POSTER 714

COMPARISON OF A 3-STEP ACNE SYSTEM CONTAINING SOLUBILIZED BENZOYL PEROXIDE VERSUS BENZOYL PEROXIDE/CLINDAMYCIN: A MULTICENTER, INVESTIGATOR-BLIND, RANDOMIZED STUDY

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INTRODUCTION

Benzoyl peroxide (BPO) can be highly effective in the treatment of both comedonal and inflammatory acne.[1] Importantly, it has a key advantage over antibiotics in that it is not associated with the development of bacterial resistance in *Propionibacterium acnes* or other bacteria.[2-4] However, BPO is poorly water soluble and can be difficult to stabilize in vehicles with high water content. This can result in aggregation of crystalline clusters of BPO which can reduce both the bioavailability and the follicular penetration of the BPO.

Previous attempts to enhance the solubility of BPO using different solvents have been hindered by stability challenges.[5] And, in an attempt to circumvent treatment issues resulting from poor solubility, many commercial BPO products are formulated as oil-in-water emulsions. These formulations consist of macrocrystals and microcrystals of various sizes suspended in a water-based emulsion. However, some of these crystals may be too large to penetrate the follicle opening. The mean diameter of a hair follicle on the surface of the forehead has been reported to be 66 µm, with the hair shaft having a mean diameter of approximately 17 µm.[6] In comparison, an evaluation of BPO clusters in a sample of three commercially available BPO formulations revealed their diameters to be 5 to 50 µm, 10 to 100 µm, and 50 to 100 µm, respectively.[7]

The combined effect of the above-mentioned factors—poor BPO water solubility and inaccessible BPO trapped in the interior of clusters in a water-based emulsion vehicle—pose a therapeutic challenge, especially when trying to optimize early efficacy. However, using patented technology, a novel solubilized formulation of BPO has now been developed that is stable. This technology has allowed the production of a uniform homogeneous solution of BPO molecules with a diameter of approximately 0.0001 µm, which facilitates enhanced bioavailability and maximum follicular penetration. Early research has demonstrated that this formulation penetrates the skin more readily than commercial formulations containing BPO and achieves relatively greater bactericidal activity both on the surface of the skin and in follicles.[8] It is possible therefore that it could also enhance the clinical efficacy of BPO. Indeed, early clinical data have shown that a 5% formulation of the solubilized BPO can result in a greater mean reduction in non-inflammatory lesion count in the early weeks of treatment than a combination BPO/antibiotic product.[9] In addition, the solubilized 5% BPO formulation has been shown to result in a comparable reduction in inflammatory lesion count relative to the combination BPO/antibiotic product.[9]

This solubilized 5% BPO formulation is available as part of a 3-step acne system for either normal to oily skin or normal to dry skin. For normal to oily skin, the solubilized 5% BPO is formulated as a gel and is designed to be used in conjunction with a proprietary 2% salicylic acid cleanser and a proprietary 2% salicylic acid toner.[10] We report here the results from a study evaluating this 3-step acne system.

METHODS

Study design

- Multicenter, randomized, investigator-blind study

Inclusion criteria

- Mild to moderate facial acne vulgaris (10-100 non-inflammatory lesions, 17-60 inflammatory lesions, and up to 2 nodulocystic lesions on the face excluding the nose)
- 12-45 years old
- Willingness to refrain from the use of any non-study acne medications, moisturizers, sunscreens, fragrances, aftershaves, and make-up (except oil-free non-comedogenic make-up, mascara, eye shadow, and lipstick were allowed)
- Willingness to avoid tanning booths and excessive exposure to the sun
- In females of childbearing potential, a negative urine pregnancy test and use of an acceptable method of contraception throughout the study

Exclusion criteria

- Current use of other medicated products on the face
- Use of:
  - Medicated facial cleanser in the preceding week
  - Topical alpha-hydroxy acid or anti-acne medication in the preceding 2 weeks
  - Topical retinoid, topical or systemic antibiotic, or topical or systemic steroid in the preceding 4 weeks
  - Estrogen/birth control pills for less than 3 months immediately before the baseline visit
  - Systemic retinoids in the preceding 6 months.
- Participation in an investigational study in the preceding 30 days
- Facial cosmetic procedure (eg, laser resurfacing, chemical peel, or dermabrasion) in the preceding 6 months
- Allergy to benzoyl peroxide, clindamycin, lincomycin, salicylic acid, sunscreens, or substances used in the study
- Uncontrolled systemic disease
- Infection with human immunodeficiency virus
- History of regional enteritis, ulcerative colitis, or antibiotic-associated colitis
- Beard or sideburns that could interfere with study evaluations
- Pregnancy, breastfeeding, or planning a pregnancy during the study

Treatment regimen

- Patients randomly assigned (1:1) to 10 weeks of facial treatment with one of the following:
  - The 3-step acne system for normal to oily skin, i.e.
    - Proprietary 2% salicylic acid cleanser, twice daily
    - Solubilized 5% BPO gel, twice daily
    - Proprietary 2% salicylic acid toner, once daily
  - BPO/clindamycin treatment, i.e.
    - Control cleanser, twice daily
    - 5% BPO/1% clindamycin gel (pump formulation), twice daily.
- All patients were provided with a moisturizer and SPF 35 sunscreen for use on an as needed basis.

