Efficacy of doxycycline versus azithromycin in the treatment of moderate facial acne vulgaris

Hamideh Moravvej, MD
Akbar Mousazadeh Halim, MD
Maryam Yousefi, MD
Soudabeh Givrad, MD

Skin Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Corresponding Author:
Maryam Yousefi, MD
Skin Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Email: myousefi_md@yahoo.com

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Background: Acne vulgaris is the most common disorder of pilosebaceous unit. Systemic antibiotics are known to be effective in its treatment. We performed this investigation to compare the efficacy of azithromycin with doxycycline in the treatment of acne vulgaris.

Method: A twelve-week study was performed on 69 patients with moderate facial acne to compare the efficacy of oral azithromycin with oral doxycycline. Sixty patients completed the study. Patients in the treatment arm one were scheduled to receive 500 mg azithromycin once daily three times a week, and patients in the treatment arm two were instructed to use 100 mg doxycycline daily. All patients administered topical tretinoin cream every other night. Clinical assessment was made at baseline and then every 4 weeks.

Result: There were statistically significant improvements in comedones and inflammatory lesion counts in both groups. Neither drug was shown to be more effective than the other.

Conclusion: This study indicated that azithromycin had similar efficacy to doxycycline in reducing acne lesions.

Keywords: acne vulgaris, azithromycin, doxycycline

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INTRODUCTION

Nearly everyone experiences acne vulgaris at some point in their life. Small non-inflammatory acne lesions may be of little importance; however, in those suffering from severe forms of inflammatory nodular acne, pain, social disturbances, and physical and psychological scars may influence the quality of life immensely [1].

Systemic antibiotics are used all over the world to treat moderate to severe inflammatory acne vulgaris [2]. Successful employment of azithromycin in treating acne was first described in a case report [3]. A number of other clinical trials demonstrated the efficacy of azithromycin and proved it to be at least as effective as minocycline, doxycycline and tetracycline [4-9].

Considering the in vitro activity of azithromycin against *Propionibacterium Acnes* (PA) [10] and its specific pharmacokinetic characteristics including fast and ample penetration into tissues [10], long half-life [11], safety and few side-effects compared to other standard antibiotics, the possibility of pulse therapy and higher tolerance profile as against other routine anti-acne treatments [12] and non-interference with the p-450 complex in the liver, it might be an appropriate alternative for routine antibiotics [11]. We performed this investigation to compare the efficacy of azithromycin with doxycycline in the treatment of acne vulgaris.

PATIENTS AND METHODS

This randomized clinical trial was conducted in the skin clinics of two major referral hospitals in Tehran; Shohada-e- Tajrish and Loghman-e- Hakim

Hospitals. Sixty-nine patients were enrolled in this study: four men and sixty-five women. Patients consisted of adults aged 18 to 30 years who referred to these clinics with the chief complaint of acne vulgaris, harboring at least 10 inflammatory lesions (no more than 3 nodules and/or pseudocysts). The local ethics committee of our Skin Research Center approved the study and an informed consent form was obtained from each patient.

The study was investigator-blinded. Either drug was prescribed by a physician who did not score the patients' acne lesions. Patients were randomly assigned to one of the two arms of treatment (using a randomized numbers table). Exclusion criteria were administration of topical or systemic agents which could possibly interfere with our course of therapy, such as oral contraceptives, intake of oral isotretinoin in the past 6 months, intake of oral systemic anti-acne medications in the past month, use of topical anti-acne treatment in the past two weeks, signs of hyperandrogenism, irregular menstruation cycles, acne fulminans, acne conglobata, acne lesions limited to the trunk, pregnancy, lactation, and past or present history of systemic ailments like liver dysfunction.

A twelve-week therapy plan was designed. Patients in the treatment arm one were scheduled to receive 500 mg azithromycin once daily three times a week, and patients in the treatment arm two were instructed to use 100 mg doxycycline daily. Moreover, all patients administered topical 0.05% tretinoin cream every other night.

Patients were assessed by one physician throughout the treatment period. The assessing physician was blinded to the type of therapy. Inflammatory lesions and facial comedones were evaluated initially prior to the treatment period and then every 4 weeks. In each visit, photographs from the right, left and front view were taken from the patients.The efficacy of each treatment regimen was evaluated by comparing the number of acne lesions at weeks 4, 8 and 12.

