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Original articles

Azithromycin Monthly Pulse vs Daily Doxycycline in the Treatment of Acne Vulgaris

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Abstract

Acne vulgaris is a common skin disease seen primarily in adolescent and young adults. As the treatment involves long term therapy with antibiotics, an agent with a long half life can be very useful in increasing the compliance. To evaluate the role of a monthly dose of azithromycin and compare it with daily doxycycline, we conducted this randomized comparative study. Sixty patients with moderate to severe acne were randomly assigned to two treatment groups, A & B. Patients in group A received 100 mg doxycycline daily in addition to topical 0.05% tretinoin cream, whereas patients in group B were given 500 mg azithromycin once a day for four days per month along with 0.05% topical tretinoin for a total of 12 weeks. Of the 60 patients, 22 in group A and 28 in group B were evaluated. The monthly dose of azithromycin was found to be as effective as daily doxycycline on a pure protocol basis and statistically significantly better than doxycycline by intention to treat analysis.

Key words: acne; azithromycin; doxycycline; treatment

Introduction

Acne vulgaris is a common skin disease, seen primarily in adolescents and young adults. Effective treatment is essential to prevent physical and psychological scarring; acne is frequently associated with profound emotional aspects. Currently, broad-spectrum antibiotics, primarily tetracycline or its derivatives, are widely used in the treatment of acne. Oral eythromycin, a macrolide antibiotic, was shown to be as effective as tetracycline in a double blind study (1). However, there is increasing evidence of development of erythromycin resistant strains of P. acnes from both the topical and systemic use of erythromycin (2). Because the treatment involves long-term therapy with these antimicrobials, an agent with a long half-life could be very useful in increasing the complicance. Azithromycin is a 9-methyl derivative of erythromycin with an average terminal half-life of 68 hours (3, 4). In comparison with erythromycin, azithromycin is better absorbed and is more extensively distributed into tissue (5). Its unique pharmacokinetic properties include a high concentration within cells (including phagocytes) (6). These attributes result in a much greater tissue or secretion drug concentration compared to the simultaneous serum concentration. To evaluate the role of monthly doses of azithromycin and compare it with that of daily doxycycline in the treatment of moderate to severe acne, we conducted this randomized comparative study.

Patients and Methods

Sixty patients with moderate to severe acne (grade 2–8) on the Burke and Cunliffe scale (7) were randomly assigned to two treatment

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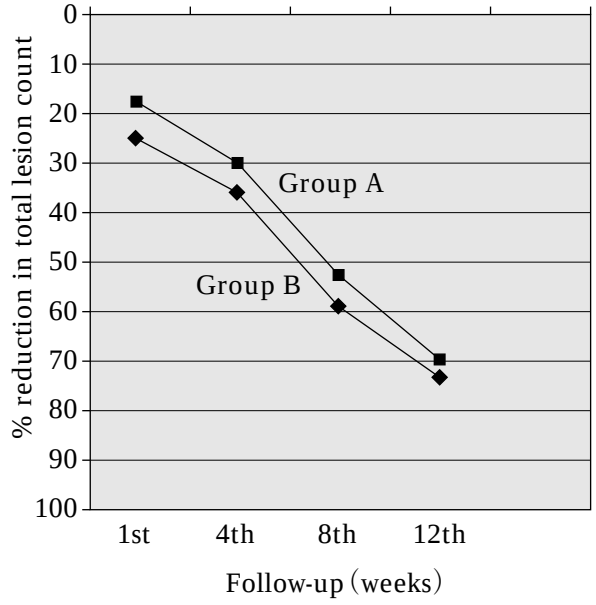

Fig. 1. Percentage reduction in total lesion count on a pure protocol basis

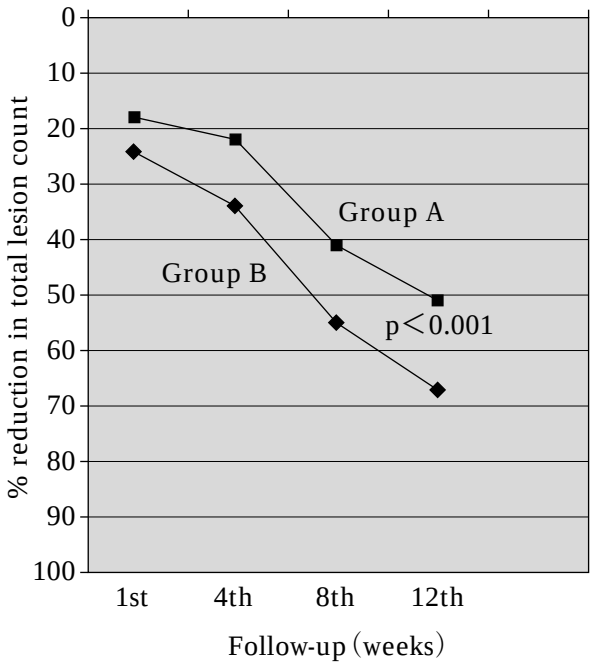

Fig. 2. Percentage reduction in total lesion count on using intention to treat analysis

Table 1. Baseline patient characteristics

	Group A	Group B
Enrolled	30	30
Sex (Males/Females)	13/17	12/18
Discontinued	8	2
Completed study	22	28
Lesion count (mean+SD)		
*Inflammatory	28.8±12.6	30.6±13.4
*Non inflammatory	32.6±16.2	39.2±14.4
Severity Grade	3.0± 0.8	3.4± 0.9

