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## A Dose-Finding Study of Azithromycin in the Treatment of Acne Vulgaris

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**SUMMARY** This open, multicenter, comparative, randomized study included 120 subjects with papulopustular stage of acne vulgaris. Subjects were randomized to one of the three treatment groups (A, total dose 4.5 g of azithromycin in 7 weeks; B, total dose 6.0 g in 10 weeks; and C, total dose 7.5 g in 13 weeks). The aim was to identify the optimum azithromycin dose in the treatment of acne vulgaris through monitoring the efficacy and safety of three dosage regimens. Clinical efficacy was assessed upon completion of study therapy and six months of therapy initiation. Post-therapeutic efficacy assessment was available in 104 subjects. The difference between three treatment groups was most pronounced in the "cure" category (36.11% in group A, 58.82% in group B and 55.88% in group C) and "failure" category (8.33% in group A, and no failures in groups B and C). Follow up efficacy assessment was available in 87 subjects. The group percentage of "cure" was lower and group percentage of "treatment failure" higher in group A than in groups B and C. Azithromycin in a total dose of 6.0 g in 10 weeks seems to be a promising agent in the treatment of papulopustular acne vulgaris with few side effects and good patient compliance.

**KEY WORDS:** acne vulgaris, drug therapy, azithromycin, pilot study

### INTRODUCTION

Acne vulgaris is one of the most common skin diseases. It affects 80% to 85% of teenagers and young adults (1). In mature adults, up to 7% may have acne persistently into the mid-30s or -40s (2). Lasting for years, acne can cause both physical and psychological scarring (3). Acne is a

multifactorial disease affecting the pilosebaceous units of the face and trunk. The pathogenesis of acne involves increased sebum production that depends on hormonal function, abnormal follicular epithelial differentiation causing comedones, and proliferation of anaerobic diphtheroid *Propionibac-*

*terium acnes* resulting in inflammation (4). Acne is characterized by a variety of non-inflamed and inflamed lesions including open and closed comedones, papules, nodules and pseudocysts (5). In case of moderate inflammatory acne, oral antibiotics are a standard choice of treatment. The mechanism of action of systemic antibiotics for acne is not entirely clear as it is not only antimicrobial; they also diminish chemotaxis of polymorphonuclear leukocytes, modify the complement pathways and inhibit the polymorphonuclear leukocyte chemotactic factor and lipase production in *Propionibacterium acnes* (6). The most commonly prescribed antibiotics for acne are still tetracyclines. In order to achieve optimal results these antibiotics have to be taken twice or three times daily for several months. Such a prolonged antibiotic use is often associated with adverse events and non-compliance. Besides this, in the past two decades there have been an increased number of literature reports of *Propionibacterium acnes* antibiotic resistance to tetracyclines and erythromycin (7,8). The increased resistance and poor patient compliance with prolonged treatment regimen imposed the need of a new antibiotic with a shorter duration of treatment.

As azithromycin is an azalide antibiotic structurally related to erythromycin and shows an excellent *in vitro* activity against *Propionibacterium acnes* (9), it was indicated to try its potential in the treatment of acne vulgaris. The efficacy and tolerability of azithromycin were tested in the treatment of acne in several clinical studies conducted in a limited number of subjects previously treated with other antibiotics without success or in whom low tolerance was recorded for other antibiotics (10-13).

The aim of this study was to identify the optimum azithromycin dose in the treatment of acne vulgaris through monitoring its efficacy and tolerance.

## SUBJECTS AND METHODS

### Subjects

The study was designed as an open, multicenter, comparative, randomized study, and was performed at four sites. A total of 120 subjects (male or female aged 16 years or older) with papulopustular acne vulgaris were enrolled. An informed consent was signed by study subjects or their parents (legal representatives). The main exclusion criteria were macrolide hypersensitivity, pregnancy, lactation, severe renal or hepatic impairment, use of oral contraceptives, glucocor-

ticoids, androgens, antiandrogens, high doses of vitamin D and oral isotretinoin in the last three months.

The study was conducted in accordance with the Good Clinical Practice guidelines and principles of the Declaration of Helsinki as modified at 52<sup>nd</sup> WMA General Assembly, Edinburgh, Scotland, October 2000.