To compare the effectiveness of both treatment regimens, the followings were used:

- Both groups were compared according to the mean comedone and inflammatory lesion counts in similar sessions.
- Efficacy was also determined by comparing two treatment groups according to the reduction of inflammatory lesion and comedone counts from baseline to the 12th week: (a reduction of 80 percent or more was labeled as good; 50-80 percent as moderate; 20-50 percent as poor and less than 20 percent as no response).
- Both groups were compared according to the patients' self-assessment of their treatment at the end of week 12: (labeled as 0=worsening; 1= no change; 2= mild improvement; 3= moderate improvement and 4= good improvement).

At each visit, patients were clinically assessed with a checklist for side effects attributable to either drug including gastrointestinal intolerance, candidal vaginitis, vertigo, angio-edema, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, hearing loss, serum sickness, benign intracranial hypertension, systemic lupus exacerbation, nail pigmentation, mucosal and skin pigmentation or exacerbation of psoriasis.

Statistical analysis

For each treatment group, Friedman test was used to evaluate the differences of facial comedones and inflammatory lesion counts in the four time points (baseline, week 4, week 8 and week 12) and Wilcoxon tests with a Bonferroni correction were employed to test pair-wise comparisons. To compare the two treatment groups at each of the four time points, the Mann-Whitney-U-Test was utilized. Statistical analysis was performed using the statistical software SPSS 16.0.0. (SPSS Inc. Chicago, IL, U.S.A.). P values less than 0.05 were considered significant.

RESULTS

Sixty patients, 30 in the doxycycline and 30 in the azithromycin group, completed the study. Four patients in the azithromycin group (1 due to pregnancy, 1 due to poor compliance and 2 due to severe diarrhea) and 5 in the doxycycline group (1 due to poor compliance and 3 due to severe epigastric pain and 1 due to severe vertigo) discontinued the study. There were no significant differences in demographic characteristics between the two treatment arms.

There was a reduction in mean comedone and inflammatory lesion counts in both treatment groups over time points (Tables 1,2). Friedman test showed that there were significant differences in

Table 1. Mean (Standard Deviation) facial comedones count in each treatment group at baseline and at 4, 8, 12 weeks after beginning treatment

	Doxycycline (n=30)	Azithromycin (n=30)
Baseline	23.7 (12)	23.2 (12.9)
4th Week	14.2 (8.2)	15.8 (10.3)
8th Week	9 (5.9)	11.2 (8.3)
12th Week	5.9 (6)	7.1 (6.8)

Table 2. Mean (Standard Deviation) facial inflammatory lesions count in each treatment group at baseline and at 4, 8, 12 weeks after beginning treatment

	Doxycycline (n=30)	Azithromycin (n=30)
Baseline	14.1 (5.9)	15.3 (8.1)
4th Week	7.4 (4.3)	8 (4.8)
8th Week	4.5 (2.8)	4.5 (3.1)
12th Week	2.3 (1.6)	2.4 (2.8)

facial comedones count and inflammatory lesions count over the four time points in both treatment groups (p-values at most 0.0001). There was no statistical significant difference between the two treatment groups at each of the four time points (Mann-Whitney-U-test, p-values at least 0.41).

Mann-Whitney-U-test showed no significant difference in patients' self-assessment of their treatment between the two groups (p=0.45) (table 3).

The two treatment groups were compared for the reduction of inflammatory lesion and comedone counts from baseline to the 12th week (Figures 1,2).

Side-effects were observed in 17.6% and 17.1%

Table 3. Patients' Self-assessment of their treatment

	Doxycycline (n=30)	Azithromycin (n=30)
Improvement, no. (%)		
Moderate improvement	8 (26.7%)	6 (20%)
Good improvement	16 (53.3%)	16 (53.3%)
Excellent improvement	6 (20%)	8 (26.7%)

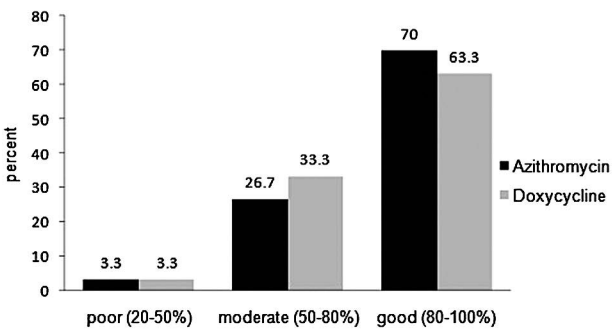

Figure 1. The reduction of inflammatory lesion counts from baseline to the 12th week

