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Treatment of 2,453 Acne Vulgaris Patients Aged 12–17 Years With the Fixed-dose Adapalene-benzoyl Peroxide Combination Topical Gel: Efficacy and Safety

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ABSTRACT

Acne vulgaris is a common disease in adolescents, and early treatment may minimize its physical and psychological effects. A fixed-dose combination gel of adapalene 0.1% and benzoyl peroxide 2.5% (adapalene-BPO) is efficacious and safe in the treatment of acne patients aged 12 years or older, as demonstrated in three randomized and controlled studies. The current study is a subgroup analysis of the efficacy and safety of adapalene-BPO among 2,453 patients aged 12–17 years. After 12 weeks of treatment, significantly more patients in the adapalene-BPO group were "clear" or "almost clear" (30.9%, $P<0.001$) compared to the monotherapies and vehicle. The percentage reduction from baseline in total, inflammatory and non-inflammatory lesions was 56, 63 and 54.5 percent in the adapalene-BPO group, respectively, significantly higher than in the monotherapy groups and vehicle (all $P<0.001$). Significantly earlier onset of effect was observed at week 1. Adapalene-BPO was also well tolerated, with the mean scores of dryness, erythema, scaling and stinging/burning less than 1 (mild) at all study visits. Overall, the adapalene-BPO combination gel provides significantly greater and synergistic efficacy and a fast onset of action compared to the monotherapies and vehicle in young acne patients aged 12–17 years.

INTRODUCTION

Acne vulgaris is a very common disease that usually starts during late childhood or early-adolescence, affecting more than 90 percent of males and 80 percent of females by the age of 21 years.[1,2] Since adolescence is an important period for psychosocial development, clinically significant acne vulgaris that causes visible disfiguration is known to have marked adverse effects on young patients' quality of life. The disease is reported to be associated with embarrassment, anxiety, depression and social inhibition.[3–6] Due to the high prevalence and large impact of acne among adolescents, early treatment may be useful to minimize physical, social and cosmetic effects of the disease. Therefore, it is important to assess the efficacy and safety of current treatments in the adolescent population.

Combination therapies are frequently used in treatment of acne, due to the multi-factorial pathogenesis of the disease.[7–9] A once-daily, antibiotic-free, fixed-dose combination gel with adapalene 0.1% and benzoyl peroxide 2.5% (adapalene-BPO) has recently been developed and approved for treatment of acne vulgaris.[10,11] Adapalene possesses anticomedogenic, comedolytic, anti-inflammatory and immuno-regulating activities,[12] whereas BPO is a potent bactericidal agent which minimizes the development of antimicrobial resistance.[13] The complementary modes of action of the two agents make adapalene-BPO a logical choice for treatment of all but the most severe acne. In three large-scale, randomized and controlled studies, adapalene-BPO demonstrated a favorable efficacy/safety profile, providing significantly superior efficacy compared to the adapalene or BPO monotherapy and the gel vehicle among patients aged 12 years or older.[14–16] High patient satisfaction was also reported in those studies for the adapalene-BPO treatment.[15,16]

