ORIGINAL RESEARCH ARTICLE

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A Multicentre, Double-Blind, Parallel-Group Study to Evaluate 3% Erythromycin/5% Benzoyl Peroxide Dual-Pouch Pack for Acne Vulgaris

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Abstract

Objective: The combination of erythromycin and benzoyl peroxide has proven to be a well-tolerated and effective topical treatment for acne vulgaris. A novel 3% erythromycin/5% benzoyl peroxide formulation provides a single unit-dose of erythromycin and benzoyl peroxide from a dual-pouch package and eliminates the need for pharmacist compounding and refrigeration. This study assessed the tolerability and efficacy of this formulation in patients with acne vulgaris.

Design and patients: Multicentre, randomised study in 223 patients with moderate to moderately severe acne who received 3% erythromycin/5% benzoyl peroxide via the dual-pouch package or matching vehicle control for 8 weeks.

Results: Active treatment was significantly more effective than vehicle control in reducing total number of acne lesions (31.9 and 23.1, respectively; $p = 0.004$) and the percentage reduction of inflammatory acne lesions (69.2 and 48.1%, respectively; $p = 0.001$) from baseline to week 8. Statistical significance for these parameters was observed within 2 weeks and continued to study endpoint. At week 8, treatment success was demonstrated in a significantly greater proportion of patients in the active treatment group (34.8%) compared with the vehicle control group (14.4%; $p < 0.001$). No treatment-related serious adverse events were reported. The most common adverse event was dry skin, which occurred in 12.5 and 5.4% of patients administered active treatment or vehicle, respectively.

Conclusion: This novel formulation was demonstrated to be well tolerated and effective in the treatment of acne vulgaris. The 3% erythromycin/5% benzoyl peroxide dual-pouch pack is an alternative to the currently marketed topical gel for patients with moderate to moderately severe acne vulgaris. This combination antimicrobial product provides an innovative unit-dose delivery system and offers the consumer more convenience by eliminating the need for pharmacist compounding and refrigeration.

Acne vulgaris is a disease of the sebaceous follicles, primarily occurring on the face, chest, and back.[1] It has been estimated that acne vulgaris affects between 40 and 50 million individuals in the United States.[2,3] Acne generally begins in adolescence but is not limited to young adults; approximately 85% of all adolescents aged 12 to 24 years experience some degree of acne.[1,4] The disease is not life-threatening, although young adults and adolescents may experience severe psychosocial effects, often deeper and more disastrous than the blemishes on the cutaneous surface.[5,6] Lasek and Chren reported that acne vulgaris causes emotional effects similar to those of psoriasis and adversely affects the overall quality of life in these patients.[7]

The basic cause of acne remains unknown, although the interaction of four factors has been implicated in its pathophysiology. These include increased sebum production, abnormal keratinisation processes, proliferation of *Propionibacterium acnes*, and inflammation caused by sebum and chemotactic factors generated by *P. acnes*.[1,5] Acne may initially develop as non-inflammatory lesions in pilosebaceous follicles. When the follicle wall is disrupted, inflammatory lesions develop, including papules, pustules, nodules and cysts. The first step in lesion management is to correctly classify acne severity, since therapy must be individualised to the fluctuating severity of this disorder.[1,5] While severe acne may require isotretinoin therapy, mild to moderately severe inflammatory acne may be treated by topical agents. Topical agents include antibiotics, such as erythromycin or clindamycin, benzoyl peroxide, and various forms of retinoids.[1,6] Synergistic combinations, including retinoids/antimicrobials or erythromycin/benzoyl peroxide, may also be used.[1]

