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Jerry TAN[1]
Robert BISSONNETTE[2]
David GRATTON[3]
Nabil KERROUCHE[4]
Juliana Machado CANOSA[5]

[1] 300-2224 Walker Road, Windsor, ON N8W 5L7, Canada
[2] 1851 Sherbrooke East, Montreal, Quebec H2K 4L5, Canada
[3] 3550 Cote des Neiges, Suite 740 Montreal H3H 1V4, Quebec, Canada
[4] Nestlé Skin Health - Galderma R&D, 2400 Route des Colles, 06410 Biot, France
[5] Nestlé Skin Health - Galderma International, Tour Europlaza, 20 avenue André Prothin, 92927 La Défense, France

Reprints: J. Tan
<jerrytan@bellnet.ca>

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The safety and efficacy of four different fixed combination regimens of adapalene 0.1%/benzoyl peroxide 2.5% gel for the treatment of *acne vulgaris*: results from a randomised controlled study

Background: Combined use of a retinoid and antimicrobial is recommended for acne, however, local tolerability issues may compromise patient adherence and treatment outcome. *Objectives:* This multicentre, single-blinded controlled study was designed to determine whether modified adapalene/benzoyl peroxide (A/BPO, Epiduo®, Galderma, France) regimens improve local tolerability during the first four weeks of treatment without impairing efficacy at Week 12. *Materials & Methods:* In total, 120 subjects with mild-to-moderate acne received, during the first four weeks, A/BPO daily overnight (A/BPO-EN), A/BPO daily for three hours (A/BPO-3h), A/BPO daily overnight and a provided moisturizer lotion (A/BPO-moisturizer), or A/BPO every other night (A/BPO-EoN). Local tolerance assessments included signs and symptoms, global worst score (GWS), and total sum score (TSS). Efficacy was assessed based on lesion counts, investigator global assessment (IGA), and total lesion count reduction. Adherence, subject satisfaction, and overall safety were also assessed. *Results:* The mean TSS was significantly reduced at Week 1 with A/BPO-EoN vs. A/BPO-EN ($p<0.05$), and A/BPO-EoN led to the lowest GWS and a decrease in severity of stinging/burning and erythema ($p<0.05$). The A/BPO-moisturizer regimen prevented dryness and scaling compared with the A/BPO-EN regimen. The median decrease in lesions from baseline was similar in all groups: up to 67% for total, 72% for inflammatory, and 70% for non-inflammatory lesion counts. Adherence, IGA, patient satisfaction, and overall safety were excellent. *Conclusions:* Modulating treatment regimens during the first four weeks improved local tolerability without impacting overall efficacy outcome after 12 weeks and may improve treatment adherence during the first weeks of therapy.

Key words: acne, adapalene/benzoyl peroxide, emollient lotion, treatment regimen, moisturizer, management of treatment side effects

Acne vulgaris is a chronic skin disease that occurs commonly among adolescents and some adults [1]. Due to its multi-factorial pathogenesis, combination therapy utilizing agents with complementary mechanisms, such as a topical retinoid and an antimicrobial, is recommended for the management of the disease [2, 3].

To enhance the combined use of a retinoid and benzoyl peroxide, a fixed-dose combination gel with adapalene 0.1% and benzoyl peroxide 2.5% (A/BPO, Epiduo®, Galderma France) has been developed. Based on their complementary mode of action, as well as their individually demonstrated efficacy and safety, this combination makes a rational choice for the treatment of all but the most severe cases of acne [4-9]. In several multicentre, double-blinded, randomised and controlled studies, once-daily application in the evening of A/BPO provided significantly greater efficacy compared with A alone, BPO alone, or the gel vehicle combined [10-14]. Moreover, A/BPO acted more rapidly than each component individually, with an onset of action as early as Week 1, with improved quality of life and patient adherence to treatment [10, 11, 13, 15, 16].

However, local tolerability issues during the first two weeks of treatment might play a role in adherence to treatment; an important issue to consider as this impacts overall treatment effectiveness [17-20]. In clinical practice, regimens of topical retinoids or retinoid-containing agents may be modified during the first weeks of treatment to allow for skin adaptation [21]. Specifically, patients may be advised to apply agents for a shorter duration or at a reduced

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frequency at treatment initiation. Also, moisturizers may be recommended as an adjunctive measure to enhance tolerability [4]. However, the effects of these modified regimens on local tolerability and efficacy have never previously been formally evaluated.
The aim of the present study was to determine whether modified regimens with A/BPO improve local tolerability during the first four weeks of treatment compared with the standard, once-daily, overnight application of A/BPO.