### Treatment

Each subject was randomly allocated (Microsoft Excel 5.0, RAND() function) at 1:1:1 ratio to one of the three treatment groups (group A, total dose 4.5 g of azithromycin in 7 weeks; group B, total dose 6.0 g in 10 weeks; and group C, total dose 7.5 g in 13 weeks).

Study treatment was initiated with a 3-day course of 500 mg azithromycin tablet once daily followed by one 500 mg azithromycin tablet *per* week for another 6 weeks in group A, 9 weeks in group B, and 12 weeks in group C. During the study, the subjects were only allowed to apply a keratolytic lotion topically twice daily (Rp. *Resorcinum* 0.5; *Acidum salicylicum* 1.5; *Aethanolum dilutum* 40% ad 100.0). The use of any additional antimicrobial therapy concomitantly with azithromycin was prohibited. In the period following completion of study therapy subjects were not allowed to take any macrolides, tetracyclines or clindamycin. The use of isotretinoin, oral contraceptives, androgens or antiandrogens, glucocorticoids, adrenocorticotrophic hormone, iodide, bromide, isoniazid, topiramate, and high vitamin D doses was also prohibited.

### Clinical assessment

Clinical examination with recording the number of inflamed facial acne lesions was performed before treatment initiation and subsequently at each study visit. Efficacy was assessed at the first visit following completion of study therapy (post-therapeutic assessment), at 7 weeks of therapy initiation in group A, at 10 weeks of therapy initiation in group B, at 13 weeks of therapy initiation in group C, and at final visit 6 months of therapy initiation in all study subjects (follow up assessment).

Clinical efficacy of the treatment was assessed using one of the following categories: "cured", efflorescence count reduced by  $\geq 75\%$  in relation to the pre-treatment status; "improvement", efflorescence count reduced by  $\geq 50\%$ -74%; "moderate improvement", efflorescence count reduced by  $\geq 25\%$ -49%; and "failure", efflorescence count reduced by less than 25%, or deterioration of symptoms during azithromycin treatment, or no

improvement, or deterioration in acne symptoms at 6 months of therapy initiation requiring another therapy.

### Safety assessment

Adverse events were recorded in all subjects during the study. Along with description of the adverse event, the date of onset, duration, severity and possible relationship to study treatment were recorded.

### Statistics

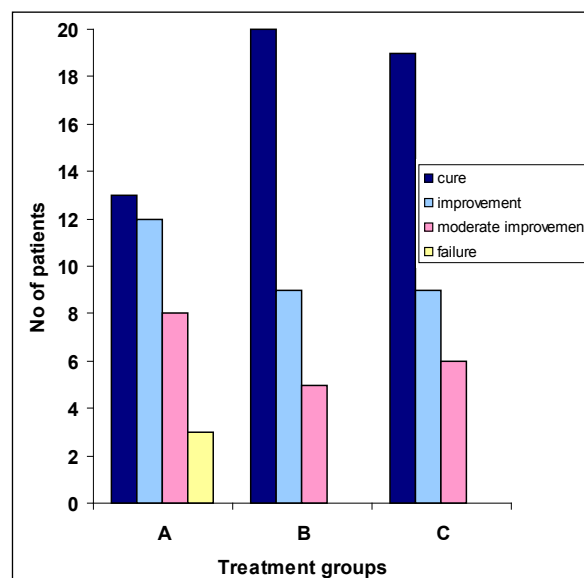
Statistical analysis was performed using the SAS® Stat software (SAS® System, Version 8.00, License No. 0082582002). Data were statistically analyzed using Fisher exact test and Kruskal-Wallis test. A probability value of  $p < 0.05$  indicated a statistically significant difference.

## RESULTS

The study included 120 subjects, 38 male and 82 female, aged 16-37. There were no statistically significant differences among treatment groups according to age, body height, body weight, or pre-treatment number of facial lesions. Of 120 subjects enrolled, 93 completed the study, i.e. 30 in group A, 31 in group B and 32 in group C. Post-therapeutic efficacy assessment was available in 104 subjects. The distribution of clinical outcomes in the 3 treatment groups is shown in Figure 1. There was no statistically significant between group difference (Fisher exact test,  $p = 0.28$ ) in clinical outcome.