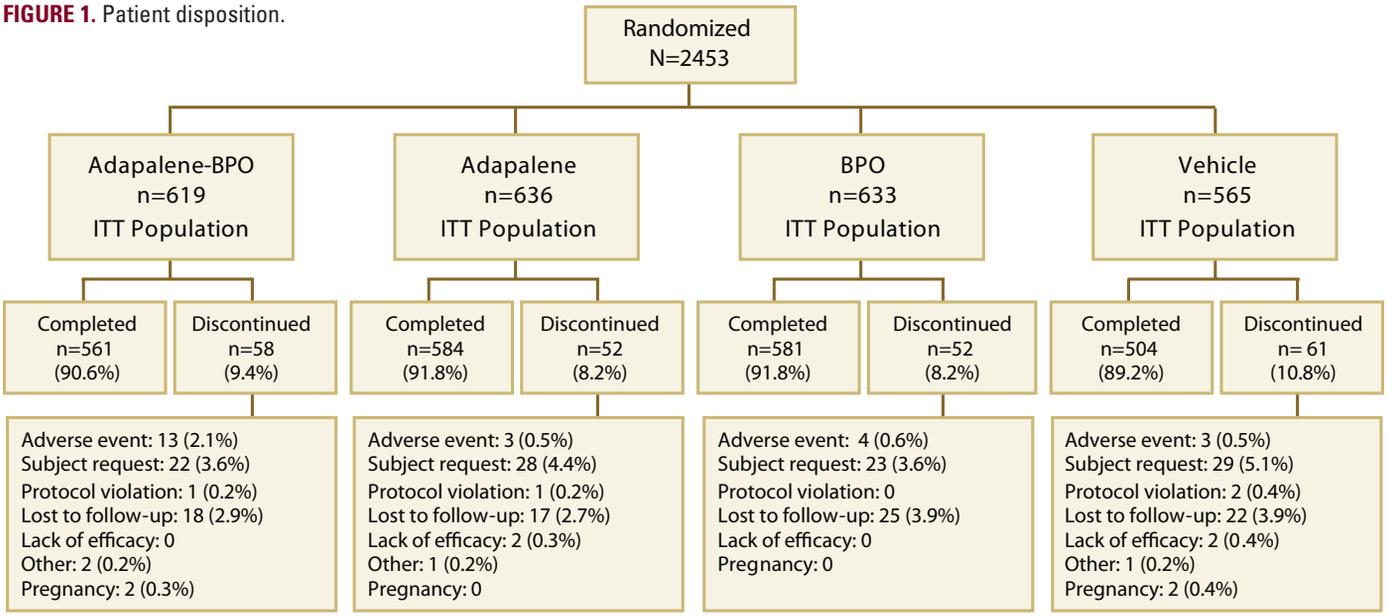
In this analysis, the authors aimed to assess the efficacy and safety of the adapalene-BPO combination gel in the treatment of acne patients aged 12–17 years. To this end, they combined the data from three studies and performed a subgroup analysis.

METHODS AND MATERIAL

Study Design

The efficacy and safety of adapalene-BPO were compared to those of adapalene, BPO and the gel vehicle in three random-

FIGURE 1. Patient disposition.



ized, multicenter, double-blind, active- and vehicle-controlled studies conducted at 157 centers in the United States (U.S.), Canada, Puerto Rico and Europe.[14–16] Patients were randomized to receive adapalene-BPO gel (Epiduo®, Galderma Laboratories), adapalene gel, BPO gel or gel vehicle, once daily in the evening for 12 weeks. Adapalene and BPO used in the studies were formulated in the same gel vehicle as adapalene-BPO. Blinding integrity was ensured by packaging the medication in identical tubes and by requiring a third party other than the investigator/evaluator to dispense the medication. Efficacy and safety evaluations were performed at baseline and at weeks 1, 2, 4, 8 and 12.

The three studies were conducted in accordance with the Declaration of Helsinki, Good Clinical Practices and local regulatory requirements. Studies were reviewed and approved by the appropriate institutional review boards/ethics committees. All patients provided their written informed consent prior to entering the study.

Subjects

Enrolled subjects were 12 years or older, male or female of any race. Data from subjects aged 12–17 years are presented here. Eligible subjects presented facial acne with 20–50 inflammatory lesions (IL), 30–100 non-inflammatory lesions (NIL) and no more than one nodule at baseline. Lesion counts were assessed on the face only, excluding the nose. Specified washout periods were required for subjects taking certain topical and systemic treatments. Exclusion criteria prohibited the enrollment of subjects with severe acne requiring isotretinoin therapy or other dermatologic conditions requiring interfering treatment. Female subjects were excluded if they were pregnant, nursing or planning a pregnancy, as were male subjects with facial hair that would interfere with the assessments.