Methods

This multicentre, randomised, single-blinded controlled trial was conducted between April and September 2009 at three investigational sites in Canada. The study was conducted in accordance with local legal requirements, and local ethics committee approval was obtained.
Subjects between 12 and 35 years of age with mild-to-moderate facial *acne vulgaris,* assessed using the Investigator Global Assessment Scale (IGA of 2 or 3 on a scale from 0=clear to 5=very severe) with a minimum of 10 inflammatory lesions, 10 to 100 non-inflammatory lesions, and no more than one nodule or cyst on the face, as well as Phototype of I to IV on the Fitzpatrick scale, were included in the study [22]. Subjects were equally randomised in a 1:1:1:1 ratio to: A/BPO overnight (A/BPO-EN); A/BPO for three hours (A/BPO-3h) followed by a rinse-off using a provided mild cleanser (Cetaphil® cleanser, Galderma, France); A/BPO daily overnight and a provided moisturizer lotion to be applied in the morning (A/BPO-moisturizer [Cetaphil® lotion, Galderma France]); or A/BPO every other night (A/BPO-EoN) during the first four weeks. Except for the subjects randomised to the A/BPO-moisturizer group, none were allowed to use emollients or moisturizers during the first four weeks of the study.
During the subsequent eight weeks, all subjects received A/BPO-EN with provided moisturizer to be used as necessary. The total treatment period was 12 weeks.
Study visits took place at baseline and Weeks 1, 2, 4, 8 and 12. Clinical assessments at these visits included evaluation of the four individual signs and symptoms (dryness, scaling, stinging/burning, and erythema) and each was rated on a scale from 0 (none) to 3 (severe); acne lesion counts and the IGA were assessed at all visits except Visit 1. Other criteria included the percent change in inflammatory, non-inflammatory, and total lesion counts from baseline, overall safety based on reporting of adverse events, and subject satisfaction at Week 4 and Week 12 using a questionnaire.
The primary safety variables (individual signs and symptom scores, rated from 0 to 3), global worst score (GWS, defined as the highest score among the four local tolerability parameters, rated from 0 to 3), total sum score (TSS, defined as the mean sum of all four local tolerability scores, rated from 0 to 12), and patient satisfaction were analysed using the Cochran-Mantel-Haenszel (CMH) test stratified by centre, after Ridit transformation with row mean difference statistics, to test the hypothesis of equality. Each test was two-sided with a significance threshold of 0.050. Due to the small sample size, efficacy parameters were only summarised descriptively.

Results

Demographic and baseline disease characteristics

A total of 123 subjects were included: 32 in the A/BPO-3h group, 29 in the A/BPO moisturizer group, 32 in the A/BPO-EoN group, and 30 in the A/BPO-EN group. Of these, 105 (85.4%) completed the study. Five (one in the A/BPO-moisturizer, one in the A/BPO-EoN, and three in the A/BPO EN group) discontinued due to adverse events. The majority were Caucasian (80.5%) females (71; 57.7%) with Phototype I-III (100; 81.3%) and a mean age of 20.6±6.43 years.
At baseline, all subjects had mild or moderate *acne vulgaris*. In the A/BPO-moisturizer and A/BPO-EN group, more subjects had mild acne (18 [62.1%] and 18 [60.0%], respectively); lesion counts were similar between groups. Detailed demographic and baseline disease characteristics are provided in *table 1*.

Local tolerance

Individual signs and symptoms

A significantly higher percentage of subjects in the A/BPO-moisturizer group than in the A/BPO-EN group demonstrated no worsening of dryness or scaling (64.3% vs. 26.7% for both; $p<0.005$). The mean peak scores at Week 1 were also significantly lower for both dryness (0.36±0.56 vs. 0.82±0.72; $p<0.01$) and scaling (0.39±0.63 vs. 0.89±0.69; $p<0.01$) with A/BPO-moisturizer than with standard A/BPO-EN.
A lower percentage of those with A/BPO-EoN compared to standard regimen demonstrated worsening of stinging/burning with moderate or severe symptoms (12.5% vs. 40.0%; $p<0.05$). Corresponding mean scores at Week 1 were significantly lower with EoN than with standard regimen (0.55±0.51 vs.0.59±0.69; $p<0.041$).
Fewer subjects (15.6%) in the EoN group had a worst score of moderate erythema compared to those on standard regimen (26.7%).
Results for worsening of individual local signs and symptoms during the first four weeks of treatment are provided in *figure 1*.

