Adapalene–Benzoyl Peroxide Once-Daily, Fixed-Dose Combination Gel for the Treatment of Acne Vulgaris: A Randomized, Bilateral (Split-Face), Dose-Assessment Study of Cutaneous Tolerability in Healthy Participants

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Combination therapy is an effective approach to simultaneously target multiple pathogenic factors of acne. International consensus guidelines recommend the use of topical retinoids and benzoyl peroxide (BPO) for acne treatment. These drugs are often prescribed as a free combination without any safety concern associated with antibiotic use. A 3-week, randomized, controlled, investigator-blinded, single-center, bilateral (split-face), dose-assessment study was conducted comparing the cutaneous tolerability of 2 adapalene-BPO fixed-dose combination products versus various concentrations of BPO monotherapy applied once daily. Sixty healthy participants were randomized to one of the following treatment groups: adapalene 0.1%–BPO 2.5% combination product versus BPO 2.5% monotherapy; adapalene 0.1%–BPO 2.5% combination product versus BPO 5% monotherapy; adapalene 0.1%–BPO 5% combination product versus BPO 5% monotherapy; and adapalene 0.1%–BPO 5% combination product versus BPO 10% monotherapy. Assessments included total sum score (TSS) of irritation signs/symptoms (erythema, scaling/desquamation, dryness, pruritus, stinging/burning) averaged over all postbaseline visits, individual irritation signs/symptoms (worst score), and adverse events. The overall cutaneous tolerability profile of the adapalene 0.1%–BPO 2.5% combination product was better than the combination with BPO 5% and similar to BPO 2.5% or 5% monotherapy. The combination product with BPO 5% induced significantly more irritation than BPO 5% monotherapy (P<.001) or BPO 10% monotherapy (P=.001). In conclusion, the new fixed-dose adapalene 0.1%–BPO 2.5% combination product provided the best overall cutaneous tolerability profile relative to BPO monotherapy.

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Combination therapy is often used in clinical practice to simultaneously target multiple pathogenic factors in the management of acne because there is no topical monotherapy that is effective against all 4 of the major pathophysiologic features of acne (abnormal keratinization, sebum production, bacterial proliferation, inflammation).[1-5] International consensus guidelines for the management of acne developed by the Global Alliance to Improve Outcomes in Acne recommend combination therapy with a topical

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retinoid and antimicrobial agents for all but the most severe cases of acne. Selection of which topical retinoid and antimicrobial agent to use in combination therapy should include a careful evaluation of the irritation potential of the individual acne medication, as the use of multiple agents is often associated with increased irritation, which can have an impact on treatment adherence and hinder successful outcomes.[4]

The safety and efficacy profile of topical retinoids and benzoyl peroxide (BPO), 2 agents with complementary modes of action, make them a logical choice for combination therapy. Adapalene, a receptor-selective naphthoic acid derivative with anti-inflammatory, comedolytic, and anticomedogenic properties,[6-13] is the most well-tolerated topical retinoid. BPO, a well-established antimicrobial agent with no evidence of microorganism resistance, is another safe and effective agent for the treatment of acne.[4,14-16] It already has been established that effectiveness does not increase with BPO titration, unlike skin irritancy.[17] A once-daily, fixed-dose combination gel with adapalene 0.1%–BPO 2.5% has been developed. Preclinical studies showed that a formulation containing adapalene and BPO has an overall preclinical profile similar to the individual agents.[18] Moreover, unlike tretinoin, adapalene is stable when combined with BPO in the presence or absence of light.[19] To determine the optimum combination of adapalene and BPO regarding tolerability, the current study compared the cutaneous tolerability of 2 combinations of adapalene 0.1%–BPO versus various concentrations of BPO monotherapy applied once daily in a 3-week, randomized, bilateral (split-face), dose-assessment study in healthy participants.

Methods

Study Design—A 3-week, randomized, controlled, investigator-blinded, single-center, bilateral (split-face), dose-assessment study was conducted comparing the cutaneous tolerability of 2 combinations of adapalene with BPO versus various concentrations of BPO monotherapy applied once daily. Eligible study participants were healthy men and women at least 18 years of age with Fitzpatrick skin types I to III who were willing and able to comply with the requirements of the protocol. Washout periods were required for participants taking certain topical and systemic treatments. Women were excluded if they were pregnant, breastfeeding, or planning a pregnancy. Individuals with a known allergy to any component of the study products were excluded from the study.

The participants were randomized to 4 parallel treatment groups to compare 2 adapalene 0.1%–BPO combination products with 3 concentrations of BPO applied as monotherapy. Each treatment group compared 2 treatments: a combination product and a monotherapy product (Table 1). Study products were applied once daily for 3 weeks. Within each treatment group, the 2 treatments were randomized to be applied to either the left side or right side of the face. During the 22 days of the study, applications and scoring were performed at the study site once daily (excluding weekends) for a total of 15 applications and 16 evaluations.

