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Clinical evaluation of Double Strength Isotrexin™ versus Benzamycin® in the topical treatment of mild to moderate acne vulgaris

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BACKGROUND: Topical retinoid therapy has been shown to be an effective means of treating both the inflammatory and non-inflammatory lesions of acne vulgaris.

AIM: To assess the efficacy and safety of the test product, a gel containing isotretinoin 0.1% w/w and erythromycin 4.0% w/w, with a currently used and effective treatment for mild to moderate acne vulgaris, a gel containing benzoyl peroxide 5.0% w/w and erythromycin 3.0% w/w.

METHODS: This multi-centre, single-blind (investigator blind), parallel group study compared the efficacy and safety of isotretinoin/erythromycin gel (Double Strength Isotrexin™) once daily against benzoyl peroxide/erythromycin gel (Benzamycin®) twice daily in the topical treatment of mild to moderate acne vulgaris. Patients ($n = 188$) with a history (mean duration 3.3 years) of facial acne vulgaris and with 15–100 inflammatory lesions and/or 15–100 non-inflammatory lesions, but not more than three nodulocystic lesions, were included. At baseline and weeks 2, 4, 8 and 12, the investigator assessed efficacy (total number and severity of inflammatory and non-inflammatory lesions and acne grade) while subjective global change assessments of facial acne from baseline and symptom-specific skin tolerance were assessed by the patient. The investigator recorded an overall global assessment of skin tolerability at week 12. Adverse events were recorded throughout.

RESULTS: The treatments were comparable with regard to their effects on inflammatory and non-inflammatory lesions and acne grade. Few adverse events were considered to be treatment-related. Both the isotretinoin/erythromycin and benzoyl peroxide/erythromycin gels were generally well tolerated. Compliance was better with the isotretinoin/erythromycin gel, which had the advantages of not requiring mixing or storage in a refrigerator, and was applied once rather than twice daily.

CONCLUSIONS: Isotretinoin/erythromycin gel given only once daily showed comparable efficacy with benzoyl peroxide/erythromycin given twice daily in the treatment of mild to moderate acne vulgaris of the face. (*J Dermatol Treat* (2002) **13:** 111–117)

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Introduction

Topical retinoid therapy has been shown to be an effective means of treating both the inflammatory and non-inflammatory lesions of acne vulgaris.[1–3]

It can be considered that topical erythromycin therapy reduces the percentage of surface free fatty acids, which is thought to be due to inhibition of both lipase activity and lipase production by *Propionibacterium acnes*.[4] Erythromycin also inhibits leukocyte chemotaxis.[5] The main therapeutic effect of erythromycin is inhibition of inflammation caused by bacteria.[6]

High efficacy and tolerability has previously been demonstrated with combined topical retinoid/antibiotic preparations in the treatment of acne vulgaris.[7–10]

The results of a multi-centre, single-blind, controlled study comparing the efficacy and safety of a gel containing isotretinoin/erythromycin *once daily* with benzoyl peroxide/erythromycin *twice daily* for the topical treatment of mild to moderate acne vulgaris are now reported.

Patients and methods

Aims and objectives

The aim of the study was to assess the efficacy and safety of the test product, isotretinoin/erythromycin gel, with a currently used and effective treatment for mild to moderate acne vulgaris, benzoyl peroxide/erythromycin gel.

Test medications

The gel containing isotretinoin 0.1% w/w and erythromycin 4.0% w/w in a vehicle of butylated hydroxytoluene, hydroxypropylcellulose and ethanol (Double Strength Isotrexin™), was manufactured by Stiefel International R & D (Maidenhead, Berkshire, UK). The comparator gel contained benzoyl peroxide 5.0% w/w and erythromycin 3.0% w/w (Benzamycin®) and was manufactured by Rhône-Poulenc Rorer, Puerto Rico Inc, Puerto Rico and distributed by Bioglan Laboratories Ltd, Hitchin, Herefordshire, UK.