Global worst score

After four weeks of treatment, the percentage of subjects not experiencing worsening of GWS was 12.9%, 17.9%, 28.1%, and 23.3% in the A/BPO-3h, A/BPO moisturizer, A/BPO-EoN, and A/BPO-EN groups, respectively. Distribution of the GWS was significantly different between the A/BPO-EN and A/BPO-EoN groups; a smaller percentage of subjects in the A/BPO-EoN group had a maximum score corresponding to moderate or severe (21.9% vs. 50.0%; $p=0.039$). Therefore, the A/BPO-EoN group had less worsening of the GWS compared to the A/BPO-EN group. The evolution of GWS over time is provided in *figure 2*.

Total sum score

After four weeks of treatment, the percentages of subjects who did not experience worsening of their TSS was 0%, 17.9%, 9.4%, and 16.7% for the A/BPO-3h,

Table 1. Demographic and baseline characteristics.

	A/BPO-3h (*n*=32)	A/BPO-moisturizer (*n*=29)	A/BPO-EoN (*n*=32)	A/BPO-EN (*n*=30)
Age, years (Mean±SD)	20.2±6.5	20.9±6.83	20.4±6.39	20.8±6.31
Gender, N (%)				
Male	12 (37.5)	13 (44.8)	13 (40.6)	14 (46.7)
Female	20 (62.5)	16 (55.2)	19 (59.4)	16 (53.3)
Phototype, N (%)				
I	2 (6.3)	-	3 (9.4)	3 (10.0)
II	8 (25.0)	12 (41.4)	8 (25.0)	5 (16.7)
III	17 (53.1)	12 (41.4)	13 (40.6)	17 (56.7)
IV	5 (15.6)	5 (17.2)	8 (25.0)	5 (16.7)
IGA				
2: Mild	14 (43.8)	18 (62.1)	17 (53.1)	18 (60.0)
3: Moderate	18 (56.3)	11 (37.9)	15 (46.9)	12 (40.0)
Median lesion counts				
Inflammatory lesions	23.5	19	24.5	21
Non-inflammatory lesions	35	37	34.5	33
Total lesions	62.5	54	60.5	51