Efficacy and Safety Assessments

Efficacy assessments included success rate (the percentage of subjects rated "clear" or "almost clear" on the investigator's global assessment scale [IGA] of acne severity) and percentage change from baseline in lesion counts (IL, NIL and total lesion) at each study visit, as well as subject's assessment of acne improvement at the end of the study. IGA was evaluated on a scale ranging from 0 (clear: residual hyperpigmentation and erythema may be present) to 4 (severe: entire face is involved, covered with comedones, numerous papules and pustules, and few nodules and cysts). Subject's assessment was evaluated on a scale from 0 (complete improvement) to 5 (worse).

Safety was assessed through evaluations of local tolerability and adverse events. At each visit, the investigator rated dryness, erythema, scaling and stinging/burning on a scale ranging from 0 (none) to 3 (severe). Adverse events were also reported and evaluated at each study visit.

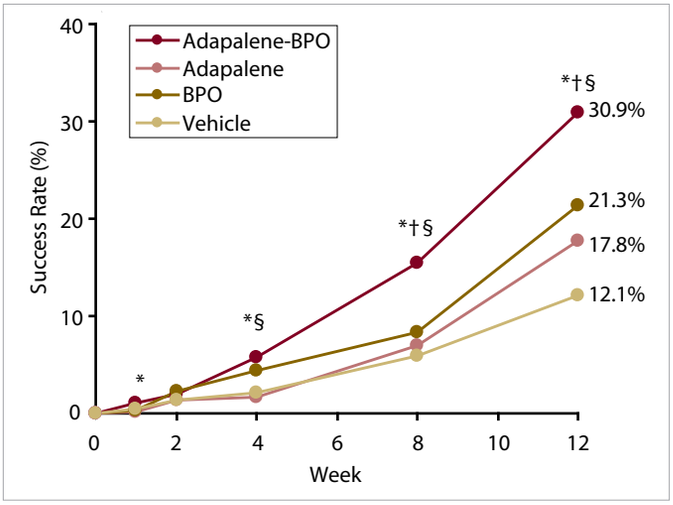
Statistical Analyses

The analyses were performed on a subgroup of subjects between 12 and 17 years old. Data from the three studies were pooled and analyzed. Efficacy was evaluated on the intent-to-treat (ITT) population, which included randomized subjects who received study medication, using the last observation carried forward (LOCF) method to impute missing values. Safety was evaluated in the safety population, which included randomized subjects who were treated at least once.

TABLE 1.

Demography and Baseline Characteristics					
	Adapalene-BPO (n=619)	**Adapalene (n=636)**	**BPO (n=633)**	**Vehicle (n=565)**	**Total (n=2453)**
Age, Year					
Mean	14.9	14.8	14.7	14.7	14.8
12–13 year, %	18.7	21.1	21.8	23.9	21.3
14–17 year, %	81.3	78.9	78.2	76.1	78.7
Gender, n (%)					
Male	376 (60.7)	367 (57.7)	390 (61.6)	320 (56.6)	1453 (59.2)
Female	243 (39.3)	269 (42.3)	243 (38.4)	245 (43.4)	1000 (40.8)
Race, n (%)					
Caucasian	474 (76.6)	472 (74.2)	477 (75.4)	418 (74.0)	1841 (75.1)
Black	53 (8.6)	71 (11.2)	70 (11.1)	65 (11.5)	259 (10.5)
Asian	7 (1.1)	9 (1.4)	8 (1.3)	13 (2.3)	37 (1.5)
Hispanic	69 (11.1)	70 (11.0)	66 (10.3)	63 (11.2)	268 (10.9)
Other	16 (2.6)	14 (2.2)	12 (1.9)	6 (1.0)	48 (2.0)
Mean Lesion Counts					
Total	82.5	83.8	83.0	84.0	83.3
Inflammatory	30.0	30.0	30.2	30.1	30.1
Non-inflammatory	52.5	53.9	52.9	53.9	53.3
Global Severity, n (%)					
2: Mild	21 (3.4)	21 (3.3)	11 (1.7)	8 (1.4)	61 (2.5)
3: Moderate	593 (95.8)	606 (95.3)	614 (97.0)	554 (98.2)	2367 (96.5)
4: Severe	5 (0.8)	9 (1.4)	8 (1.3)	2 (0.4)	24 (1.0)

FIGURE 2. Success rate.