The assignment of treatments to specific sides of the face (left or right) was randomly generated. To maintain the integrity of the blinding, the investigator did not apply study products, and personnel other than the investigator were required to dispense study medications. Participants were instructed to apply the appropriate product to the assigned side of the face once daily for 3 weeks.

Evaluations occurred each weekday during study visits (16 total evaluations). At each visit, the investigator assessed the local cutaneous tolerability parameters (erythema, scaling/desquamation, dryness, pruritus, stinging/burning) on a scale of 0 (no reaction) to 3 (severe). The primary evaluation was the total sum score (TSS) of the cutaneous tolerability signs/symptoms, averaged over all evaluation visits except baseline. The mean worst score

Table 1.

Comparison Treatment Groups

Treatment Group	Adapalene-BPO Combination Product	BPO Monotherapy	Participants, n
1	Adapalene 0.1%–BPO 2.5%	BPO 2.5%	15
2	Adapalene 0.1%–BPO 2.5%	BPO 5%	16
3	Adapalene 0.1%–BPO 5%	BPO 5%	15
4	Adapalene 0.1%–BPO 5%	BPO 10%	14

Abbreviation: BPO, benzoyl peroxide.

for participants observed during all postbaseline visits was calculated for each tolerability parameter. If severe irritation (ie, score of 3 for any tolerability parameter) occurred on one side of the face, applications were stopped on both sides. Adverse events were monitored during the study and classified based on severity and relationship to study products.

This study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and Good Clinical Practices and in compliance with local regulatory requirements. This study and all appropriate amendments were reviewed and approved by an institutional review board. All participants provided their written informed consent prior to entering the study.

Statistical Analyses—All data analyses were carried out according to a preestablished analysis plan. A standard sample size for this type of study is 25 participants. To account for possible participant discontinuations, a total of 30 participants were to receive each combination product. This population was considered sufficient to evaluate the irritation potential of each combination product compared with different concentrations of a known anti-acne product. The TSS averaged across postbaseline evaluation time points was submitted to an analysis of variance that included in the model the participant, side of the body (left or right), and treatment. Least squares means were calculated for each product, and each combination was compared with the 2 corresponding adjacent doses of BPO monotherapy using estimate statements from SAS PROC MIXED. The TSS criterion also was analyzed after imputing missing data using last-observation-carried-forward methodology. The worst score for each sign/symptom was summarized in tables that reported frequency, mean, and standard deviations, and was compared between the 2 treatments within each treatment group using the Wilcoxon signed rank test.

Results

Participant Disposition and Baseline Characteristics—A summary of participant disposition and baseline characteristics is provided in Table 2. Sixty healthy participants (mean age, 39 years; 75% female [45/60]) were enrolled in the study. Fifty participants (83%) completed the study. Seven participants discontinued prematurely because of an adverse event (2 cases of irritant dermatitis with the adapalene 0.1%–BPO 2.5% combination product, 4 cases of irritant dermatitis with the adapalene 0.1%–BPO 5% combination product, 1 case of irritant dermatitis due to reactions with BPO 5% monotherapy). Three participants discontinued prematurely for a reason unrelated to the study (participant's request).

Tolerability/Safety Evaluation—The TSS of the signs/symptoms of irritation (erythema, scaling/desquamation, dryness, pruritus, stinging/burning) averaged over all postbaseline visits are shown in Table 3. The analysis of the primary safety variable demonstrated that the TSS for the adapalene 0.1%–BPO 2.5% combination product was not statistically different from BPO 2.5% monotherapy ($P=.088$) or BPO 5% monotherapy ($P=.061$). However, the TSS for the adapalene 0.1%–BPO 5% combination product was statistically significantly higher than either BPO 5% monotherapy ($P<.001$) or BPO 10% monotherapy ($P=.001$). The severity of the cutaneous tolerability parameters would be characterized as mild for the adapalene 0.1%–BPO 2.5% combination product as well as the BPO monotherapy groups. The results were similar when missing data were imputed with last-observation-carried-forward methodology.

The worst postbaseline scores (the average of the highest scores observed for each participant for all postbaseline visits) for each tolerability parameter (erythema, scaling/desquamation, dryness, pruritus, stinging/burning) are shown in Table 4. The adapalene 0.1%–BPO 2.5% combination product had comparable tolerability to BPO 2.5% monotherapy, with no statistically significant differences observed between the 2 treatment groups in each of the individual signs/symptoms. The cutaneous tolerability of the adapalene 0.1%–BPO 2.5% combination product also was comparable to BPO 5% monotherapy, though significant differences in the worst postbaseline scores of scaling/desquamation ($P=.016$) and dryness ($P=.035$) were observed. For the adapalene 0.1%–BPO 5% combination product, significant differences were observed in scaling/desquamation ($P<.001$), dryness ($P=.002$), and stinging/burning ($P=.004$) relative to BPO 5% monotherapy. BPO 10% monotherapy was significantly less irritating for all evaluations versus the adapalene 0.1%–BPO 5% combination product ($P<.05$ for all) except pruritus ($P=.250$).