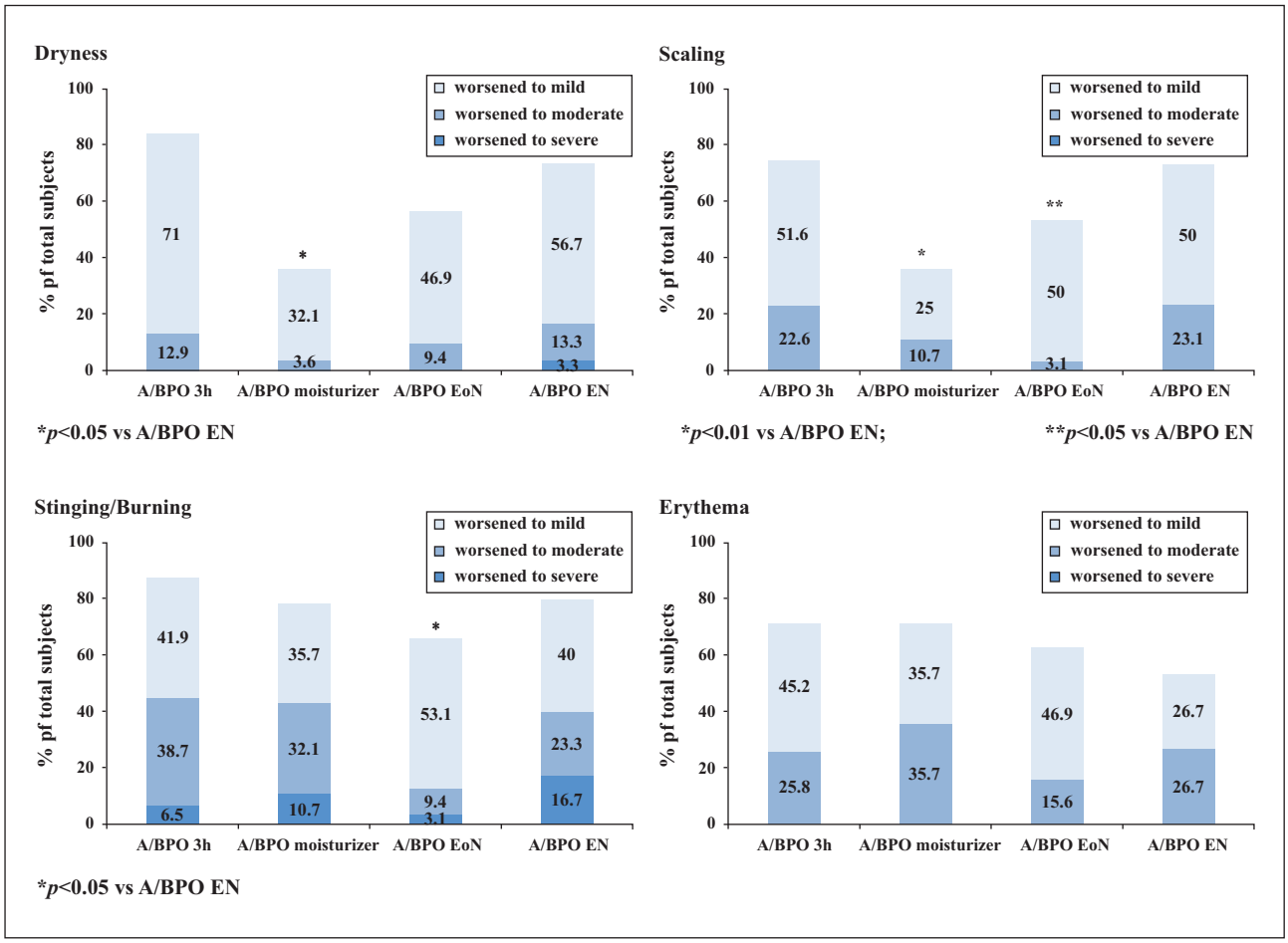

Figure 1. Worsening of local signs and symptoms during the first four weeks of treatment.

A/BPO-moisturizer, A/BPO-EoN, and A/BPO-EN groups, respectively. Significantly more subjects in the A/BPO-3h group experienced less worsening compared with A/BPO-EN (p=0.020). The mean worst score was significantly lower with A/BPO-EoN than with A/BPO-EN (3.06±1.92 vs. 4.13±2.45; p<0.05) and tended to be significant with A/BPO-moisturizer (3.25±2.05). Therefore, both A/BPO-EoN and A/BPO-moisturizer helped to reduce the local tolerability signs and symptoms assessed in the study. The evolution of TSS over time is provided in *figure 3*.

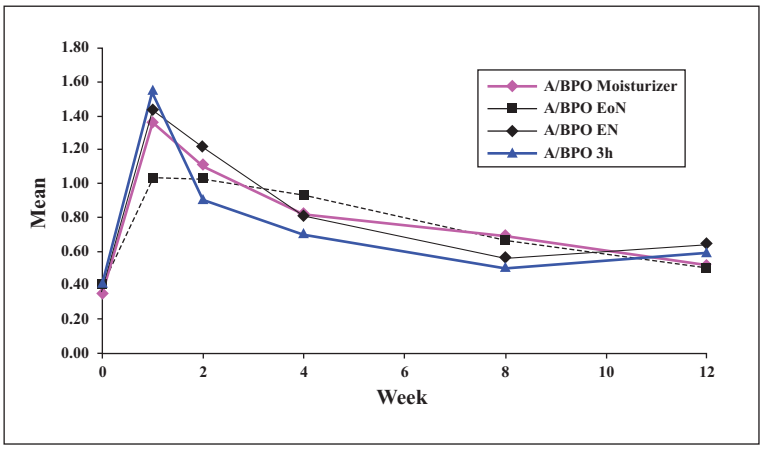

Figure 2. Global worst score.

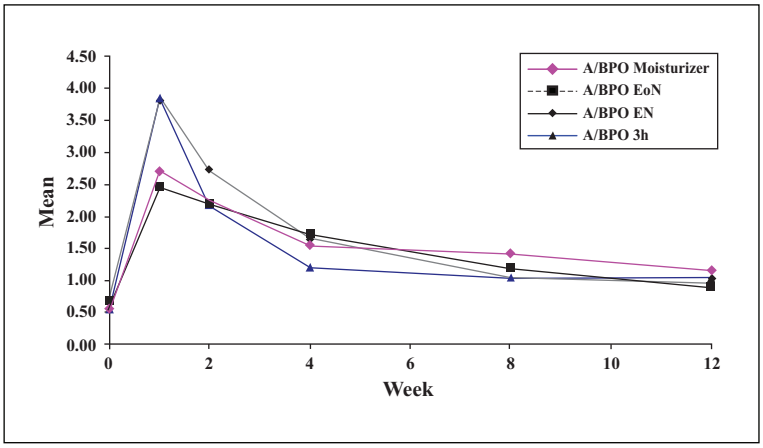

Figure 3. Total sum score.