Study design

This multi-centre, single-blind, parallel group study was conducted by 11 primary care centres throughout England, Wales and Ireland. The primary care centres were coordinated by Profiad Limited.

Patients recruited for the study were assigned according to a pre-determined randomization schedule to receive either isotretinoin/erythromycin gel or benzoyl peroxide/erythromycin gel. Each patient was given verbal and written instructions by the investigator regarding the correct use of study gel, which was to be applied as a thin layer to the entire affected areas of skin (15 minutes after washing) for 12 consecutive weeks. Patients were required to return for assessment after 2 (visit 2), 4 (visit 3), 8 (visit 4) and 12 (visit 5) weeks. During the study period and 1 month prior to recruitment, no other acne treatment was allowed.

The isotretinoin/erythromycin gel was stored at room temperature. According to the manufacturer's instructions, patients were requested to store the benzoyl peroxide/erythromycin gel in the fridge.

Selection criteria

A total of 188 patients, aged between 12 and 33 years (inclusive), were recruited into the study. To be able to detect a 30% absolute difference between active treatments, at the two-sided 5% significance level, with 95% statistical power, a total of 148 patients (74 completing each treatment) was required.

Patients with facial acne vulgaris having 15–100 inflammatory lesions and/or 15–100 non-inflammatory lesions, but not more than three nodulocystic lesions, were eligible for the study. Counts were made by assessors who were trained according to the method of Burke and Cunliffe.[11] The baseline numbers of inflammatory and non-inflammatory lesions and acne grade were recorded at the admission visit.

Assessment of efficacy and safety

At weeks 2, 4, 8 and 12, the following assessments were performed.

The primary efficacy variables were the total number of inflammatory lesions, non-inflammatory lesions and the acne grade. Under standard light conditions, using the methods of Burke and Cunliffe,[11] the assessors counted the total number of inflammatory (papules and pustules) and non-inflammatory (closed and open comedones) lesions on each patient's face, and also graded the severity of their acne. All 22 assessors who counted the lesions and graded the acne were trained by Ann Eady (Principal Research Fellow, University of Leeds).

For each patient, the investigator subjectively assessed the overall facial acne condition as a global change score (very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse) after 2, 4, 8 and 12 weeks of therapy. This assessment was intended as a secondary efficacy variable; however, it is recognized that the global change scores are exploratory in this clinical trial because baseline photographs were not taken.

The secondary efficacy variable was the patient's self-rating assessment, where patients self-rated the overall change in their facial acne as a patient's self-rating assessment (improved, no change or worse) after 2, 4, 8 and 12 weeks of therapy. The investigator asked the patient how, in his/her opinion, his/her condition had changed since commencing therapy.

Adverse events

Adverse events were classified into body system and pre-

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ferred term using COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms).[12] Any skin tolerability parameters (erythema, scaling, dryness, burning or pruritus) were graded as 'none', 'mild', 'moderate' or 'severe' and, if present, whether intermittent or persistent. Any skin tolerability parameter graded as severe was also recorded as an adverse event.

Compliance with dosage regimen

Patients kept diary cards in which they noted the number of applications. The study nurse/pharmacist noted on the case report forms whether or not the patients had applied the medication according to the protocol (yes/no). If no, the approximate per cent of applications was noted (>75%, >50% and ⩽75%, >25% and ⩽50% and ⩽25%). Major violations were defined as less than or equal to 50% compliant at their last visit. The weight of the medication (⩽25%, >25%, ⩽50%, >50%, ⩽75%, >75%) was recorded at each return visit.

Statistical methods

The results of the study were analysed by Hartington Statistics and Data Management, UK. Efficacy data were compared using analysis of variance (ANOVA) and logistical regression analysis. The chi-squared test or the Fisher's exact test (where frequencies were small) and 95% confidence intervals (95% CIs) were used to compare safety data on all randomized patients receiving at least one application of study medication. Treatment groups were compared using two-tailed hypothesis tests at the 5% significance level.