*P<0.05 versus adapalene; †P<0.05 versus BPO; §P<0.05 versus vehicle.

Success rate and percentage change in lesion counts were analyzed using the Cochran-Mantel-Haenzsel (CMH) test stratified by analysis center, using general association for success rates and row mean differences by relative to identified distribution (RIDIT) transformed scores for percentage change in lesion counts. Subject's assessment of acne improvement was analyzed using the CMH test. All tests were two-sided, with significance declared at 0.05 level.

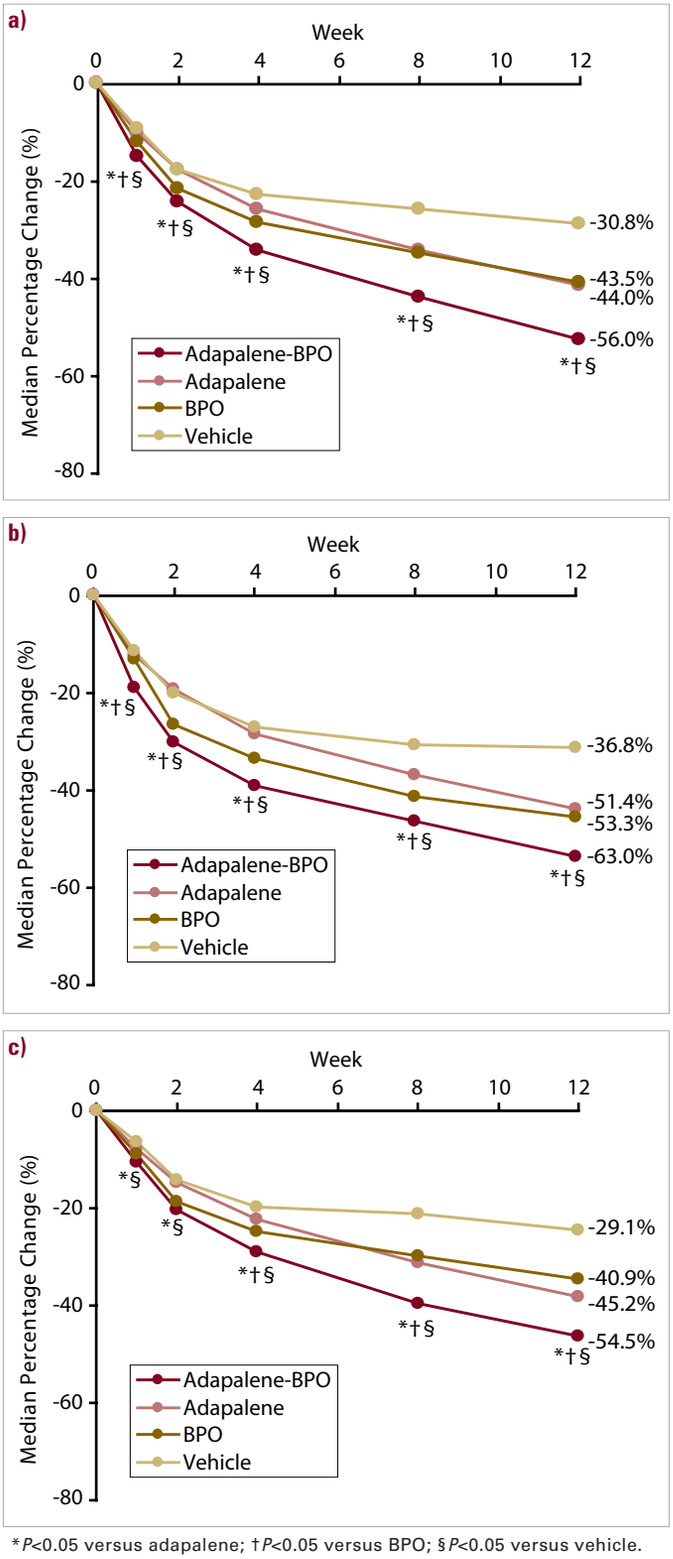
RESULTS

Subject Disposition and Baseline Characteristics

A total of 2,453 subjects between 12 and 17 years old were included in the ITT population: 619 received adapalene-BPO, 636 received adapalene, 633 received BPO and 565 received vehicle (Figure 1). Subject disposition was similar among the treatment groups. Overall, 90.9 percent of subjects reported normal study completion. Similar discontinuation rates were observed among the different treatment groups. Slightly more subjects (2.1%) in the adapalene-BPO discontinued due to adverse events compared to the other groups. However, this rate was very low for all groups (0.5–2.1%).

The baseline characteristics of the ITT population are summarized in Table 1. The four treatment groups were comparable with respect to the demographic characteristics and baseline disease severity scores. Most of the subjects were male (59.2%), consistent with the report that acne is more common among

FIGURE 3. Median percentage changes from baseline in **a)** total lesions **b)** inflammatory lesions and **c)** non-inflammatory lesions



*P<0.05 versus adapalene; †P<0.05 versus BPO; §P<0.05 versus vehicle.

