Original Research Article

Comparison efficacy of azithromycin vs. doxycycline in patients with acne vulgaris

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A B S T R A C T

Comparing the efficacy of doxycycline and azithromycin in the treatment of patients with acne vulgaris. A total of 120 patients with moderate to severe acne vulgaris participated in this randomized, double-blinded clinical trial and were randomly assigned to two groups (azithromycin and doxycycline). global scoreswere determined and recorded at baseline. Patients were followed up for three months Clinical assessment was made at baseline and at the end of each month and a global score was determined at each visit. Data was analyzed using SPSS, P value <0.05 was considered significant. There was no significant difference between the two groups in terms of demographic data and baseline global scores. Based on global acne grading system, mean percentage of improvement of the lesions was 75.33% in azithromycin group and 73.23% in doxycycline group. statistical analysis showed that at the end of the first and second months, azithromycin was more effective than doxycycline and the difference was found significan (P=0.005) for the second month, that might reflect the faster and more effective improvement of acne with azithromycin, although the difference wasn't significant at the end of the treatment period. Side effects for Doxycycline was 7 (11.7%) for gastrointestinal and3 (5%) for dermatologic that was higher than azithromycin 2 (3.3%) and 1 (1.7%) respectively. Our results showed that azithromycin a long acting macrolide has faster and more effective improvement with lower side effects and can be a suitable alternative for doxycycline in treatment of acne vulgaris.

K e y w o r d s

Acne vulgaris,
Doxycycline,
Azithromycin

Introduction

Acne vulgaris is a multifactorial disorder of pilosebaceous unit. Clinical presentations vary from mild acne with comedones to systemic inflammatory disease. Although acne might affect all age groups, it is primarily considered an adolescence disease (1). Characteristics of this disorder include, comedone, erythematose papules and pustules and nodules, deep pustules or psuedocysts and sometimes scarring. Acne

has been reported to be most prevalent in 14-17 years old females (45% of them are affected) and 16-19 years old males (35% of them are affected). In cases with very mild acne, it is considered a physiologic problem which is found in nearly 24% of female teenagers. Female patients present with acne earlier than males due to lower puberty age. The disease improves gradually after 20-25 years, although in 7-17% of patients it persists after 25 years. Acne might persist to fourth decade in 1% of male and 5% of female patients (2).

Four main factors are involved in pathogenesis of acne vulgaris: increase in production of sebum, increase in keratinocytes of pilosebaceouse follicle, change in microbial floraof the skin (proliferation of *Propionibacterium acnes*) and inflammation (3). Impact of genetic factors has been proved through monozygotic and dizygotic twin studies. They showed that the number of comedones and the severity of acne is similar in monozygotic twins in contrast to dizygotic twins (4). A study reported 45% frequency of acne in the parents of boys affected with acne while only 8% of parents of healthy boys had acne. Patients with persistent acne after 30 years were found to have stronger family history than those with adolescence acne (5).

Association of severe acne with XXY syndrome has been reported (6). Studies on various races have also showed the impact of genetic and environmental factors together. Acne in African-Americans is more severe than Caucasians. In addition, severity of acne in Japanese is found to be lower than Caucasians. Incidence of acne has been shown to increase in Eskimos changing their diet from fish to processed foods containing saturated lipids. Same findings have been seen in Japanese immigrants in Hawaii taking American diet

habits (6).

Without treatment, acne vulgaris might lead to complications such as inflammatory lesions, post inflammation hyperpigmentation (PIH), inflammatory painful nodules, nodular hypertrophic scars, cystic lesions and …etc. It might also result in very ugly shaped exudative or hemorrhagic nodules. In rare cases, there might be sinus tracts between deep nodules or pustules. Lesions in severe acne vulgaris might become very painful, chronic and refractory to treatment and even cause psychological complications particularly in young females (7).

Mild cases of acne are treated using topical agents such as retinoids or topical antibiotics. Systemic antibiotics including doxycycline are used in treatment of moderate and moderate to severe acne, mild acne in depressive and dysphoric patients, and PIH. During the past three decades, oral broad spectrum antibiotics such as tetracyclines (doxycycline and …) and macrolides have been used in treatment of inflammatory acne, which have required administration of several doses daily for a long period (at least 6 months) due to short half-life. In addition, systemic antibiotics might result in several side effects such as gastrointestinal disturbances. Azithromycin is a derivative of Erythromycin with a long half-life and thus it can be prescribed in less frequent doses and according to the studies, it has minor side effects, is cost effective and well tolerated with a high patient compliance rate (8,12).