The tolerability and efficacy of combination erythromycin/benzoyl peroxide have been established for a number of years.[8-10] In 1983, Chalker and colleagues compared the tolerability and efficacy of combination 3% erythromycin and 5% benzoyl peroxide with that of 3% erythromycin gel, 5% benzoyl peroxide gel and vehicle during a 10-week study involving 165 patients. The investigators found the combination product was more effective for pustular and papular lesions than any of the other treatments. The most dramatic effect was observed with combined inflammatory lesions (papules and pustules).[8] This earlier formulation requires pharmacist compounding and refrigeration to maintain stability, which may be inconvenient for the patient. Therefore, a modification of the original formulation and packaging has been developed. This novel formulation contains 6% erythromycin gel and 10% benzoyl peroxide gel, each individually packaged in a dual-pouch unit-dose pack. When the entire contents of this dual-pouch pack are mixed in the patient's palm after extrusion, a single dose of 3% erythromycin and 5% benzoyl peroxide is formed. This novel dual-pouch pack does not require compounding by the pharmacist or refrigeration and has the added benefit of convenient, unit-dose packaging. This current study compared the efficacy and tolerability of 3% erythromycin/5% benzoyl peroxide dual-pouch pack (EBP) [Dermik Laboratories, Berwyn, PA] with its matching vehicle control (VC) for the treatment of acne vulgaris.

Patients and Methods

Study Design and Treatment

This multicentre, randomised, double-blind, parallel-group study enrolled 223 patients with moderate to moderately severe acne vulgaris at four study centres. During this 8-week trial, 112 patients were randomised to receive EBP and 111 patients were randomised to matching VC. Patients were randomised to treatment regimens in a ratio of 1 : 1. After washing the face, patients were instructed to apply the entire contents of 1 unit in a thin layer to the entire face twice daily (morning and evening). Patients were taught to squeeze the entire contents of the package into the palm of the hand and blend together for approximately 5 seconds prior to application. The first application was performed under direct supervision at the study site.

Baseline evaluations included a Physician's Global Acne Severity Score, comedo counts, papule/pustule counts, cyst counts and oiliness scores. At each follow-up visit, scheduled at 2, 4, 6 and 8 weeks, facial lesions were counted and the Physician's Global Acne Severity Score was obtained to determine comparative efficacy. The Physician's Global Acne Severity Score, the physician's comprehensive evaluation of the patient's overall acne condition at the time of evaluation, was based on number of lesions and overall acne condition, including lesion size, overall degree of inflammation, general facial erythema, and skin condition. Patients scored a 0 (clear; no inflammatory lesions), 1 (comedones, some small inflammatory lesions, minimal erythema), 2 (comedones, moderate number of small inflammatory lesions, erythema increasing), 3 (numerous comedones, papules, and pustules with larger inflamed lesions, erythema pronounced), or 4 (severe or cystic acne; excluded from study) based on acne severity. Oiliness was ranked as 0 (none), 1 (mild; limited area), 2 (moderate; entire face), or 3 (severe; requiring removal more than once per day). At study conclusion, the Patient's Global Improvement Score allowed patients to rank their overall improvement as 3 (much better), 2 (better), 1 (somewhat better), 0 (no change) or worse. Patients also rated treatment acceptability at the final study visit. The determination of relative efficacy was based on the summaries of the results of the last week (week 8).

Unused medication was retrieved at each visit, and a study drug supply sufficient to last until the patient's next visit was dispensed. Compliance was assessed by counting the number of unused units of study medication returned by the patients and recording missed doses.

This study was performed in accordance with the principles stated in the Declaration of Helsinki and with all Food and Drug Administration regulations. Local institutional review boards approved the study protocol and all patients provided written informed consent prior to study enrolment.

Study Participants

Male and female patients aged ≥13 years with moderate to moderately severe acne were eligible for study enrolment. Eligible patients had an overall acne severity score ≥1.5 on the Physician's Global Acne Severity Scale, 15 to 80 inflammatory lesions, 20 to 140 comedones, and ≤2 nodules or cysts measuring greater than 5mm. The comedo count did not include the nasal and nasolabial fold area. Discontinuation of treatment with systemic antibiotics known to affect acne and systemic corticosteroids 4 weeks prior to study enrolment was required, as was discontinuation of oral retinoids 6 months prior to enrolment. A 2-week washout period was required for topical antibiotics and/or anti-acne medication, topical corticosteroids, and topical retinoids. Patients were excluded if they were either pregnant or nursing, had beards or long sideburns, had cystic acne, or had any other diseases affecting their condition or interfering with treatment evaluation.

