Randomized, Phase 2, Dose-Ranging Study in the Treatment of Rosacea With Encapsulated Benzoyl Peroxide Gel

James J. Leyden MD
University of Pennsylvania, Philadelphia, PA

ABSTRACT

Objective: Compare the safety and efficacy of 1% and 5% silica encapsulated benzoyl peroxide (E-BPO) in patients with papulopustular rosacea.
Design: Multi-centered randomized, double blind, vehicle controlled parallel group, 12 week treatment in 92 patients with papulopustular rosacea. Primary endpoints were dichotomized IGA with success defined as clear/near clear and reduction in inflammatory lesions.
Patients: 92 patients: 74% graded as moderate IGA, 14% severe and 12% mild. The mean inflammatory lesion count was 24.
Intervention: Once daily treatment for 12 weeks with vehicle, 1% or 5% E-BPO.
Results: 1% and 5% E-BPO were superior to vehicle in reducing papulopustular lesions P=0.01 and P=0.02. 5% E-BPO was superior to vehicle for IGA P=0.0013.

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INTRODUCTION

A subset of patients with rosacea developed papules and pustules (PPR), which are currently viewed to be inflammatory follicular lesions.[1,2] While recent studies employing gene array profiles, immunohistochemical and molecular techniques have helped define various pathways of inflammation, the stimulus or trigger for follicular inflammation remains uncertain.[3,4,5] The mite Demodex Folliculorum remains a most prominent direct or indirect suspect.[6,14] Current FDA approved therapies include topical metronidazole, azelaic acid and systemic low dose doxycycline all of which are viewed to act as anti-inflammatory agents.[7,8,9] Two studies have shown the combination of benzoyl peroxide and clindamycin to be effective in PPR with the combination more effective than clindamycin but not more effective than benzoyl peroxide. In both studies there were patients who experienced difficulty tolerating benzoyl peroxide. Despite a paucity of studies, clindamycin is widely believed to have in vivo anti-inflammatory activity in acne and rosacea. Only one uncontrolled study was published in which clindamycin was used as a mono therapy. As a result, the individual contribution of benzoyl peroxide or clindamycin to the substantial benefit reported from the combination of these two agents in PPR[10,11] is not clear.

METHODS

This study was conducted in compliance with Food and Drug Administration (FDA) regulations, the ethical principles of the Declaration of Helsinki, and the current International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines.

Patients: 92 patients with PPR were enrolled (Table1). While a minimum of 12 inflammatory lesions were required for entry into the study, the majority of patients had a moderate IGA (74%) and 14% had a severe IGA The median number of inflammatory lesions for each group was similar. Vehicle 19.9%; 1% E-BPO, 28.6%; 5% E-BPO, 22.9%

Patients were treated once daily for 12 weeks with either vehicle, 1% or 5% E-BPO.

Patients were evaluated at base line and after 4, 8, and 12 weeks of therapy for lesion counts and IGA. Signs of irritation were evaluated at the latter time points and after 2 weeks cessation of treatment.

Primary efficacy endpoints were:

- Proportion of subjects with the primary measure of success; defined as a 2-grade improvement in the IGA relative to baseline at week 12, with the week 12 IGA of clear or almost clear.
- Change in inflammatory lesion count at week 12

Secondary efficacy endpoints were:

- Proportion of subjects with a measure of success; defined as a 2-grade improvement in the IGA relative to baseline at week 12.
- IGA at week 12.
  - Inflammatory lesion erythema assessment at week 12
  - Rosacea erythema assessment at week 12
  - Telangiectasia assessment at week 12

In this trial we studied the efficacy and safety of encapsulated BPO in patients with PPR. Using a unique process, benzoyl peroxide[12] is encapsulated in porous silicon dioxide (silica)

TABLE 1.

Summary of Subject Demographic Characteristics (ITT Population)				
	Vehicle Gel (N=30)	1% E-BPO Gel (N=32)	5% E-BPO Gel (N=30)	Total (N=92)
Age (years)				
Mean	50.5	51.0	52.2	51.2
SD	12.56	13.50	12.66	12.80
Median	50.5	51.5	52.0	51.0
Min. to Max.	28 to 74	25 to 78	23 to 82	23 to 82
Gender				
Male	8(26.7%)	10 (31.3%)	7 23.3%)	25 (27.2%)
Female	22 (73.3%)	22 (68.8%)	23 (76.7%)	67 (72.8%)
Ethnicity				
Hispanic/Latino	6 (20.0%)	5 (15.6%)	5 (16.7%)	16 (17.4%)
Not Hispanic/Latino	24 (80.0%)	27 (84.4%)	25 (83.3%)	76 (82.6%)
Race				
White	30 (100.0%)	30 (93.8%)	30 (100.0%)	90 (97.8%)
Black/A.American	0 (0.0%)	1 (3.1%)	0 (0.0%)	1 (1.1%)
Multiple/Other[a]	0 (0.0%)	1 (3.1%)	0 (0.0%)	1 (1.1%)

[a]Other: Biracial-Black/White
A. American=African American

TABLE 2.