Results

Between 19 October 1998 and 17 June 1999, a total of 188 patients, from 11 primary care centres in the UK, with mild to moderate acne vulgaris were recruited into the study and randomized to treatment (intention-to-treat population) with isotretinoin/erythromycin ($n=95$) or benzoyl peroxide/erythromycin ($n=93$). See Table I.

Patients were excluded from the per-protocol population from the visit at which the major violation was recorded, if applicable. Major violations were less than 50% compliance, attendance more than 15 days before or after their scheduled visits, and use of concomitant medication before study start. If the violation was recorded at visits 1 or 2, the patient was completely excluded from the per-protocol population. Major protocol violations at visits 1 or 2 occurred in three patients in the isotretinoin/erythromycin group and seven patients in the benzoyl peroxide/erythromycin group, leaving 178 efficacy-evaluable patients (per-protocol population). In all, 21 patients (22%) from the isotretinoin/erythrosmycin and 30 (32%) from the benzoyl peroxide/erythromycin groups discontinued at various times during the study, due to lack of treatment efficacy ($n=0$ and 2, respectively), adverse events ($n=8$ and 9, respectively), refusal to cooperate ($n=6$ and 12, respectively), development of exclusion criteria ($n=4$ and 8, respectively), and other reasons ($n=3$ and 0, respectively). One patient in the benzoyl peroxide/erythromycin group had two reasons for withdrawal.

Of the 188 patients (106 females, 82 males, mean age 17 years) recruited into the study, 185 were Caucasian; the mean duration of their history of acne was 3.7 years for the isotretinoin/erythromycin group and 2.9 years for the benzoyl peroxide/erythromycin group. The two groups were well matched with respect to inflammatory and non-inflammatory lesions as well as for the severity of acne grade. The demographic characteristics for the intention-to-treat population are summarized in Table II.

Efficacy

Mean changes from baseline (with 95% CI) of non-inflammatory lesions, inflammatory lesions and acne grade for the intention-to-treat population are presented in Table

Centre no.	Investigator	Study centre	Patients treated with isotretinoin/ erythromycin gel	Patients treated with benzoyl peroxide/ erythromycin gel
1	Dr Chris Kyle	Rosehall Surgery, Co. Antrim	9	8
2	Dr Malcolm McCaughey	The Health Centre, Co. Antrim	8	8
3	Dr Adrian Darrah	Whiteabbey Health Centre, Belfast	8	9
4	Dr Sarah Morgan	Four Elms Surgery, Cardiff	15	13
5	Dr Huw Charles	Ely Bridge Health Centre, Cardiff	9	9
6	Dr Chris Morgan	Old School Surgery, Mid Glamorgan	8	6
7	Dr Philip Marazzi	The Medical Centre, Surrey	8	9
8	Dr Peter Harvey	Crouch Oak Family Practice, Surrey	12	11
9	Dr Dayantha Fernando	The Surgery, Surrey	8	9
10	Dr Sally Barnard	Newnham Walk Surgery, Cambridgeshire	4	4
11	Dr Katrina Young	St Mary's Surgery, Cambridgeshire	6	7

Table I
Number of patients treated at each primary care centre

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Baseline characteristic	Treatment groups	
	Isotretinoin/ erythromycin gel (n = 95)	Benzoyl peroxide/ erythromycin gel (n = 93)
Gender, n (%)		
Male	45 (47)	37 (40)
Female	50 (53)	56 (60)
Race, n (%)		
Caucasian	95 (100)	90 (97)
Mongoloid	0 (0)	3 (3)
Age, years		
Mean (SD)	17.1 (5.0)	16.9 (3.6)
Range	12–33	12–30
Weight, kg		
Mean (SD)	63.9 (12.6)	64.4 (10.8)
Duration of acne, years		
Mean	3.7	2.9
Previous acne treatment, mean (SD)		
Yes	28 (66.7)	30 (69.8)
Non-inflammatory lesions		
Mean (SD)	45.3 (25.0)	43.6 (22.0)
Minimum	3	7
Maximum	111	95
Inflammatory lesions		
Mean (SD)	33.2 (17.5)	36.2 (18.8)
Minimum	7	15
Maximum	90	93
Acne grade		
Mean (SD)	1.25 (0.55)	1.25 (0.63)
Minimum	0.3	0.1
Maximum	3.0	3.0