Table 2. Percentage reduction in severity grade in both the treatment groups

% reduction Mean±S.D.	Group A	Group B
Week 1	18.2± 3.6	24.2± 4.2
Week 4	31.4± 6.8	33.4± 7.6
Week 8	53.2±12.2	56.4±14.1
Week 12	75.5±12.2	77.6±14.1
ITT Analysis		
Week 1	17.6± 4.2	23.2± 5.1
Week 4	22.4± 6.8	31.6± 7.9
Week 8	41.7±13.2	53.6±14.8
Week 12	60.2±13.8	75.6±13.2

groups, A and B. Exclusion criteria were as follows: individuals of less than 16 years of age, individuals with sensitivity to any drugs used in this study, females who were pregnant, planning a pregnancy, or nursing a child. Patients in group A received 100 mg doxycycline in addition to topical 0.05% tretinoin cream. Patients in group B were given azithromycin 500 mg once a day for four days per month for a total of 12 weeks along with topical 0.05% tretinoin. Efficacy evaluations were carried out at baseline and each scheduled visit by counting each type of facial lesion and evaluating the global severity according to the Leeds technique (7). Global assessment of the improvement was evaluated for the face, chest and back (when affected) at 12 weeks. Global assessment of improvement was evaluated at week 12 in comparison with the baseline, using a 4 point scale: –1=worsened (exacerbation in the quantitative assessment of lesions); 0=unchanged (acne showed no changes); 1=improved (improvement in quantitative assess-

ment of lesions); 2=clear (no lesions). Variables of the two groups such as sex, age, duration of disease and the entry-level total scores were compared. Discrete variables were analyzed by Fishers Exact Test supplemented by categorical linear models. The studen's t test was used to analyze the differences in means. Chi-square test with or without Yates correction was applied. Intention to treat analysis was also used. Intention to treat includes all randomized patients in the groups to which they were randomly assigned, regardless of the treatment they actually received, and regardless of subsequent withdrawal from the treatment on division from the protocol. There are two reasons why one might use this approach first; intention to treat preserves the effect of ramdomization. Second, intention to treat often provides an assessment of the practical impact of a treatment.

Results

Of 60 patients, 22 in group A and 28 in group B could be evaluated (Table 1). Three patients in group A discontinued treatment because of intolerable side effects of doxycycline and five patients discontinued for non-medical reasons (protocol violation, loss to follow up etc.). Two patients in group B discontinued because of reasons unrelated to the study. All the patients enrolled in the study were retained for the intention to treat analysis (ITT). There was no significant difference at baseline in disease severity parameters between the two groups.

Two patients in group A complained of severe nausea and one developed photosensitivity with doxycycline and withdrew from the study. Two patients developed vaginitis and five complained of mild to moderate gastrointestinal discomfort. Monthly doses of azithromycin were well tolerated except for patients who complained of mild and transient gastrointestinal discomfort. Three patients in group A and four patients in group B complained of mild irritation from the topical tretinoin application.

Efficacy results—lesion counts:

Figure 1 shows the efficacy results of both the treatments in term of percentage reduction in inflammatory as well as non-inflammatory lesion counts. Both treatment groups showed reductions in lesions from the baseline at each evaluation time. There were no significant differences in the lesion counts between the two treatment groups on a pure protocol basis. The ITT showed a highly statistically significant decrease in lesions in group B patients (Azithromycin) (Fig. 2).

Efficacy results—severity grade:

The efficacy was also determined from the global severity grade and is shown in Table 2. There were no significant differences in the baseline severity grade. The scores of both groups decreased from baseline to week 12 with no statistically significant differences. However, ITT showed a highly statistically significant decrease in severity score in the azithromycin group.

Efficacy results—global assessment of improvement:

Eighteen patients in group A and 23 patients in group B were rated as improved; the Chi-square test and ITT indicated statistically significant improvement in the azithromycin group.

Discussion

The unique pharmacokinetics of azithromycin makers it a highly suitable agent for the treatment of acne. It appears that tissue fibroblasts act as a natural reservoir for the drug *in vivo* and that transfer of the drug to phagocytes is easily accomplished. These phagocytic cells could act as a vector for delivering azithromycin to the site of infection. Azithromycin shows activity against many anaerobic species, including *Propionobacterium acnes,* which is inhibited in vitro at a minimum inhibitory concentration of 0.15 μg/ml or even less for 90% of isolates. Whether its action is medicated through antimicrobial activity or through some anti-inflammatory activities is not yet clear. A decrease in free fatty acid formation has been reported with erythromycin. No pharmacokinetic drug-drug interactions have been observed in trials studying the concomitant

use of azithromycin and other medications (8, 9). Azithromycin at a dose of 250 mg three times a week was shown to be safe and effective in the treatment of acne in an open trial by Fernandez-Obergon (10, 11). Similarly, Gruber et al. (12) compared azithromycin 500 mg for 4 days every 10 days with minocycline. They concluded that azithromycin is at least as clinically effective and well tolerated as minocycline in the treatment of facial comedonic and papulopustular acne. In our study a monthly dose of azithromycin was found to be as effective as daily doxycycline on a pure protocol basis and statistically significantly better than doxycycline by ITT analysis.

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