Efficacy and Tolerability Evaluations

The primary efficacy evaluations were lesion reductions from baseline and treatment success. Lesion reductions from baseline included inflammatory lesions, comedones and total lesions (inflammatory and comedones). Patients who achieved treatment success were defined as those patients with a score of 0 or 0.5 on the Physician's Global Acne Severity Scale at the end of the study. Secondary efficacy evaluations included Physician's Global Acne Severity Scores, facial oiliness scores, Patient Global Improvement Scores, and patient treatment acceptability. Tolerability evaluations were based on the incidence and severity of adverse events. Adverse events of all types, including those possibly related to treatment and those affecting the skin, were summarised by treatment group. The intent-to-treat population included all patients randomised to active treatment or VC.

Statistical Analysis

Lesion reduction counts and global acne severity scores were fit by analysis of co-variance models, with treatment group and site factors and a baseline co-variate. A term for the treatment by investigator interaction was included in the model if a preliminary evaluation found $p < 0.10$ for the interaction effect. The proportion of patients in each treatment group with successful treatment outcome and proportions indicating treatment acceptability were compared between treatments based on the Cochran-Mantel-Haenszel (CMH) test stratified by study site. The analysis of variance (ANOVA) model for patient evaluations of global improvement included effects of investigator and study site and, if a preliminary evaluation found $p < 0.10$, the site by investigator interaction. Facial oiliness scores were also compared between treatments based on the CMH test stratified by study site. The percentage reductions from baseline were evaluated within each treatment group using the Wilcoxon test. Patient demographics and baseline acne severity measures were compared between treatment groups and among study sites using ANOVA and CMH tests. A p-value <0.05 was considered statistically significant.

Results

Patient Characteristics

Demographic patient characteristics at baseline are summarised in table I. Some 49.8% of patients in the intent-to-treat population were female, and the average age was 18.5 years. The average duration of acne was 4.8 years, and 74% had used a previous acne treatment. There were no significant differences in patient characteristics between the EBP and VC groups; however, there was a relatively higher ratio of white to black patients (8:1) in the EBP group compared with the vehicle group (5:1). No differences were observed between the EBP and VC groups with regard to baseline global severity, lesion counts or oiliness score frequencies (table II).

Efficacy

At endpoint, intent-to-treat patients in the EBP group experienced significantly greater total lesion reductions from baseline ($p = 0.004$), significantly greater inflammatory lesion reductions from base-

Table I. Demographic and patient characteristics in the intent-to-treat population

Characteristic	EBP (n = 112)	VC (n = 111)	All patients (n = 223)
Age [y (mean ± SD)]	18.7 ± 6.2	18.2 ± 5.4	18.5 ± 5.8
Gender [n (%) of patients]			
Female	57 (50.9)	54 (48.6)	111 (49.8)
Male	55 (49.1)	57 (51.4)	112 (50.2)
Race [n (%) of patients]			
White	94 (83.9)	82 (73.9)	176 (78.9)
Black	12 (10.7)	18 (16.2)	30 (13.5)
Asian	3 (2.7)	1 (0.9)	4 (1.8)
Hispanic	3 (2.7)	10 (9.0)	13 (5.8)
Complexion [n (%) of patients]			
Fair	51 (45.5)	50 (45.0)	101 (45.3)
Medium	44 (39.3)	38 (34.2)	82 (36.8)
Dark	17 (15.2)	23 (20.7)	40 (17.9)
Acne duration [y (mean ± SD)]	4.9 ± 4.8	4.6 ± 4.6	4.8 ± 4.7
Previous therapy [n (%) of patients]			
Yes	87 (77.7)	78 (70.3)	165 (74.0)
No	25 (22.3)	33 (29.7)	58 (26.0)

EBP = 3% erythromycin/5% benzoyl peroxide dual-pouch pack; **SD** = standard deviation; **VC** = vehicle control.