In 2001 Fernandez and Obregon investigated the role of azithromycin in treatment of acne and found that it was effective in more than 80% of the cases, while other therapeutic agents including tetracycline, erythromycin, minocycline and doxycycline were averagely effective in

77.1% of the cases, however, the difference wasn't statistically significant (9).

In another study in 1998, Gruber et al compared therapeutic effects of azithromycin and minocycline in acne vulgaris. Satisfactory results were found in 75.8% of patients treated by azithromycin and 70.5% of patients receiving minocycline at the end of the treatment period. Both antibiotics were well tolerated, minor adverse effects were found in 10.3% of patients in azithromycin group and 11.7% in minocycline group. They concluded that in acne treatment, azithromycin is at least as effective and tolerable as minocycline (10).

In the study of Fernandez et al in 1997, patients were satisfied by azithromycin treatment, no side effects was observed and up to 80% improvement was found after four weeks of treatment (11). Kapadia and Talib in their study in 2004 found significant improvement in more than 82.9% of patients after four weeks of treatment with azithromycin. Maximum improvement was detected after 12 weeks of treatment. Adverse effects including nausea, and heart burn were only seen in 11.4% of cases (13).

Rafiei and Yaghubi in 2006 investigated therapeutic effects of tetracycline and azithromycin in acne patients. Their results showed considerable improvement in both groups, while azithromycin was found to be somewhat more effective than tetracycline in reducing inflammatory lesions (84.7% vs. 79.8%). They concluded that azithromycin is a safe and efficient therapeutic choice in inflammatory acne (15). In another study by Lucky et al in 2008, azithromycin was shown to result in significant improvement in 80% of patients after four weeks of treatment, without causing any serious side effects, while in doxycycline group, improvement was found in only 53% of patients (14).

Given the high prevalence of acne in adolescence particularly in females, and the mentioned literature review, we decided to conduct a randomized clinical trial with the aim of comparing the effect of azithromycin and doxycycline in treatment of moderate to severe acne.

Materials and Methods

This double- blinded randomized clinical trial was conducted on patients with moderate to severe acne vulgaris

Referred to Farshchian Hospital . Diagnosis was confirmed due to clinical criteria. Patients with multiple papules, pustules and nodules or scars on face or trunk were considered to have moderate to severe acne. The severity of acne was determined according to global acne grading system (GAGS) developed by Dermatology Department of Harvard University. Study population consisted of all patients with moderate to severe acne vulgaris attending dermatology clinic and department of Farshchian Hospital.

Patients who met the diagnostic criteria were enrolled in the study if they didn't have a history of taking systemic and topical treatment for their acne during the past four and two weeks respectively and hadn't received oral isotertinoin for the past 6 months. Female patients all required to have a negative pregnancy test and were asked to use a safe contraception method other than OCP during the study period. Exclusion criteria were history of drug sensitivity, medical diseases including endocrine or gastrointestinal, smoking and hyperandrogenism manifestations in girls. After taking informed consents, patients were enrolled in the study and randomly assigned to two treatment groups: case group received 250 mg azithromycin daily

and control group received 100 mg doxycycline daily for three months. All patient received instructions about correct method of taking the drugs. Clinical assessment was made at baseline and at the end of each month and a global score was determined at each visit. The score for each area (Local score) is calculated by multiplying a factor assigned to each area of the body (according to GAGS) in the grade of severity of the lesions (0-4).

Global score is the sum of local scores. A score of 0 means no lesions; 1-18 is considered mild acne; 19-30, moderate acne; 31-38, severe acne; and higher than 39 very severe acne. Drug side effects including gastrointestinal, neurologic and dermatologic signs and symptoms were checked and recorded during each visit. Patients were asked to evaluate the treatment at the end of the third month by grading: 0, worse; 1, no change; 2, mild improvement; 3, moderate improvement; 4, considerable improvement.

Study was designed as double blinded so that patients were not informed of the study structure and researchers didn't know about the type of the treatment each patient was receiving and just studied the manifestations of the disease and complications of the treatment. Medications were prescribed by dermatology attending and then patients were referred to the research unit.

Data was analyzed using SPSS. Mean global scores were compared using t-test. Qualitative variables were compared using chi-2 test. As shown on the table, gastrointestinal side effects are more frequently seen with doxycycline (11.7%) than azithromycin (3.3%).

According to the table, dermatologic adverse effects of doxycycline (5%) is higher than azithromycin (1.7%), however. No patients demonstrated neurologic side effects.

Accordingly patients' evaluation of treatment is moderate to good in 95% of patients in azithromycin group and 93.3% of patients in doxycycline group and the difference isn't significant.