Overall safety

During the study, 10 subjects reported 12 treatment-related adverse events. Somewhat more related AEs were reported with A/BPO-EN (four subjects and five events) than with A/BPO-3h (two subjects and three events), A/BPO-moisturizer (three subjects and three events), and A/BPO-EoN (one subject and one event). Adverse events leading to study discontinuation were reported in one subject in the A/BPO-moisturizer group (skin burning sensation), one in the A/BPO-EoN group (contact dermatitis), and three subjects in the A/BPO-EN group (contact dermatitis, erythema, and skin irritation). All related AEs were mild or moderate in intensity. No serious AEs were reported.

Efficacy

Lesion count

After the first four weeks of treatment, a similar efficacy in reducing median total lesion counts was observed in all groups (-30%, -34%, -40%, and -38% for A/BPO 3h, A/BPO moisturizer, A/BPO-EoN, and A/BPO-EN, respectively), although a smaller reduction was observed at Week 2 with A/BPO-3h than with A/BPO-EN. At Week 12, a similar reduction in total lesion counts was observed in all groups, with a median change of -64%, -61%, -67%, and -66% reported for A/BPO-3h, A/BPO-moisturizer, A/BPO EoN, and A/BPO-EN, respectively (*figure 4*). The maximum between-group difference (6%) corresponded to four inflammatory lesions (ILs).

The four groups demonstrated similar efficacy with regards to reduction in the number of ILs at Weeks 2 and 4. At Week 12, a median change of -66%, -72%, -61%, and -66% was reported for the IL count with A/BPO-3h, A/BPO-moisturizer, A/BPO-EoN, and A/BPO-EN, respectively, with a maximum between-group difference of 11% corresponding to about three lesions. At Week 4, a slightly lower level of efficacy in reducing non-inflammatory lesions (NILs) was observed in both A/BPO-3h and A/BPO-moisturizer groups than in the A/BPO-EN group. However, similar efficacy was observed for all four groups for the NIL count at Week 12, with a median change of -70%, -62%, -67%, and -67% reported for A/BPO-3h, A/BPO-moisturizer, A/BPO-EoN, and A/BPO-EN. A maximum between-group difference of 8% corresponded to about two NILs.

Investigator global assessment

At Week 4, a slightly lower efficacy in terms of mean IGA score was observed for A/BPO-3h than for A/BPO-EN. However, similar IGA mean scores were observed for all

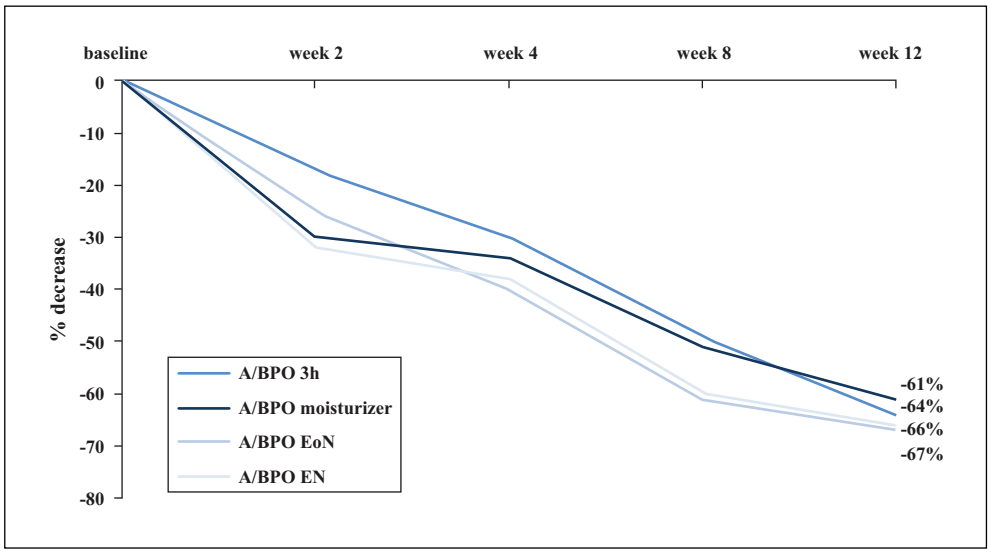

Figure 4. Median percentage change in total lesion counts from baseline.