Table II. Mean baseline acne characteristics and efficacy variables in the intent-to-treat population

	EBP (n = 112)	VC (n = 111)
Primary variables (mean ± SD)		
Total lesion count	72.4 ± 31.0	71.5 ± 25.5
Inflammatory lesion count	31.1 ± 15.7	29.3 ± 11.7
Comedo count	41.3 ± 26.0	42.2 ± 21.4
Secondary variables (mean ± SD)		
Physician's Global Acne Severity Score[a]	2.1 ± 0.5	2.1 ± 0.5
Facial oiliness score[b]	1.6 ± 0.6	1.7 ± 0.7

a 0 = clear; 1 = comedones, small inflammatory lesions, minimal erythema; 2 = comedones, moderate number of small inflammatory lesions, increasing erythema; 3 = numerous comedones, larger inflamed lesions, pronounced erythema; 4 = severe/cystic acne.

b 0 = none; 1 = mild; 2 = moderate; 3 = severe.

EBP = 3% erythromycin/5% benzoyl peroxide dual-pouch pack; **SD** = standard deviation; **VC** = vehicle control.

Table III. Efficacy evaluations at week 8 (last week of study) in the intent-to-treat population

	EBP (n = 112)	VC (n = 111)	p-Value[a]
Least squares mean reduction from baseline in			
Total lesions	31.9	23.1	0.004
Inflammatory lesions	16.5	9.6	<0.001
Comedones	15.2	13.3	0.347
Treatment success (% of patients)[b]	34.8	14.4	<0.001
Mean Physician's Global Acne Severity Score[c]	1.2	1.6	<0.001
Mean facial oiliness[d]	0.7	0.8	0.026
Patient-rated			
Improvement (mean)[e]	2.0	1.6	0.001
Acceptability (% of patients)	88.2	72.5	0.004

a Treatment contrasts using analysis of variance and Cochran-Mantel-Haenszel analyses.

b Defined as patient at endpoint with Physician's Global Acne Severity Score of 0 (clear) or 0.5 (sparse comedones with very few or no inflammatory lesions present).

c 0 = clear; 1 = comedones, small inflammatory lesions, minimal erythema; 2 = comedones, moderate number of small inflammatory lesions, increasing erythema; 3 = numerous comedones, larger inflamed lesions, pronounced erythema; 4 = severe/cystic acne.

d 0 = none; 1 = mild; 2 = moderate; 3 = severe.

e −1 = worse; 0 = no change; 1 = somewhat better; 2 = better; 3 = much better.

EBP = 3% erythromycin/5% benzoyl peroxide dual-pouch pack; **VC** = vehicle control.

line ($p < 0.001$), and demonstrated a significantly greater proportion of treatment success than patients using VC ($p < 0.001$) [table III]. Patients using EBP experienced significantly greater reductions in inflammatory lesions from baseline at weeks 2, 4, 6 and 8 ($p \leq 0.002$) [figure 1]. At week 8, patients in the EBP and VC groups experienced a 69.2 and 48.1% reduction in inflammatory lesion counts from baseline, respectively. Treatment success, defined by Physician's Global Acne Severity Scores of 0 or 0.5, was significantly higher by week 4 in the EBP group compared with the VC group and continued through the duration of the study ($p \leq 0.02$) [figure 2]. Comedo reductions from baseline were not significantly different between groups, although a more favourable trend in comedo reduction was observed in patients treated with EBP compared with VC.

At the end of the study, results of the secondary variables, including the Physician's Global Acne Severity Score, facial oiliness and patient-rated global improvement, all reflected the greater efficacy of EBP over VC (table III). The Physician's Global Acne Severity Scores were significantly

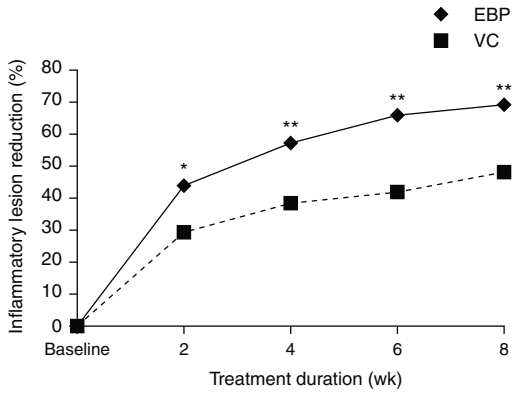

Fig. 1. Percentage of inflammatory lesion reduction from baseline by treatment week.
* p = 0.002 *vs* vehicle control, ** p < 0.001 *vs* vehicle control.
EBP = 3% erythromycin/5% benzoyl peroxide dual-pouch pack; **VC** = vehicle control.