A total of 27 participants experienced 32 adverse events. No serious adverse events were reported. Twelve treatment-related adverse events were observed in 11 participants: 5 were reported for the adapalene 0.1%–BPO 2.5% combination product (irritant dermatitis), 5 for the adapalene 0.1%–BPO 5% combination product (4 instances of irritant dermatitis and 1 transient edema), none for BPO 2.5% monotherapy, 1 for BPO 5% monotherapy (irritant dermatitis), and 1 for BPO 10% monotherapy (transient edema of the cheek). Seven related adverse events led to treatment discontinuation: 2 for the adapalene 0.1%–BPO 2.5% combination product, 4 for the adapalene 0.1%–BPO 5% combination product, and 1 for BPO 5% monotherapy. The adapalene 0.1%–BPO 5%

Table 2.

Participant Disposition and Baseline Characteristics

	Adapalene 0.1%–BPO 2.5% Combination Product vs BPO 2.5% Monotherapy	Adapalene 0.1%–BPO 2.5% Combination Product vs BPO 5% Monotherapy	Adapalene 0.1%–BPO 5% Combination Product vs BPO 5% Monotherapy	Adapalene 0.1%–BPO 5% Combination Product vs BPO 10% Monotherapy	All
Enrolled, n (%)	15 (25.0)	16 (26.7)	15 (25.0)	14 (23.3)	60 (100)
Discontinued, n (%)	0 (0)	3 (18.8)	4 (26.7)	3 (21.4)	10 (16.7)
Adverse event, n (%)	0 (0)	3 (18.8)	2 (13.3)	2 (14.3)	7 (11.7)
Participant request, n (%)	0 (0)	0 (0)	2 (13.3)	1 (7.1)	3 (5.0)
Completed, n (%)	15 (100)	13 (81.3)	11 (73.3)	11 (78.6)	50 (83.3)
Age, y					
Mean	46	40	34	37	39
Minimum	22	19	20	20	19
Maximum	66	64	51	53	66
Gender, n (%)					
Male	7 (46.7)	2 (12.5)	2 (13.3)	4 (28.6)	15 (25.0)
Female	8 (53.3)	14 (87.5)	13 (86.7)	10 (71.4)	45 (75.0)
Race, n (%)					
White	14 (93.3)	16 (100)	15 (100)	14 (100)	59 (98.3)
Black	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	1 (6.7)	0 (0)	0 (0)	0 (0)	1 (1.7)
Fitzpatrick skin type, n (%)					
I	0 (0)	1 (6.3)	0 (0)	0 (0)	1 (1.7)
II	0 (0)	4 (25.0)	1 (6.7)	2 (14.3)	7 (11.7)
III	15 (100)	11 (68.8)	14 (93.3)	12 (85.7)	52 (86.7)

Abbreviation: BPO, benzoyl peroxide.

combination product induced twice as many instances of irritant dermatitis that led to discontinuation than the adapalene 0.1%–BPO 2.5% combination product (4 participants [13.8%] versus 2 [6.5%], respectively). No sensitization was reported during the study.

Comment

This study was designed to compare the cutaneous tolerability of once-daily, fixed-dose combinations of adapalene 0.1%–BPO versus BPO monotherapy to determine the optimum combination of adapalene and BPO regarding irritation potential. Overall, the formulation containing adapalene 0.1%–BPO 2.5% provided the best overall cutaneous tolerability profile relative to BPO monotherapies in this dose-assessment tolerability study. The overall cutaneous tolerability profile of the combination product with BPO 2.5% was better than the

Table 3.