Summary of Primary Efficacy Endpoints (ITT Subjects)			
	Vehicle Gel (N=30)	1% E-BPO Gel (N=32)	5% E-BPO Gel (N=30)
Week 12			
Dichotomized IGA – Primary Success			
Failure	24 (80.0%)	20 (62.5%)	14 (46.7%)
Success	6 (20.0%)	12 (37.5%)	16 (53.3%)
Inflammatory Lesion Count - Change from Baseline			
Mean	-7.4	-21.6	-14.1
SD	17.24	23.31	8.78
Median	-10.0	-12.5	-15.0
Min. to Max.	-45 to 67	-94 to -5	-34 to 5
LS Mean[a]	-8.8	-21.5	-14.7
LS SE[a]	3.16	3.04	3.15
95% CI for LS Mean[a]	[-15.1, -2.5]	[-27.5, -15.4]	[-21.0, -8.4]

[a]Obtained from an ANCOVA with factors of treatment, analysis center, and Baseline IGA.
Primary success: 2-grade improvement from Baseline in the IGA, with visit IGA of clear or almost clear.
LOCF used to impute mission observations.

microcapsules. The microcapsules create an imperceptible barrier between the active ingredient and the skin. This technology was previously demonstrated to improve tolerance and efficacy in acne patients.[13]

STATISTICS

Statistical processing for the intent to treat population was performed using SAS®, Version 9.2, or later. Descriptive statistics included the number of subjects (N), mean, median, standard deviation (SD), minimum (Min), and maximum (Max) for continuous variables and frequency counts, and percentages for categorical variables. The statistical significance for the proportion of subjects with the primary measure of success were derived from a model with factors of treatment, analysis center, and baseline IGA using SAS PROC GENMOD with binomial distribution, logit link, and likelihood ratio test. An analysis of covariance with factors of treatment, analysis center, and baseline IGA or baseline inflammatory lesion count using SAS PROC GLM provided the *P*-values for the percent change in inflammatory lesion count when baseline IGA or inflammatory lesion count was the covariate, respectively.

RESULTS

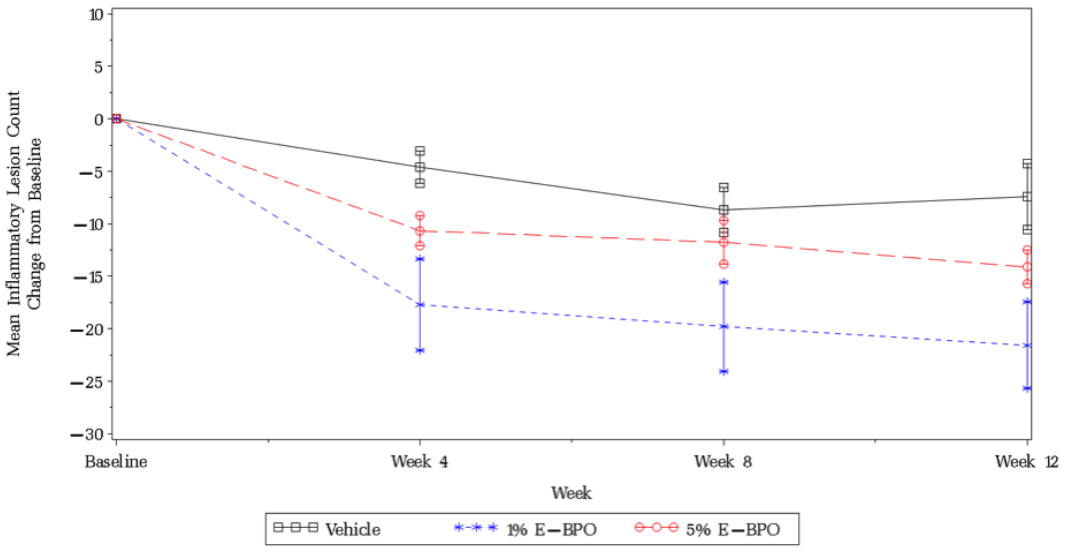
Primary efficacy end points are summarized in Table 2 and *P*-values are summarized in Table 3. Both E-BPO formulations significantly reduced inflammatory lesions (Figure 1). There was a median reduction of 10 lesions in the vehicle group compared to 12.5 for 1% E-BPO and 15 for the 5% E-BPO formulation. 5% E-BPO was significantly superior to vehicle for IGA and showed a trend for superiority for the 1% formulation.

TABLE 3.

P-values				
P-values		*P*-values		
Variable at Week 12	Covariate	1% E-BPO vs. Vehicle	5% E-BPO vs. Vehicle	1% E-BPO vs. 5% E-BPO
Dichotomized IGA[a]	Baseline IGA	0.0836[b]	0.0013[b]	0.1606[b]
Percent change in inflammatory lesion count	Baseline IGA	0.0123[c]	0.0202[c]	
	Baseline inflammatory lesion count	0.0140[d]	0.0200[d]	0.7609[d]

[a] Primary Success: 2-grade improvement from Baseline in the IGA, with visit IGA of clear or almost clear.
[b] *P*-value from model with factors of treatment, analysis center, and baseline IGA using PROC GENMOD with binomial distribution, logit link, and likelihood ratio test.
[c] *P*-value from ANCOVA with factors of treatment, analysis center, and baseline IGA using PROC GLM.
[d] *P*-value from ANCOVA with factors of treatment, analysis center, and baseline inflammatory lesion count using PROC GLM.
Last observation carried forward used to impute missing observations

FIGURE 1. Mean inflammatory lesion count change from baseline (ITT population).