Although not statistically significant, the difference among the 3 treatment groups was most pronounced in the "cure" category: group A, 13/36 (36.11%); group B, 20/34 (58.82%); and group C, 19/34 (55.88%), whereas "failure" category was exclusively recorded in group A, 3/36 (8.33%).

The difference between the pretherapeutic count of facial lesions and post-therapeutic efficacy assessment was significantly lower (Kruskal-Wallis test,  $p = 0.02$ ) in the low dose (group A) than



**Figure 1.** Distribution of post-therapeutic clinical efficacy outcomes in three treatment groups (n=104)

in the mid-dose (group B) and high dose (group C) groups (Table 1). The sum of facial lesions at first efficacy (post-therapeutic) assessment was also significantly higher (Kruskal-Wallis test,  $p = 0.03$ ) in the low dose group A as compared with the mid-dose and high dose groups B and C, respectively (Table 2).

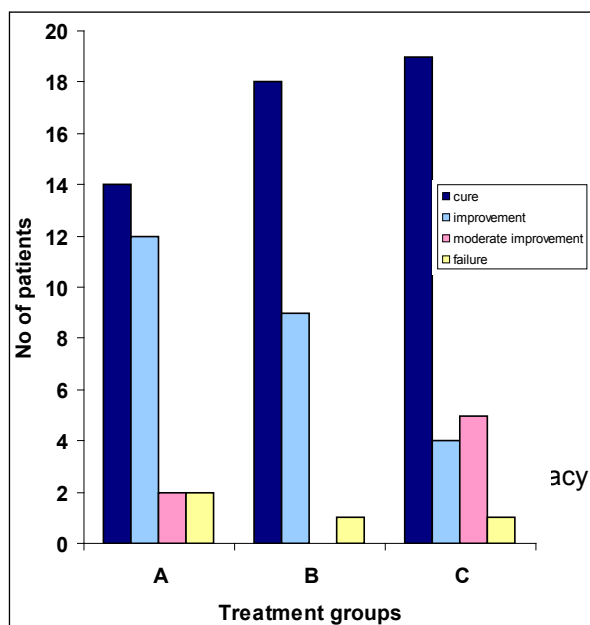
Follow up efficacy assessment was available in 87 subjects. The distribution of definitive clinical outcomes in each treatment group is shown in Figure 2. At follow up, there were no statistically significant differences (Fisher exact test,  $p = 0.07$ ) in the distribution of clinical outcomes. Although not statistically significant, the percentage of "cure" was lower in group A (14/30 (46.67%)) as compared with groups B and C (18/28 (64.29%) and 19/29 (65.82%), respectively). The group percentage of "treatment failure" was higher in group A (2/30 (6.67%)) than that in group B (1/28 (3.57%)) and group C (1/29 (3.45%)).

**Table 1.** Percentage of difference in number of facial lesions before treatment and at post-therapeutic efficacy assessment (descriptive statistics included mean and range)

|  | Group A (n=36) |                 | Group B (n=34) |                 | Group C (n=34) |                 |
|--|----------------|-----------------|----------------|-----------------|----------------|-----------------|
|  | Mean           | Range (min-max) | Mean           | Range (min-max) | Mean           | Range (min-max) |
| Difference in number of facial lesions (%) | 61             | 9 - 100         | 73             | 34 - 100        | 74             | 29 - 100        |

**Table 2.** Sum of facial lesions at post-therapeutic efficacy assessment (descriptive statistics included mean and 95% confidence interval)

|                       | Group A (n=36) |             | Group B (n=34) |            | Group C (n=34) |            |
|-----------------------|----------------|-------------|----------------|------------|----------------|------------|
|                       | Mean           | 95% CI      | Mean           | 95% CI     | Mean           | 95% CI     |
| Sum of facial lesions | 15.4           | 12.4 – 18.4 | 11.4           | 8.1 – 14.6 | 9.1            | 7.4 – 10.7 |



**Figure 2.** Distribution of follow up clinical efficacy outcomes in three treatment groups (n=87)

Safety assessment was performed in all subjects that received at least one dose of azithromycin. A total of 27 adverse events in 21 subjects were recorded. The majority of adverse events included laboratory findings, i.e. elevation of liver enzymes, and gastrointestinal adverse events. All of these adverse events were previously known and none of the reported adverse events was reported as unexpected. The incidence of adverse events according to treatment groups is presented in Table 3. There was no statistically significant difference in the occurrence of adverse events between the three treatment arms (Fisher exact test,  $p = 0.07$ ). The distribution of adverse events, possibly and definitely connected and not connected to the treatment, is presented in Table 4.