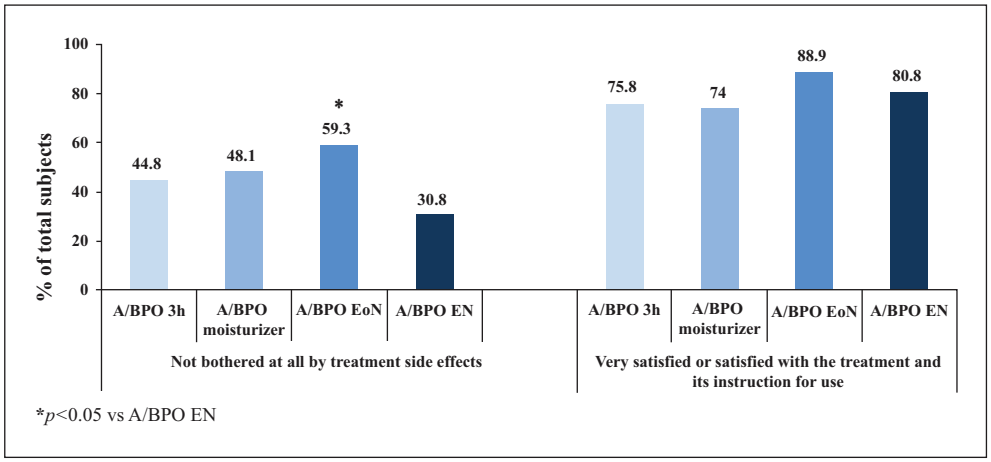

Figure 5. Subject satisfaction at Week 4.
*$p<0.05$ vs A/BPO EN

four groups at Week 12, with scores of 1.7, 1.7, 1.8, and 1.7 reported for A/BPO-3h, A/BPO-moisturizer, A/BPO-EoN, and A/BPO-EN, respectively.

Subject satisfaction

At Week 4, higher percentages of subjects with the three modified A/BPO regimens were "not bothered at all" by the treatment's side effects (44.8%, 48.1%, and 59.3% for A/BPO-3h, A/BPO-moisturizer, and A/BPO-EoN, respectively) compared to A/BPO-EN (30.8%), with a statistically significant difference ($p<0.05$) between A/BPO-EoN and A/BPO EN.

A high percentage of subjects reported to be "very satisfied" or "satisfied" with treatment effectiveness at Week 4. A very high percentage of subjects were "very satisfied" or "satisfied" with the treatment and its instructions for use at both Weeks 4 and 12. A relatively lower percentage of subjects were satisfied with the A/BPO-moisturizer regime at Week 12, compared with the other three groups, while the responses at Week 4 were similarly positive for all four groups.

Detailed results for subject satisfaction at Week 4 are provided in *figure 5*.

Overall, a majority of subjects in each group "would consider using this treatment and its directions for use again" and "would recommend this treatment and its directions for use" to their friends.

Adherence

During the first four weeks of the study, more than 92% of all subjects in each group reported adherence of at least 75% with A/BPO-EN or A/BPO-EoN. Adherence for A/BPO-moisturizer was 96.3% and for A/BPO-3h was 96.7%. During the entire study, at least 90.0% of all subjects in each group reported adherence of at least 75% with their A/BPO regimen.

Discussion

The aim of this study was to compare the local tolerability (dryness, scaling, stinging/burning, and erythema) of three

modified regimens of 0.1%/2.5% A/BPO gel to that of the standard regimen of A/BPO during the first four weeks of treatment.

Results of the efficacy of the regimens show that the A/BPO-moisturizer regimen prevented dryness and scaling, compared with the A/BPO-EN regimen which reduced severity of the stinging/burning and erythema. Overall, A/BPO/EoN led to the lowest GWS, and the mean TSS was furthermore significantly decreased as early as Week 1 ($p<0.05$ for A/BPO-EoN vs. A/BPO-EN). This was also the case for the A/BPO-moisturizer regimen, even though the difference was not statistically significant.

Overall, the four A/BPO regimens led to similar efficacy at Week 12, with a median reduction from baseline of 61 to 67% in total lesion counts, 61 to 72% in inflammatory lesion counts, and 62 to 70% in non-inflammatory lesion counts.