TSS of the Signs/Symptoms of Irritation (Erythema, Scaling/Desquamation, Dryness, Pruritus, Stinging/Burning) Averaged Over All Postbaseline Visits

	TSS, mean±SEM	Least Squares Mean of Difference, estimate±SEM	*P* Value
Adapalene 0.1%–BPO 2.5% combination product vs BPO 2.5% monotherapy (n=15)			
Adapalene 0.1%–BPO 2.5% combination product	1.05±0.29		
BPO 2.5% monotherapy	0.45±0.17	0.60±0.35	.088
Adapalene 0.1%–BPO 2.5% combination product vs BPO 5% monotherapy (n=16)			
Adapalene 0.1%–BPO 2.5% combination product	1.68±0.34		
BPO 5% monotherapy	1.03±0.33	0.64±0.34	.061
Adapalene 0.1%–BPO 5% combination product vs BPO 5% monotherapy (n=15)			
Adapalene 0.1%–BPO 5% combination product	2.12±0.29		
BPO 5% monotherapy	0.72±0.22	1.40±0.36	<.001
Adapalene 0.1%–BPO 5% combination product vs BPO 10% monotherapy (n=14)			
Adapalene 0.1%–BPO 5% combination product	2.62±0.41		
BPO 10% monotherapy	1.33±0.28	1.29±0.36	.001

Abbreviations: TSS, total sum score; SEM, standard error of the mean; BPO, benzoyl peroxide.

combination product with BPO 5% and similar to BPO 2.5% or 5% monotherapy, which showed that adding adapalene 0.1% to BPO 2.5% or 5% does not lead to increased irritation. The combination product with BPO 5% induced significantly more irritation than BPO 5% monotherapy ($P<.001$) or BPO 10% monotherapy ($P=.001$).

Tolerability is an important factor when choosing a therapeutic regimen for acne, especially when using multiple agents.[4] For example, the increased irritation associated with the use of multiple therapies must be carefully considered when choosing a treatment regimen. A well-tolerated, fixed-dose combination product may help reduce the complexity of acne management for patients and physicians by reducing the number of medications a patient has to remember to take on a daily basis, thereby potentially improving treatment adherence. Adapalene is a rational choice for a fixed-dose combination therapy, as previous studies have shown the use of combination therapy with adapalene 0.1% may be more tolerable and associated with a lower rate of adverse events relative to the other topical retinoids.[20-24] Consistent with the results of these previous data as well as the current study, a recently completed large, double-blind, controlled clinical study in participants with moderate to severe inflammatory acne showed that a concomitant treatment with adapalene and BPO was more effective and had a quicker onset of action than monotherapy, with a safety profile comparable with adapalene monotherapy.[25] Long-term safety and efficacy of this combination also has been demonstrated in a recent study.[26]

These findings support international consensus recommendations emphasizing the importance of aggressive combination therapy for acne because of the complex, multifactorial, pathophysiologic features of the condition.[4] The guidelines strongly recommend including topical retinoids (alone or in combination) in the acute and maintenance management

Table 4.

Mean Worst Score Difference (Adapalene-BPO Combination Product Minus BPO Monotherapy) for the Signs/Symptoms of Irritation

	Worst Score Difference (Adapalene-BPO Combination Product Minus BPO Monotherapy), mean±SD	*P* Value
Adapalene 0.1%–BPO 2.5% combination product vs BPO 2.5% monotherapy		
Erythema	0.13±0.64	.750
Scaling/Desquamation	0.33±0.90	.281
Dryness	0.27±0.59	.219
Pruritus	0.40±0.83	.156
Stinging/Burning	0.53±0.92	.072
Adapalene 0.1%–BPO 2.5% combination product vs BPO 5% monotherapy		
Erythema	0.25±1.29	.469
Scaling/Desquamation	0.75±1.00	.016
Dryness	0.50±0.73	.035
Pruritus	0.19±0.66	.500
Stinging/Burning	0.44±1.36	.219
Adapalene 0.1%–BPO 5% combination product vs BPO 5% monotherapy		
Erythema	0.50±0.76	.063
Scaling/Desquamation	1.07±0.73	<.001
Dryness	0.93±0.83	.002
Pruritus	0.14±0.66	.750
Stinging/Burning	1.07±1.07	.004
Adapalene 0.1%–BPO 5% combination product vs BPO 10% monotherapy		
Erythema	0.50±0.65	.031
Scaling/Desquamation	0.64±0.63	.008
Dryness	0.50±0.52	.016
Pruritus	0.43±0.85	.250
Stinging/Burning	0.79±0.89	.008

Abbreviations: BPO, benzoyl peroxide; SD, standard deviation.

of most patients with acne. The complementary mechanisms of action of topical retinoids and antimicrobial agents produce a highly effective treatment regimen, and the tolerability profile of adapalene and BPO makes these 2 agents a good choice for a fixed-dose combination.

Conclusion

Data from this study indicate that the new fixed-dose adapalene 0.1%–BPO 2.5% combination product has comparable tolerability relative to BPO monotherapy and is the optimum combination of these 2 agents. This combination contains the lowest effective dose of

each component while limiting the irritation potential to a level that is likely to be acceptable to patients that follow a once-daily application schedule. A once-daily, fixed-dose adapalene-BPO combination product for the treatment of acne vulgaris will expand the therapeutic armamentarium available for acne management and provide greater flexibility for customizing both short-term and long-term care.

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