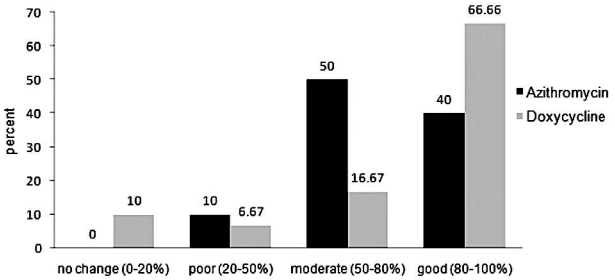

Figure 2. The reduction of comedones counts from baseline to the 12th week

of the participants in the azithromycin and doxycycline groups respectively most of which were mild, transient and self-limited. They include epigastric pain, diarrhea, vomiting, abdominal pain, constipation, malaise, mild headache and vertigo. There was no significant difference between the two treatment groups in this regard. Side-effects due to topical tretinoin were observed in a few patients not necessitating discontinuation of therapy.

DISCUSSION

This study was designed to compare the efficacy and safety of azithromycin and doxycycline in treating inflammatory acne vulgaris during a 12-week treatment period. Both treatments (in combination with topical tretinoin) were successful in decreasing and improving inflammatory and non-inflammatory lesions over the course of the study. Our study supported the previous reports, demonstrating azithromycin as a safe and effective choice in treating acne, at least as effective as doxycycline [3-9].

Upon comparison with a study performed by Kus et al, our study showed a more effective response obtained in a shorter period of time in both treatment arms. Kus et al, reported a significant therapeutic response in the average number of inflammatory lesions in both treatment groups after the second month of therapy; however, as for comedones, a therapeutic response was observed in the doxycycline group at the end of the second month and in the azithromycin group at the end of the third month [8]. Nevertheless, in our study, a significant decrease was observed in facial comedones and inflammatory lesion counts over the four time points in both treatment groups. Some studies propose that using a combination of antibiotics in addition to topical retinoids will

result in a more effective and a quicker response as opposed to monotherapy [2]. Therefore, our patients may have shown a better and more rapid response due to the addition of topical tretinoin to their treatment regimen.

Various studies have shown a prevalence of 8 to 19% of side effects in patients using azithromycin [4,5,7,8]. These side effects, necessitating the discontinuation of the treatment in some instances [8], mainly included diarrhea, nausea, heart burn and vaginitis [5].

Long term employment of antibiotics in patients harboring acne lesions has lead to concerns regarding bacterial resistance and colonization with potential pathogen agents [1]. In fact, P.acnes resistance has increased considerably [13] and the presence of antibiotic resistant P. acnes is correlated with a weaker clinical response [2,14]. Moreover, streptococcus pyogenes (not staphylococcus aureus) resistance is accompanied by a history of antibiotic treatment for acne [15]. In our research, we were not able to identify any reports on P.A. resistance to azithromycin. However, a 20 to 27.4% resistance to azithromycin has been documented in streptococcus pyogenes species [15,16]. Consequently, clinicians should employ strategies to prevent bacterial resistance and in cases where pathogen agents are resistant, they have to use therapeutic approaches to decrease it.

Topical retinoids do not cause any resistance in P.A. [13]; therefore, utilizing these agents to shorten treatment period and exposure to antibiotics could be beneficial. Antibiotic treatment should be approximately carried on for 3 months. Longer periods of treatment may be necessary in some cases but to decrease the risk of developing resistance, the treatment protocol should be combined with benzoyl peroxide combinations [2]. Weak compliance is known to be a risk factor for developing resistance in P. acne [17]; therefore, it is of importance to take patient's compliance into account prior to initiation of the treatment.

Our study demonstrated that in case of moderate facial acne vulgaris, combination therapy with azithromycin and topical tretinoin or doxycycline and tretinoin could reduce lesions effectively. We also showed that the efficacy and tolerability of azithromycin were similar to doxycycline as well. Therefore, azithromycin can be considered as a proper alternative for the treatment of acne vulgaris.

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