At Week 12, most subjects in all four groups were not bothered by the treatment side effects and were highly satisfied with the treatment effectiveness and its directions for use. A high percentage of subjects reported to be "very satisfied" or "satisfied" with the treatment effectiveness at both Week 4 and Week 12, consistent with the efficacy results assessed by the investigators and the previously-established efficacy of A/BPO (10-14). A slightly lower percentage of subjects was satisfied with the effectiveness of the A/BPO-moisturizer regimen, compared with the other three groups, possibly due to the mandatory usage of the moisturizing lotion, which is not specifically adapted for facial usage. It should also be noted that a lower quantity of A/BPO gel was applied in this group during the study.

All A/BPO regimens were safe and well-tolerated with no specific issue reported for the standard treatment regimen, A/BPO-OD.

Although the efficacy of A/BPO has been demonstrated clinically in several studies, the management of acne patients remains challenging in daily clinical practice. Cutaneous side effects, such as dryness, scaling, stinging/burning, and erythema, have been reported to be associated with A/BPO treatment [10-13, 23-25]. The local irritations that typically occur are usually mild and appear during the first two weeks, with a peak after one week of treatment [26, 27]. As a result, patients may adhere poorly to their treatment, resulting in insufficient treatment, even though events are mainly mild in severity [28]. Kown *et al*. reported in 2015 that tutorials on application methods improve local tolerance issues as well as the final clinical outcome of the condition [29]. Therefore, tutorials may be an alternative. However, such tutorials have already been implemented and in real-life situations, these are not always followed by the patients once they return home.

The present study demonstrates that modifying the standard treatment regimen of a fixed combination of 0.1%/2.5% A/BPO during the first four weeks improves local tolerability, while not impacting the efficacy outcome after the recommended 12-week treatment period, hence supporting an increased treatment adherence from the beginning of the therapy.

These two outcomes are of importance as adapting the treatment regimen to the patient's skin during the first weeks may improve adherence without impacting the efficacy of treatment. Patients prone to dry and scaly skin may thus benefit from a treatment regimen in which A/BPO is combined with a moisturizer lotion which allows for improved easiness-to-spread and occlusive, humectant, and emollient effects. On the other hand, patients suffering from stinging/burning or prone to erythema may benefit from a treatment regimen administered once every other day. Conversely, a short-contact regimen of A/BPO and a cleanser may not be the most suitable regimen as this requires different steps to be followed in the evening, therefore leading to reduced patient adherence and increased local tolerance issues if not followed correctly. Moreover, modulating the topical combination treatment with oral antibiotics, currently suggested for the treatment of severe acne, may increase the chances for the condition to heal [30].

Despite the fact that only three investigators participated in this clinical study, which therefore limited the number of prescribers, the results of this study confirm that modifying treatment regimens of a topical acne treatment during the first four weeks improves local tolerance while not impacting overall efficacy outcome after 12 weeks of treatment. ■

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References

1. Leyden JJ. New understandings of the pathogenesis of acne. *J Acad Am Dermatol* 1995; 32: S15-25.

2. Nast A, Dreno B, Bettoli V, *et al*. European evidence-based (S3) guideline for the treatment of acne - update 2016 - short version. *J Eur Acad Dermatol Venerol* 2016; 30: 1261-8.

3. Zaenglein AL, Pathy AL, Schlosser BJ, *et al*. Guidelines of care for the management of acne vulgaris. *J Acad Am Dermatol* 2016; 74: 945-73.e33.

4. Gollnick H, Cunliffe W, Berson D, *et al*. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *J Acad Am Dermatol* 2003; 49: S1-37.

5. Thiboutot D, Gollnick H, Bettoli V, *et al*. New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne group. *J Acad Am Dermatol* 2009; 60: S1-50.

6. Brogden RN, Goa KE. Adapalene. A review of its pharmacological properties and clinical potential in the management of mild to moderate acne. *Drugs* 1997; 53: 511-9.

7. Michel S, Jomard A, Demarchez M. Pharmacology of adapalene. *Br J Dermatol* 1998; 139: 3-7.

8. Waugh J, Noble S, Scott LJ. Adapalene: a review of its use in the treatment of acne vulgaris. *Drugs* 2004; 64: 1465-78.

9. Leyden JJ. Current issues in antimicrobial therapy for the treatment of acne. *J Eur Acad Dermatol Venerol* 2001; 15: 51-5.

10. Thiboutot DM, Weiss J, Bucko A, *et al*. Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: results of a multicenter, randomized double-blind, controlled study. *J Acad Am Dermatol* 2007; 57: 791-9.

11. Gollnick HP, Draelos Z, Glenn MJ, *et al*. Adapalene-benzoyl peroxide, a unique fixed-dose combination topical gel for the treatment

of acne vulgaris: a transatlantic, randomized, double-blind, controlled study in 1670 patients. *Br J Dermatol* 2009; 161: 1180-9.

