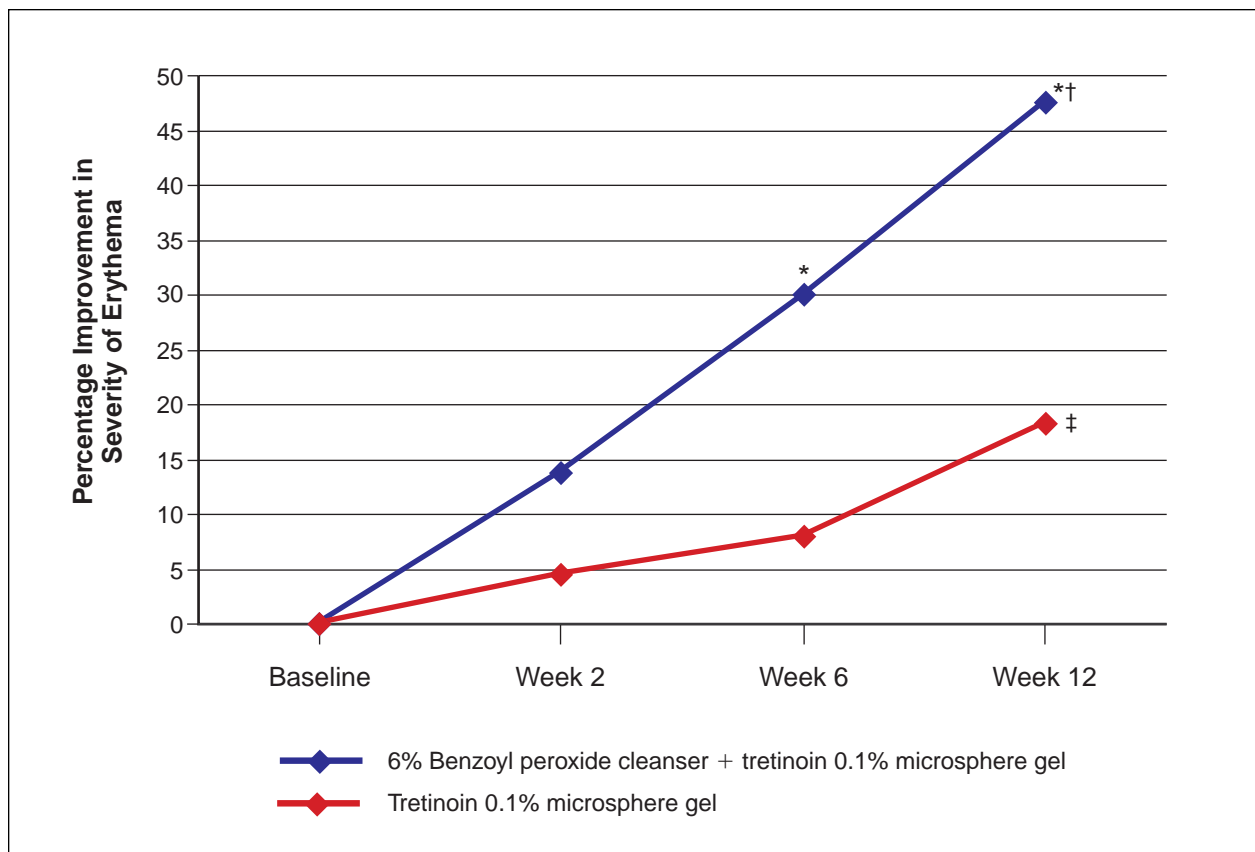


Figure 3. Percentage improvement in severity of erythema associated with the subjects' acne lesions in the combination group (benzoyl peroxide 6% cleanser and tretinoin 0.1% microsphere gel) vs the monotherapy group (tretinoin 0.1% microsphere gel). Asterisk indicates $P=.008$ combination group vs monotherapy; dagger, $P=.001$ vs combination group baseline value; double dagger, $P=.07$ (not significant) vs monotherapy group baseline value.

Outcome Measures—Three primary outcome measures were considered: (1) a change in each subject's lesion count, (2) each investigator's evaluation of the change in the severity of each patient's acne, and (3) each investigator's evaluation of the severity of each patient's localized skin irritation.

Secondary outcome measures included the investigators' overall opinions of the test products and the subjects' evaluations of the change in the severity of their acne, the symptoms of their skin irritation, and the products' aesthetics. In addition, the subjects gave their overall opinion of the test medication.

Statistical Analysis—The paired t test was used for within-treatment comparisons. Comparisons between treatment groups were analyzed using the analysis of variance test.

RESULTS

Data Set

Eighty-seven subjects were enrolled in the study and 56 completed the entire 12-week protocol,

30 from the combination group and 26 from the monotherapy group. Only those subjects who completed the 12-week protocol were included in outcome measures. All subjects who used the test medications were considered for safety analysis. There were no significant differences between treatment groups for subject demographics.