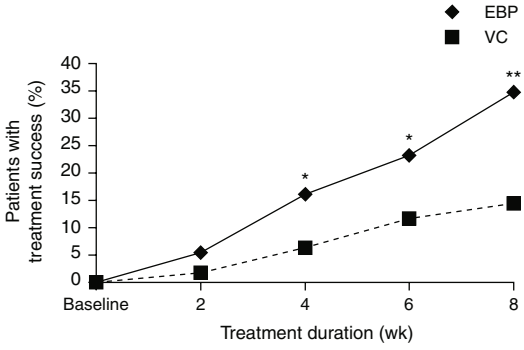

Fig. 2. Percentage of acne patients (intent-to-treat population) with treatment success (score of 0 or 0.5 on the Physician's Global Acne Severity Scale).
* p ≤ 0.021 *vs* vehicle control (based on Cochran-Mantel-Haenszel, stratified by site), ** p < 0.001 *vs* vehicle control (based on Cochran-Mantel-Haenszel, stratified by site).
EBP = 3% erythromycin/5% benzoyl peroxide dual-pouch pack; **VC** = vehicle control.

lower in the EBP group compared with the VC group at weeks 2, 4, 6 and 8 (all p ≤ 0.001). Facial oiliness scores were also significantly lower in the EBP group versus the VC group at week 2 (p = 0.005), week 4 (p = 0.014), and week 8 (p = 0.026). At the conclusion of the study, 71% of those using EBP and 56% of those using VC rated global improvement better or much better. The active treatment was associated with significantly greater treatment acceptability compared with the VC (p = 0.006).

Tolerability

No treatment-related serious adverse events were reported during the study. One patient in the VC group discontinued the study prematurely because of dryness and itching experienced during the first 2 weeks of treatment. Nineteen patients in the EBP group and 10 patients in the VC group reported at least one treatment-related adverse event. The most frequent adverse event was dry skin, reported in 14 (12.5%) patients receiving EBP and six (5.4%) patients using VC. Other treatment-related adverse events included application site reactions (3.6 and 1.8% of EBP and VC recipients, respectively) and pruritus (0.9 and 1.8% of EBP and VC recipients, respectively) [table IV]. Overall, EBP treatment was considered safe and well tolerated.

Discussion

The results of this 8-week study clearly demonstrated that twice-daily treatment with EBP is more effective than VC in patients with moderate to moderately severe acne. Patients in the EBP group had significantly greater total lesion reductions from baseline, and a significantly greater proportion of EBP recipients experienced treatment success compared with patients in the VC group. As early as week 2, statistically significant reductions were observed in inflammatory and total lesions and global severity. The difference in the

Table IV. Incidence of most commonly reported treatment-related adverse events [n (%) of patients]

	EBP (n = 112)	VC (n = 111)
Dry skin	14 (12.5)	6 (5.4)
Application site reaction	4 (3.6)	2 (1.8)
Pruritus	1 (0.9)	2 (1.8)

EBP = 3% erythromycin/5% benzoyl peroxide dual-pouch pack; **VC** = vehicle control.

proportion of patients with treatment success was observed as early as week 4. Patients using EBP had significantly lower oiliness scores at weeks 2, 4 and 8 compared with VC. Although these scores were based solely on visual inspection, they provide data on a parameter often overlooked in acne clinical trials. Numerically better reductions from baseline in facial comedones were observed in patients using EBP, indicating that EBP treatment has some degree of comedolytic activity. Global improvement and treatment acceptability as rated by the patients at endpoint were significantly more favourable in the EBP group compared with the VC group. EBP was well tolerated and was associated with a low incidence of treatment-related adverse events. The most frequently observed adverse event, dry skin, occurred in 12.5% of the EBP group and 5.4% of the VC group. Application site reactions and pruritus occurred infrequently.

The novel formulation and packaging of EBP are beneficial in several ways. The unit-dose packaging allows the patient to extrude a single dose of each drug from the dual pouch and mix the gels just prior to application, eliminating the need for pharmacist compounding. Because the packaging system eliminates the requirement for refrigeration, EBP is more convenient to use than the currently marketed formulation, which may be difficult for patients to use while travelling. The new formulation and innovative packaging allow more flexible medication storage and lengthened shelf-life for the consumer and may improve patient compliance, resulting in improved outcomes.