boys than girls.[2] A majority of subjects were Caucasian (75.1%), with moderate acne (96.5%) at the study baseline.

Efficacy

At study endpoint (week 12-LOCF), the adapalene-BPO combination was significantly superior to adapalene, BPO and vehicle in achieving treatment success (all P<0.001; Figure 2). The success rate increased continuously throughout the course of the study, with significant difference in the percentage of patients assessed as "clear" or "almost clear" by week 8 in favor of adapalene-BPO compared with the other groups (all P<0.001). At week 12-LOCF, the benefit of combination relative to vehicle (18.7%) was greater than the sum of the benefit obtained with the individual components (5.7% for adapalene plus 9.2% for BPO), indicating a synergistic therapeutic activity of the components in the fixed-dose combination. This synergistic effect in the increase of success rate was also observed at weeks 1, 4 and 8.

At study endpoint (week 12-LOCF), the adapalene-BPO combination gel was also significantly more efficacious than adapalene, BPO and the gel vehicle in terms of percentage change from baseline in inflammatory, non-inflammatory and total lesion counts (all P<0.001; Figure 3). An onset of action was observed as early as week 1, with significantly greater reduction of total, inflammatory and non-inflammatory lesion counts observed in the adapalene-BPO group compared with all other treatment groups (all P<0.01). The only exception was adapalene-BPO compared to BPO in the reduction of non-inflammatory lesion counts, which demonstrated an onset of action at week 4 (P<0.001). Synergistic activity of the combination was observed at weeks 1, 2, 4 and 8 for the reduction of total lesion counts and at weeks 1, 2 and 4 for the reduction of IL and NIL counts.