Compliance

Compliance with the study medications was high among the subjects who completed the entire 12-week protocol. In both treatment groups, only 1.4% of possible doses were missed.

Outcome Measures

Acne Lesion Counts—The average baseline papule lesion count for the combination group was 16.0; the count for the monotherapy group was 15.3. For those subjects using the combination regimen, the reduction in the papule count from baseline to week 2 was significantly different (13.5; $P=.037$). Significant reductions continued at week 6 (12.3;

Relationship of Adverse Events to Test Medications

Relationship	Benzoyl Peroxide 6% Cleanser + Tretinoin 0.1% Microsphere Gel	Tretinoin 0.1% Microsphere Gel
Related	Mild peeling	—
Probably Related	Moderate cracked skin	Mild peeling
	Mild burning	Moderate burning
	—	Moderate peeling
Possibly Related	—	Moderate erythema
	—	Moderate fissure on earlobe
	—	—
Unrelated	4 adverse events	2 adverse events

$P=.036$) and at week 12 (7.0; $P=.000$). Papule counts also were reduced for subjects in the monotherapy group; however, significant reductions were not seen until week 12 (11.3; $P=.013$). Significant differences were seen between the 2 treatment groups—the combination group results were significantly better than the monotherapy group results at weeks 2 and 12 ($P=.000$).

For pustule lesion counts, there were no significant differences between the treatment groups.

For inflammatory lesion counts, the reduction for those subjects using the combination regimen was significantly different from the baseline counts at week 6 (7.2; $P<.01$) and again at week 12 (3.9; $P<.01$). Inflammatory lesion counts were significantly reduced from baseline for the monotherapy group at week 12 (6.6; $P<.001$). Results for the combination regimen were significantly better than results for monotherapy at week 12 ($P<.01$)(Figure 1).

For noninflammatory lesion counts, there were no significant differences between the treatment groups. However, both groups had significant reductions from baseline lesion counts.

Investigators' Evaluation of Severity of Acne—At baseline, the average acne severity score as rated by the investigators for both treatment groups was moderate: 6.4 for the combination group and 6.3 for the monotherapy group. The change from baseline for both treatment groups was significant at each evaluation visit. Differences between groups were significant by week 12 ($P<.001$)(Figure 2).

The average score at baseline for the severity of erythema associated with the subjects' acne lesions

was 3.3 for the combination group and 3.4 for the monotherapy group. Comparing the 2 treatment groups, the improvement in the severity of erythema associated with acne lesions was significantly in favor of the combination treatment group at week 6 (2.3 compared with 3.1; $P<.01$) and week 12 (1.7 compared with 2.8; $P<.01$)(Figure 3).

Investigators' Evaluation of Localized Irritation—The average measure for dryness was none to mild for both treatment groups at all evaluation times. There were no significant changes or differences from baseline within the treatment groups.

The average erythema rating was mild for both treatment groups at all evaluation times. There were no significant differences between the treatment groups.

The average edema rating was none to mild for both treatment groups at all evaluation times. There were no significant differences between the treatment groups.

The peeling rating was highest at the week 2 visit: 1.1 for the combination group and 1.4 for the monotherapy group, tapering off again by week 12. There were no significant differences either within or between the treatment groups.

Scaling was observed to be significantly increased in the combination group at week 2, but scaling declined in severity at week 4 and continued to decline to baseline levels at week 12.

The average tightness score was none to mild for both treatment groups at all visits. There was a significant difference between the 2 treatments in favor of the monotherapy group at week 12 (0.1 compared with 0.5; $P<.05$).

Investigators' Overall Opinion of the Test Medication—The investigators considered the subjects' tolerability to both treatment regimens to be very good. There were no significant differences with respect to this parameter.

The average rating of the test medications' effectiveness for clearing acne in the combination group was 4.1 (very good), while the rating for the monotherapy group was 3.1 (good). The difference between the treatment groups was significant ($P < .01$) in favor of the combination regimen.

The investigators' overall opinion of the test medication was significantly in favor of the combination regimen ($P < .01$). The average scores were 4.1 for the combination regimen and 3.2 for the monotherapy.

Subjects' Evaluations—There were no significant differences between the subjects in the 2 groups regarding the ratings for dryness, peeling, redness, or tightness. Subjects in both treatment groups rated their improvement as mild. Local reactions to the medications were rated as mild. Overall satisfaction with both regimens was rated as good.

Subject evaluations of the aesthetics of both products were generally favorable. Most subjects (53% of the combination group vs 58% of the monotherapy group) rated their overall opinion of the products to be "excellent to very good."

Safety—The nature and severity of the reported adverse events were similar for both treatment groups (Table).

CONCLUSION

The use of benzoyl peroxide 6% cleanser in a combined regimen with tretinoin 0.1% microsphere gel resulted in significantly faster and greater reductions in inflammatory acne lesions with no increase in localized irritation than use of tretinoin 0.1% microsphere gel alone.

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