12. Tan J, Gollnick HP, Loesche C, Ma YM, Gold LS. Synergistic efficacy of adapalene 0.1%-benzoyl peroxide 2.5% in the treatment of 3855 acne vulgaris patients. *J Dermatol Treat* 2011; 22: 197-205.

13. Gold LS, Tan J, Cruz-Santana A, *et al*. A North American study of adapalene-benzoyl peroxide combination gel in the treatment of acne. *Cutis* 2009; 84: 110-6.

14. Sittart JA, Costa A, Mulinari-Brenner F, Follador I, Azulay-Abulafia L, Castro LC. Multicenter study for efficacy and safety evaluation of a fixeddose combination gel with adapalen 0.1% and benzoyl peroxide 2.5% (Epiduo(R) for the treatment of acne vulgaris in Brazilian population. *An Bras Dermatol* 2015; 90: 1-16.

15. Gollnick HP, Funke G, Kors C, Titzmann T, Jostingmeyer P, Jackel A. Efficacy of adapalene/benzoyl peroxide combination in moderate inflammatory acne and its impact on patient adherence. *J Dtsch Dermatol Ges* 2015; 13: 557-65.

16. Gollnick HP, Friedrich M, Peschen M, *et al*. Effect of adapalene 0.1%/benzoyl peroxide 2.5% topical gel on quality of life and treatment adherence during long-term application in patients with predominantly moderate acne with or without concomitant medication - additional results from the non-interventional cohort study ELANG. *J Eur Acad Dermatol Venereol* 2015; 29: 23-9.

17. Yan AC, Treat JR. Beyond first-line treatment: management strategies for maintaining acne improvement and compliance. *Cutis* 2008; 82: 18-25.

18. Thiboutot D, Zaenglein A, Weiss J, Webster G, Calvarese B, Chen D. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% for the once-daily treatment of moderate to severe acne vulgaris: assessment of efficacy and safety in 2813 patients. *J Acad Am Dermatol* 2008; 59: 792-800.

19. Dreno B, Thiboutot D, Gollnick H, *et al*. Large-scale worldwide observational study of adherence with acne therapy. *Int J Dermatol* 2010; 49: 448-56.

20. Del Rosso JQ. A qualitative and quantitative assessment of the application and use of topical acne medication by patients. *Cutis* 2005; 76: 109-13.

21. Laquieze S, Czernielewski J, Rueda MJ. Beneficial effect of a moisturizing cream as adjunctive treatment to oral isotretinoin or topical tretinoin in the management of acne. *J Drug Dermatol* 2006; 5: 985-90.

22. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. *Arch Dermatol* 1988; 124: 869-71.

23. Andres P, Pernin C, Poncet M. 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. *Cutis* 2008; 81: 278-84.

24. Pariser DM, Westmoreland P, Morris A, Gold MH, Liu Y, Graeber M. Long-term safety and efficacy of a unique fixed-dose combination gel of adapalene 0.1% and benzoyl peroxide 2.5% for the treatment of acne vulgaris. *J Drug Dermatol* 2007; 6: 899-905.

25. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. *Lancet* 2012; 379: 361-72.

26. Troielli PA, Asis B, Bermejo A, Bittar M, Cabrera H, Castro C. Community study of fixed-combination adapalene 0.1% and benzoyl peroxide 2.5% in acne. *Skinmed* 2010; 8: 17-22.

27. Callender VD, Preston N, Osborn C, Johnson L, Gottschalk RW. A meta-analysis to investigate the relation between fitzpatrick skin types and tolerability of adapalene-benzoyl peroxide topical gel in subjects with mild or moderate acne. *J Clin Aesthet Dermatol* 2010; 3: 15-9.

28. Lott R, Taylor SL, O'Neill JL, Krowchuk DP, Feldman SR. Medication adherence among acne patients: a review. *J Cosmet Dermatol* 2010; 9: 160-6.

29. Kwon HH, Park SY, Yoon JY, Min S, Suh DH. Do tutorials on application method enhance adapalene-benzoyl peroxide combination gel tolerability in the treatment of acne? *J Dermatol* 2015; 42: 1058-65.

30. Tan J, Humphrey S, Vender R, *et al*. A treatment for severe nodular acne: a randomized investigator-blinded, controlled, non-inferiority trial comparing fixed-dose adapalene/benzoyl peroxide plus doxycycline vs. oral isotretinoin. *Br J Dermatol* 2014; 171: 1508-16.