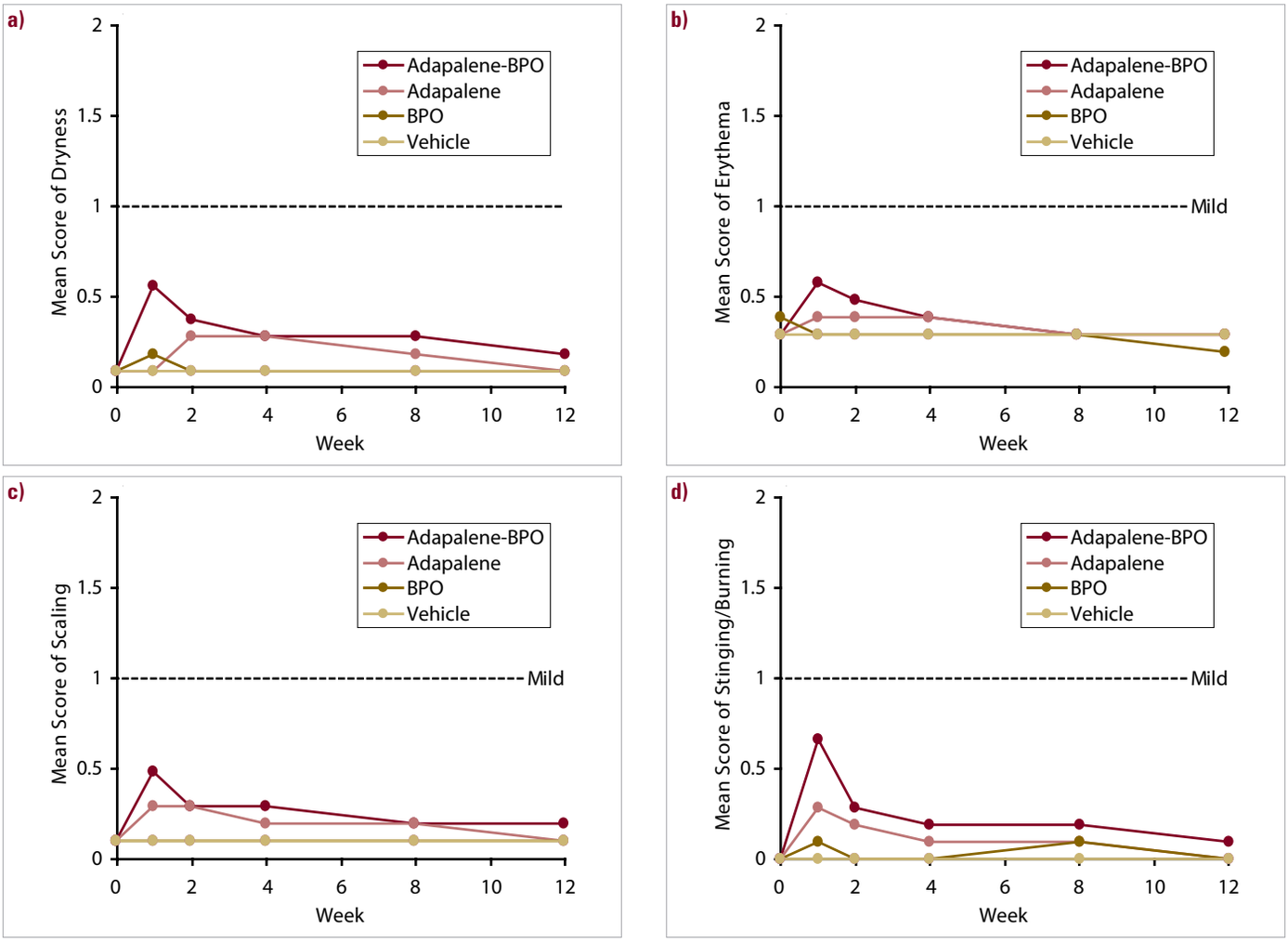
The subject's assessments were consistent with the efficacy evaluations performed by the investigators. At week 12, the percentage of subjects who reported a "complete improvement" or a "marked improvement" was 45.5 percent for adapalene-BPO, significantly higher than that for adapalene, BPO and vehicle (38.3%, 36.4% and 24.7%, respectively; all P<0.001).

Safety

Overall, the adapalene-BPO combination gel was well tolerated (Figure 4). The mean scores and the mean worst scores for the severity of erythema, scaling, dryness and stinging/burning were less than 1 (mild) for all treatment groups. Peak scores at week 1 were the highest for adapalene-BPO; however, the scores decreased rapidly at subsequent visits. A majority of subjects experienced no or only mild irritation.