Three subjects had elevated AST above the upper normal limit (UNL); only one of them had a clinically significant rise (1.5xUNL) in AST; one subject had a clinically significant rise (1.5xUNL) in ALT. One subject suffered from stomach pain and diarrhea; one subject had exacerbation of facial flat warts (*verucae planae faciei*); and one

subject sustained ankle fracture and dropped out from follow up. All these seven subjects withdrew from the study and had full recovery.

## DISCUSSION

Antibiotics have been used to treat acne for over 40 years and are still widely prescribed. They remain a common therapeutic option because of their effectiveness and relative safety on long-term use. Their mode of action is partly due to their inhibitory effects on cutaneous *Propionibacterium acnes*, the microorganisms implicated in the pathogenesis of the disease. Until the late 1970s, these organisms were uniformly sensitive to therapeutically useful antibiotics (14). Since then, an association has been found between the carriage of resistant strains and failure to respond to treatment with the corresponding antibiotic (8). The most frequently prescribed antibiotics in-

**Table 3.** Distribution of subjects with adverse event (AE) incidence in 118 subjects (frequency, row and column percent)

| Treatment | No. of subjects |          |             | Total |
|-----------|-----------------|----------|-------------|-------|
|           | Frequency       | With AEs | Without AEs |       |
| Row %     |                 |          |             |       |
| Col %     |                 |          |             |       |
| A         | n 11            | 29       | 40          |       |
|           | % 27.50         | 72.50    | 100.00      |       |
|           | % 52.38         | 29.90    | 33.90       |       |
| B         | n 6             | 33       | 39          |       |
|           | % 15.38         | 84.62    | 100.00      |       |
|           | % 28.57         | 34.02    | 33.05       |       |
| C         | n 4             | 35       | 39          |       |
|           | % 10.26         | 89.74    | 100.00      |       |
|           | % 19.05         | 36.08    | 33.05       |       |
| Total     | n 21            | 97       | 118         |       |
|           | % 17.80         | 82.20    | 100.00      |       |
|           | % 100.00        | 100.00   | 100.00      |       |

**Table 4.** Distribution of adverse events (AE), possibly and definitely connected and not connected to treatment (frequency, row and column percent)

| Treatment | No. of AEs                        |               |        |
|-----------|-----------------------------------|---------------|--------|
| Frequency |                                   |               |        |
| Row %     | Possibly and definitely connected | Not connected | Total  |
| Col %     |                                   |               |        |
| A         | n 12                              | 1             | 13     |
|           | % 92.31                           | 7.69          | 100.00 |
|           | % 52.17                           | 25.00         | 48.15  |
| B         | n 7                               | 2             | 9      |
|           | % 77.78                           | 22.22         | 100.00 |
|           | % 30.43                           | 50.00         | 33.33  |
| C         | n 4                               | 1             | 5      |
|           | % 80.00                           | 20.00         | 100.00 |
|           | % 17.39                           | 25.00         | 18.52  |
| Total     | n 23                              | 4             | 27     |
|           | % 85.19                           | 14.81         | 100.00 |
|           | % 100.00                          | 100.00        | 100.00 |

clude tetracyclines (oxytetracycline, minocycline and doxycycline) and erythromycin, which need to be taken daily for several months, thus often entailing low patient compliance, which is another parameter relevant for the treatment and its success. Due to the relatively low compliance and the emergence of tetracycline and erythromycin resistant strains of *Propionibacterium acnes*, the need of alternative antibiotic treatment with less frequent dosing and shorter therapy duration has become evident.