Outcome measures

- Non-inflammatory lesion count (open plus closed comedones)
- Inflammatory lesion count (papules plus pustules plus nodules/cysts)
- Erythema, dryness, peeling, burning/stinging, and itching (Table 1), in the overall study population and in the subgroup of patients with Fitzpatrick skin types I or II

Statistical analyses

- Sample size was not based on a power analysis but was expected to be large enough to show a clinical difference between treatments.
- Between-group differences were analyzed using a:
  - 2-sided chi-square test or Fisher's exact test for race and gender
  - 2-sided t-test or Wilcoxon rank-sum test for age and baseline lesion counts
  - Wilcoxon rank-sum test for Fitzpatrick skin type and mean tolerability scores
  - Analysis of covariance or Wilcoxon rank-sum test for percent change from baseline in lesion count.
- A P value of ≤.05 on two-tailed tests was considered statistically significant.

TABLE 1 Scales used to assess tolerability.

Score	Erythema	Dryness	Peeling	Burning/stinging	Itching
0	None – no erythema present (may be minor discoloration)	None – no dryness present	None – no peeling present	None – no burning/stinging	None – no itching
1	Mild – light pink, noticeable	Mild – slight but definite roughness	Mild – slight peeling	Mild – light warm, tingling sensation, not really bothersome	Mild – occasional, slight itching
2	Moderate – pink-red, easily noticeable	Moderate – moderate roughness	Moderate – definitely noticeable peeling	Moderate – definite warmth, tingling/stinging sensation that is somewhat bothersome	Moderate – constant or intermittent itching that is somewhat bothersome
3	Severe – deep or bright red, may be warm to the touch	Severe – marked roughness	Severe – extensive peeling	Severe – hot tingling/stinging sensation which is disturbing normal activity	Severe – bothersome itching which is disturbing normal activity

RESULTS

Patients

- 139 patients enrolled (69 in 3-step acne system group, 70 in BPO/clindamycin group), of whom 128 (92%) completed.
- Primary reason for each of the 11 premature discontinuations:
  - Lack of efficacy (BPO/clindamycin (1))
  - Voluntary withdrawal (BPO/clindamycin (4), 3-step acne system (3))
  - Pregnancy (3-step acne system (1))
  - Other (1 in each group).
- Majority of patients were white (79%), female (64%), and with a Fitzpatrick skin type of II, III, or IV (85%).
- At baseline, patients had a:
  - Mean age of 20 years (range, 12 to 46 years)
  - Mean of 52 non-inflammatory acne lesions
  - Mean of 28 inflammatory acne lesions.
- No significant between-group differences in any of these parameters at baseline.

Efficacy

- The 3-step acne system was associated with numerically greater reductions in non-inflammatory lesion count than BPO/clindamycin from weeks 2 to 6 (Figure 1), a mean of:
  - 27% vs. 13% at week 2
  - 39% vs. 25% at week 4
  - 40% vs. 33% at week 6
  - 42% vs. 42% at week 10.
- However, none of these between-group differences was statistically significant.
- Both regimens were associated with comparable reductions in inflammatory lesion count at all timepoints (Figure 2).
- The early improvement in acne with the 3-step acne system is demonstrated in Figure 3.

Tolerability

- Both treatments were generally well tolerated with mean levels of erythema, dryness, peeling, burning/stinging, and itching less than mild in both groups at all timepoints (Figures 4-7).

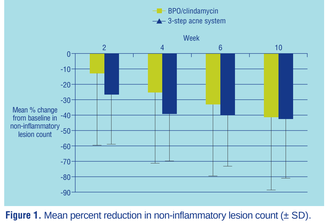

Figure 1. Mean percent reduction in non-inflammatory lesion count (± SD).

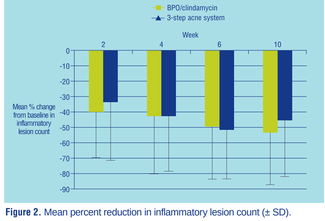

Figure 2. Mean percent reduction in inflammatory lesion count (± SD).