The percentage of subjects experiencing treatment-related adverse events was 21.5 percent for adapalene-BPO, 15.1 percent

FIGURE 4. Local tolerability signs. Mean scores for the severity of **a)** dryness, **b)** erythema, **c)** scaling and **d)** stinging/burning.



for adapalene, 8.1 percent for BPO and 5.7 percent for vehicle. Most of the related adverse events were of a dermatological nature, mild to moderate in severity, occurred early during the study and resolved without any residual effects. "Dry skin" largely accounted for the difference among treatment groups, reported in 13.4, 9.6 and 3.9 percent of subjects in the groups of adapalene-BPO, adapalene and BPO, respectively. Seven subjects reported serious adverse events, none of which were deemed to be related to the treatments.

DISCUSSIONS

The aim of this analysis was to evaluate the efficacy and safety of the fixed-dose adapalene-BPO combination gel among a large population of young acne vulgaris patients. Overall, this analysis confirmed the superior efficacy of the combination relative to monotherapies and vehicle in young acne patients, as reported previously for the entire population (12 years or older).[14–17] Specifically, adapalene-BPO was more efficacious than other treatment groups in the increase of success rate and in the reduction of all lesion counts. The combination demonstrated a significantly early onset of action at week 1 in terms of percentage change in total and inflammatory lesion counts. A greater benefit relative to vehicle was observed for the combination than the sum of the benefits for the individual components, suggesting synergistic activities of adapalene and BPO in the fixed-dose combination.

Due to the chronic nature of acne vulgaris, management of the disease is necessary and, in adolescents, an efficacious treatment to gain early control of the disease is particularly useful.[18] The 12-week treatment using adapalene-BPO resulted in a 56 percent reduction in total lesion counts. Previous studies have reported reduction of total lesion counts with tretinoin microsphere gel (35% in a population aged 11–16 years), Dapsone gel (34.6% in a population aged 12–15 years) and the tretinoin 0.025% and clindamycin 1.2% combination gel (39.3% in a population aged 12–18 years).[19–21] However, direct comparison cannot be made between these studies as

they were performed independently with differing populations of patients.

The efficacy of the adapalene-BPO combination can be explained by the distinct and yet complementary modes of action of its active ingredients. Retinoids, such as adapalene, target microcomedones, the invisible lesions that are the common precursors of all acne lesions.[7,8] Adapalene also possesses anti-inflammatory and immuno-regulating properties, besides its anticomedogenic and comedolytic activities.[12] BPO is known as the most potent bactericidal agent for treatment of acne and is effective in reducing inflammatory lesions.[13] Furthermore, since BPO does not create selective pressure for bacterial resistance, unlike the commonly used topical antibiotics such as clindamycin and erythromycin, its usage is consistent with the global strategy of World Health Organization for the containment of antimicrobial resistance and is particular suitable for treatment of young acne patients.[23] Synergistic efficacy was observed in the fixed-dose combination, possibly contributing to the significant early onset of action and the marked increase of success rate after week 4.[17] Adapalene and BPO acted synergistically and led to a decrease of 63 percent from baseline in inflammatory lesions, which are the more visible type of acne lesions and are often associated with the development of acne scar.[8]

Patient adherence is particularly important for the overall effectiveness of acne vulgaris treatments. However, adherence to topical acne medications was reported to be poor, especially in young patients.[8,24,25] Adapalene-BPO should improve patient adherence, since the treatment is highly efficacious and leads to great patient satisfaction. Although a combination treatment, adapalene-BPO is a fixed-dose, once-daily topical gel, and the easy-to-use characteristic of the medication is also expected to be associated with better patient adherence. Finally, the combination demonstrated a significant onset of action as early as week 1, which should further encourage compliance.

In summary, the adapalene-BPO combination gel is efficacious and well tolerated in treatment of acne vulgaris among 2,453 patients aged 12–17 years.

DISCLOSURES

Dr. Eichenfield has served as a clinical investigator and consultant for Galderma.

Dr Jorizzo has received honoraria and serves as a speaker for Galderma.

Dr. Dirschka received a grant and serves as advisor and speaker for Galderma.

Dr Taub has received compensation for being an investigator in this study.

Dr Lynde serves as an advisor and has received a grant for research from Galderma.

Mr. Graeber and Mr. Kerrouche are employees of Galderma.

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