Patients treated with EBP for 8 weeks experienced a 69.2% geometric mean reduction in inflammatory lesions. This finding is important, especially when compared with results from studies evaluating other topical medications in similar patient populations. In one 12-week study, the efficacy and tolerability of adapalene gel 0.1% were compared with tretinoin gel 0.025% for the treatment of patients with acne vulgaris.[11] Although adapalene gel produced numerically greater lesion reductions than tretinoin gel as early as 2 weeks following treatment, statistical differences between the two treatments were not noted until week 12. The mean percentage reduction in total lesions among patients treated with adapalene gel 0.1% and tretinoin gel 0.025% was 49 and 37%, respectively, at week 12 ($p < 0.01$).[11] Furthermore, following 12 weeks of treatment application of adapalene gel 0.1%, patients experienced a 48% reduction in inflammatory lesions compared with a 38% reduction in patients receiving tretinoin gel 0.025% ($p < 0.06$).[11]

Comparatively, the reduction in inflammatory lesions observed in EBP-treated patients is an important finding particularly because few topical acne medications achieve a reduction in inflammatory lesions of this magnitude. In addition, significant ($p \leq 0.002$) reductions were evident following 2 weeks of treatment.

Topical agents such as benzoyl peroxide and topical antibiotics have important roles in the treatment of patients with mild to moderate acne. These agents are convenient and effective and are not associated with the systemic adverse effects observed with oral agents [e.g. gastrointestinal effects (oral erythromycin); central nervous system effects (tretinoin)].[12] Benzoyl peroxide has potent bactericidal activity against *P. acnes* and effectively treats inflammatory papules and pustules. Free fatty acid levels, involved in the formation of comedones, also decrease with use.[12] Erythromycin and clindamycin are the most commonly used topical antibiotics for treating moderate acne. These agents reduce *P. acnes* colonisation on the skin surface.[12] Both have similar efficacy when used alone and exert anti-inflammatory as well as antibacterial effects.[13,14]

Studies indicate that the combination of 3% erythromycin and 5% benzoyl peroxide is more effective than either of the two agents alone in treating acne vulgaris.[1,8] In one study, the combination of 3% erythromycin and 5% benzoyl peroxide was more effective than either topical 3% erythromycin or 5% benzoyl peroxide alone at reducing both pustules and papules and significantly reduced inflammatory lesions (papules and pustules) at weeks 4, 6, 8 and 10 compared with vehi-

cle gel, 3% erythromycin, and 5% benzoyl peroxide.[8] In addition to their independent mechanisms (i.e. the keratolytic effect of benzoyl peroxide and the antibacterial effect of erythromycin), several mechanisms have been proposed for the efficacy of the combined regimen. Benzoyl peroxide may 'loosen' the stratum corneum, thereby allowing a greater degree of erythromycin penetration.[8] The combination product also may prevent the emergence of resistance to erythromycin.[8,12] Harkaway and colleagues reported that benzoyl peroxide alone, or in combination with erythromycin, prevented resistant strains of propionibacterium and staphylococci in patients with acne.[10,15] Because benzoyl peroxide kills the bacteria by direct toxicity, resistance of *P. acnes* to benzoyl peroxide has not been reported. Results of a study by Eady and colleagues suggest that the combination of 5% benzoyl peroxide and 3% erythromycin may prevent the emergence of erythromycin-resistant variants and reduce the number of resistant organisms on the skin of patients with acne.[10] A later study demonstrated significant clinical improvements in patients with high numbers of erythromycin-resistant *P. acnes* prior to treatment.[1,9]

Conclusion

The results of this study demonstrated a clear benefit for patients with moderate to moderately severe acne vulgaris who use the EBP combination therapy. The new formulation and innovative packaging are more convenient for the patient and eliminate the need for pharmacist compounding and refrigeration by the patient. This single-dose system offers the benefit of fast-acting, dual-antimicrobial therapy, provides a well tolerated and effective option for the treatment of moderate acne, and may lead to better patient compliance.

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