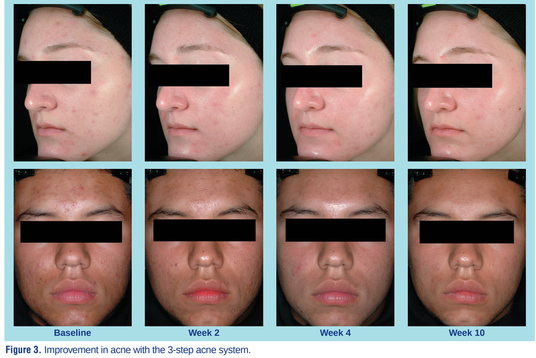

Figure 3. Improvement in acne with the 3-step acne system.

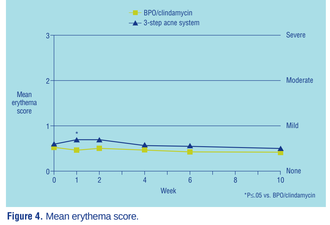

Figure 4. Mean erythema score.

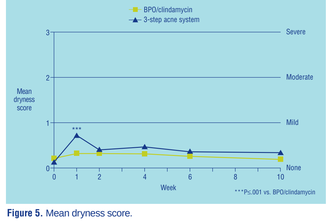

Figure 5. Mean dryness score.

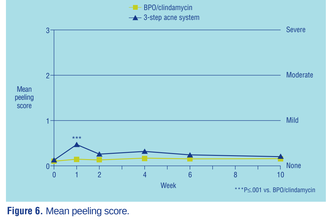

Figure 6. Mean peeling score.

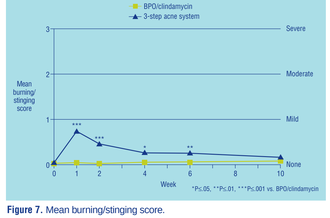

Figure 7. Mean burning/stinging score.

- Mean scores for erythema, dryness, and peeling were comparable between groups at all timepoints except at week 1 when they were transiently significantly higher with the acne system than with BPO/clindamycin (Figures 4-6).
- Mean scores for burning/stinging were significantly higher in the acne system group than in the BPO/clindamycin group at weeks 1, 2, 4, and 6 (Figure 7).
- There were no significant between-group differences in mean scores for itching.
- Among the subgroup of patients with Fitzpatrick skin types I or II (n = 36) the only significant between-group difference in any of the above-mentioned tolerability parameters was for burning/stinging at week 1.

CONCLUSIONS

The 3-step acne system is an effective antibiotic-free approach to the treatment of acne. Compared with a combination BPO/clindamycin product, the acne system is at least as effective in reducing the non-inflammatory lesion count and may enhance the speed at which these lesions are reduced. The acne system also demonstrates comparable efficacy against inflammatory lesions and comparable tolerability. Its potential for a more rapid onset of action against non-inflammatory lesions is likely attributable to the improved solubilization of BPO enhancing the bioavailability and intrafollicular penetration of the BPO. The unique solvent technology employed in the BPO formulation might also play a role in enhancing efficacy in the early weeks of treatment.

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REFERENCES

1. Belknap BS. Treatment of acne with 5% benzoyl peroxide gel or 0.05% retinoic acid cream. *Cutis* 1979;23:856-9.
2. Parry EJ, Griffiths CEM. Bacteria and antimicrobial agents in the treatment of acne. *Int J Derm* 1996;35:249-51.
3. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a global alliance to improve outcomes in acne. *J Am Acad Dermatol* 2003;49(1 Suppl):S1-S37.
4. Leyden JJ, Del Rosso JQ, Webster GF. Clinical considerations in the treatment of acne vulgaris and other inflammatory skin disorders: focus on antibiotic resistance. *Cutis* 2007;79(6 Suppl):9-25.
5. Chellquist EM, Gorman WG. Benzoyl peroxide solubility and stability in hydric solvents. *Pharm Res* 1992;9:1341-6.
6. Otberg N, Richter H, Schaefer H, et al. Variations of hair follicle size and distribution in different body sites. *J Invest Dermatol* 2004;122:14-19.
7. Data on file. Long Beach, CA: OMP, Inc, 2006.
8. Erianne J, Prince DL, Ramirez J, et al. The pharmacologic science of a novel benzoyl peroxide formulation and the implications for clinical effects. Poster presented at the 25th Anniversary Fall Clinical Dermatology® Conference, October 6-9, 2006, Las Vegas, NV.
9. Del Rosso JQ. Evaluation of a solubilized benzoyl peroxide gel: a pooled analysis from 3 randomized investigator-blinded trials. *Cos Derm* 2008;21:201-6.
10. CLENZIderm MD™ – Product Detail. OMP, Inc. web site. http://www.obagi.com/article/forpatients/obagiclenzidermmd/products/products.html. Accessed November 20, 2008.

DISCLOSURES

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