Table II
Demographic characteristics for the intention-to-treat population at baseline according to treatment group

III. ANOVA was used to compare treatment groups with respect to the changes from week 0 in the total number of non-inflammatory lesions, inflammatory lesions and acne grade at week 12. A total lesion count was not performed in the analysis and this can be derived from the data provided. The numbers of non-inflammatory lesions, inflammatory lesions and acne grade for the intention-to-treat population are shown in Figures 1, 2 and 3, respectively.

Non-inflammatory lesions

In the analysis of change from week 0 to week 12 in the total number of non-inflammatory lesions, no statistically significant difference was observed between the isotretinoin/erythromycin and benzoyl peroxide/

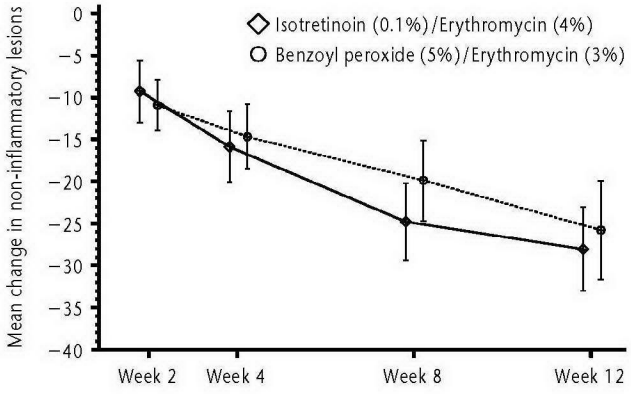

Figure 1
Mean change from week 0 in non-inflammatory lesions at weeks 2, 4, 8 and 12. Population: intention-to-treat.

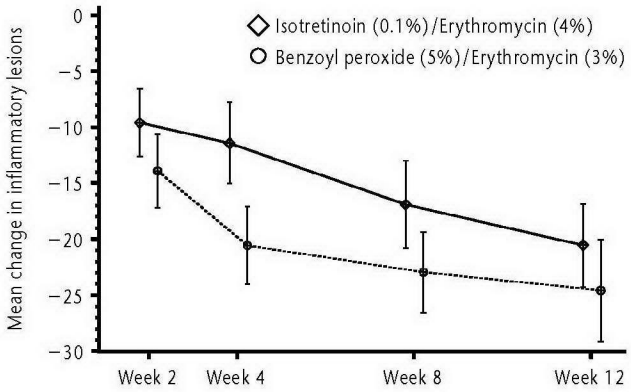

Figure 2
Mean change from week 0 in inflammatory lesions at weeks 2, 4, 8 and 12. Population: intention-to-treat.

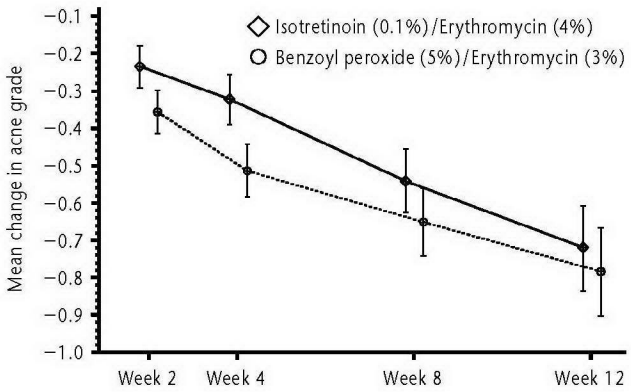

Figure 3
Mean change from week 0 in acne grade at weeks 2, 4, 8 and 12. Population: intention-to-treat.

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