Mean +/- Standard Error is presented in the figure.
Last observation carried forward (LOCF) used to impute missing observations.

Secondary end points are summarized in Table 4. The percent of patients with a 2-grade improvement in IGA was 23.3% for vehicle-treated patients compared to 37.5%, and 56.7 % for the 1% and 5% active groups, respectively. No changes in persistent erythema or telangiectasias were found. Perilesional erythema was decreased with the decrease in lesions.

"Despite a paucity of studies, clindamycin is widely believed to have in vivo anti-inflammatory activity in acne and rosacea."

All three formulations were well tolerated. Few subjects had moderate local application site irritation (dryness, scaling, pruritus, stinging, and burning) post-baseline. No subjects had severe dryness, scaling, or pruritus post-baseline. No subjects who applied Vehicle Gel or 1% E-BPO Gel had severe stinging or burning post-baseline. One subject who applied 5% E-BPO Gel had severe stinging and burning that was reported as an AE.

DISCUSSION

In this study, we found E-BPO to be effective in reducing the number of inflammatory lesion in patients with PPR. There was a clear trend of a dose response with the IGA success of 20% for the vehicle and 37% and 53% for the 1% and the 5% formulations, respectively. The reduction in inflammatory lesions also showed a trend towards a dose response. Since benzoyl peroxide has no known anti-inflammatory properties but is a potent antimicrobial agent, these results suggest a microbial factor as the stimulus or trigger for the follicular inflammation of PPR. Benzoyl peroxide is a difficult agent to do M.I.C. determinations because of its poor solubility in aqueous systems and no studies exist regarding the susceptibility of Demodex Folliculorum to this drug. The other follicular organism, Propionibacterium

TABLE 4.

Summary of Secondary Efficacy Endpoints (ITT Subjects)			
	Vehicle Gel (N=30)	1% E-BPO Gel (N=32)	5% E-BPO Gel (N=30)
Week 12– Dichotomized IGA Secondary Success			
Failure	23 (76.7%)	20 (62.5%)	13 (43.3%)
Success	7 (23.3%)	12 (37.5%)	17 (56.7%)
IGA			
0 Clear	2 (6.7%)	2 (6.3%)	4 (13.3%)
1 Almost Clear	5 (16.7%)	11 (34.4%)	14 (46.7%)
2 Mild	10 (33.3%)	8 (25.0%)	6 (20.0%)
3 Moderate	12 (40.0%)	10 (31.3%)	5 (16.7%)
4 Severe	1 (3.3%)	1 (3.1%)	1 (3.3%)
Mean	2.2	1.9	1.5
SD	0.99	1.03	1.04
Median	2.0	2.0	1.0
Min. to Max.	0 to 4	0 to 4	0 to 4
Change from Baseline			
Mean	-0.8	-1.2	-1.5
SD	1.00	1.14	1.01
Median	-1.0	-1.0	-2.0
Min. to Max.	-3 to 1	-4 to 1	-3 to 0
Inflammatory Lesion Erythema			
0 None	3 (10.0%)	6 (18.8%)	11 (36.7%)
1 Mild	13 (43.3%)	16 (50.0%)	12 (40.0%)
2 Moderate	13 (43.3%)	8 (25.0%)	5 (16.7%)
3 Severe	1 (3.3%)	2 (6.3%)	2 (6.7%)
Mean	1.4	1.2	0.9
SD	0.72	0.82	0.91
Median	1.0	1.0	1.0
Min. to Max.	0 to 3	0 to 3	0 to 3
Change from Baseline			
Mean	-0.6	-1.0	-1.1
SD	0.63	0.86	0.88
Median	-0.5	-1.0	-1.0
Min. to Max.	-2 to 0	-3 to 1	-2 to 1

Secondary success: 2-grade improvement from Baseline in the IGA.
LOCF used to impute mission observations.

acnes has not been associated with PPR but in view of the effectiveness of benzoyl peroxide this deserves study.

Patients tolerated the E-BPO formulations extremely well, which is striking in view of the increased sensitivity of facial skin of rosacea patients. Encapsulation of benzoyl peroxide clearly protected the epidermis from the potential irritant effects.

In summary, we found 1% and 5% benzoyl peroxide encapsulated in silica microcapsules, to be highly effective and well tolerated in PPR. These results need to be replicated in larger clinical trials to further confirm the safety and efficacy findings.

DISCLOSURES

The author has not disclosed any relevant conflicts.

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AUTHOR CORRESPONDENCE

James J. Leyden MD
E-mail:..... jjleyden@mindspring.com