The anti-inflammatory action of macrolides has been shown in various studies. They affect several inflammatory processes such as migration of neutrophils, oxidative burst of phagocytes and production of proinflammatory cytokines (15-17). Azithromycin has a superior pharmacokinetic profile when compared to other macrolides. It penetrates tissue rapidly, where it remains for prolonged periods. This enables less frequent dosing and shorter therapy duration. Moreover, it shows affinity for inflammatory tissues (18). Besides azithromycin effectiveness in the treatment of inflammatory acne (19), there also are reports of its effectiveness in the treatment of inflammatory rosacea (20).

Because azithromycin shows an excellent *in vitro* efficacy against *Propionibacterium acnes* with

an extended therapeutic effect after the last dose and good penetration into the skin (9), several investigators have evaluated safety and efficacy of this antibiotic in the treatment of acne vulgaris. Regardless of differences in dosing regimens and comparative treatments, the results of all these studies suggested that azithromycin could become standard therapy in the management of acne.

The safety and efficacy of azithromycin in the treatment of acne vulgaris was evaluated in subjects who had previously been unsuccessfully treated with other antibiotics. In this study, subjects received azithromycin for three months; once daily for 5 days twice a month up to a total dose of 9 g and once daily for 5 days once a month for the remaining 2 months. This intermittent dosing of azithromycin was found to be very effective and also resulted in improved compliance (10).

In a comparative study including 72 subjects with moderate to severe acne, azithromycin in a total dose of 8 g (4 cycles of 500 mg daily for 4 days) was found to be somewhat more efficacious and as well tolerated as minocycline 100 mg administered daily for 6 weeks (at the 6 week assessment clinical improvement was observed in 76% of subjects treated with azithromycin and in 71% of those treated with minocycline (12).

In a retrospective study comparing various oral antibiotic treatments for acne, azithromycin (single oral 250 mg dose of azithromycin 3 times weekly for a mean of 11.67 weeks) showed equal or better efficacy and tolerability than cefuroxime, doxycycline, erythromycin, minocycline and tetracycline (11,21).

A randomized comparative study evaluated the role of a monthly dose of azithromycin and compared it to daily doxycycline. Sixty subjects with moderate to severe acne were randomly assigned to two treatment groups. In the first group subjects received 100 mg doxycycline daily in addition to topical 0.05% tretinoin cream, whereas subjects in the second group 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. The monthly dose of azithromycin was found to be as efficacious as daily doxycycline (22).

The open-label, non-comparative study including 35 subjects with relapsing moderate to severe papulopustular acne showed that treatment with azithromycin, 500 mg three times weekly for 12 weeks, was effective in 82.9% of subjects with a nearly 60% reduction of lesions in the first 4 weeks and 80% in 12 weeks (13).



In our open, multicenter, randomized study we compared three dosage regimens of azithromycin in pulse therapy of acne vulgaris: a cumulative dose of 4.5 g, 6.0 g, and 7.5 g over 7, 10 and 13 weeks, respectively. The initial efficacy assessment was performed at the end of therapy in each treatment group, and follow up evaluation at 6 months of inclusion into the study. The results indicated that there were differences among treatment groups when comparing the sum of lesions or its change over time. With respect to these two efficacy measures, treatment with 4.5 g azithromycin was found to be less effective than treatments with 6 g and 7.5 g.

There was no statistically significant difference in the occurrence of adverse events (in total or with respect to treatment) among the three treatment arms. The majority of adverse events including those that were labeled as potentially treatment-related occurred in the low dose group A. These findings indicated that the adverse events observed could not be linked to treatment duration or cumulative dose of azithromycin received.

In conclusion, no significant difference was found in the efficacy and safety between the treatment groups receiving 6.0 g and 7.5 g of azithromycin, but it seemed that the advantage of mid-dose azithromycin (6.0 g) might result in better patient compliance and definitely in lower cost. So, it appears that azithromycin in a total dose of 6.0 g is a promising agent in the treatment of papulopustular stage of acne vulgaris with its few side effects and good patient compliance. These 10 weeks of pulse therapy represented a rationale for launching a pivotal, comparative study to establish the potential clinical benefit of azithromycin in the treatment of acne vulgaris.

#### Acknowledgment

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