According to the table, change in mean global score from baseline to the end of the third month of therapy was from 24.35 to 6.51 in doxycycline group and from 24.91 to 6.15 in azithromycin group, showing similar efficacy for two drugs. The difference between mean global scores at baseline and at the end of the first and third months not found to be statistically significant, however, at the end of the second month azithromycin group had a significantly lower mean global score than doxycycline that was significant (P=0.005).

Result and Discussion

Statistical analysis showed no significant difference between the two groups regarding demographic characteristics and mean global score at baseline, therefore comparison of the results between the two groups was more precise. As mentioned, few patients were excluded from the study due to medication side effects or inability to afford azithromycin and were substituted with new cases.

Mean GS at the end of each month of treatment was significantly decreased when compared with baseline which indicates the therapeutic efficacy of both drugs. Moreover, statistical analysis showed that at the end of the first and second months, azithromycin was more effective than doxycycline and the difference was found significant for the second month that might reflect the faster and more effective

improvement of acne with azithromycin, although the difference wasn't significant at the end of the treatment period.

Fernandez and Obregon in 2001 investigated efficacy of azithromycin in acne treatment. In their study a total of 99 inflammatory episodes of acne were treated in 79 patients using several antimicrobial medications including tetracycline, azithromycin, minocycline, and doxycycline. Patients who could not tolerate any of the mentioned drugs were treated using azithromycin. Azithromycin was administered as 250 mg/day. Side effects of all drugs were evaluated. It was shown that azithromycin was effective in 85.7% of patients while the other three antibiotics had anaverage efficacy of 77.1%; however, the difference wasn't statistically significant (9).

Kapadia and Talib in 2004 studied the effect of 250 mg azithromycin daily for 12 weeks on 35 patients with moderate to severe acne and found considerable improvement in 82.9% of them with maximum improvement (more than 80%) being recorded after 12 weeks of treatment. Side effects including nausea and heart burn were only seen in 4 (11.4%) patients. This study reported daily 250 mg azithromycin as a safe therapeutic regimen for acne with minor side effects (13). Their study period was 3 months similar to ours and they also found maximum improvement after 12 weeks of therapy. They reported gastrointestinal adverse effects of azithromycin in 4 patients while we foundonecase of abdominal pain and one case of nausea in our study.

Yucelten in 2005 compared the efficacy of azithromycin and doxycycline in acne treatment on 50 patients assigned randomly to two therapy groups: azithromycin group received azithromycin 500 mg/day on 3 consecutive days per week in the first, on 2 consecutive days in the second and on 1 day

per week in the third month. The second group took doxycycline twice a day for the first month, and daily for the second and third months. Clinical response to therapy was similar in the two groups and persisted 3 months after discontinuation of the treatment. Three cases of diarrhea were reported in azithromycin group while two patients in doxycycline group developed photosensitivity. This study suggested that azithromycin is at least as effective as doxycycline in treatment of acne (14). Consistently in our study, gastrointestinal side effects were found in azithromycin group including 2 cases with abdominal pain and nausea, and dermatologic side effects were seen in doxycycline group including two cases of photosensitivity and one case of skin rash.

Rafiei and Yaghoobi in 2006 compared tetracycline and azithromycin in treatment of acne on 290 patients for three months. Azithromycin was administered 500 mg/day for 3 consecutive days per week on the first and 250 mg/day every other day for the next two months. The results showed improvements of the lesions in both groups, however, azithromycin was slightly more effective than doxycycline in reducing inflammatory lesions (84.7% vs. 79.7%) and it was concluded that azithromycin is a safe and effective alternative in treatment of inflammatory acne (15).

Study population in their investigation was larger than ours which is more appropriate statistically. The schedule in their study was 3 consecutive days for azithromycin and every other day for doxycycline, but in our study both drugs were administered daily. Lucky et al (2008) studied the effect of azithromycin 500 mg/day and doxycycline 100mg/day on 70 patients with acne. After 2 months of therapy, satisfaction rate was 60% in doxycycline group and 80% in azithromycin group. Therapeutic effect was

65% and 80% in doxycycline and azithromycin groups, respectively (14). Study population was similar to our study; however, they administered azithromycin 500 mg/day and doxycycline 100 mg/day for three months. Nevertheless it is interesting that they found azithromycin to be significantly more effective than doxycycline while in our study the efficacy was similar and only in second month of administration was significant. Muron in 2009 studied the effect of azithromycin and doxycycline on acne treatment in 16-18 years old adolescents for a six-month period. Ninety patients received 250 mg azithromycin and ninety other were given 100 mg doxycycline daily.

Therapeutic effect of the two drugs was nearly 79% and similar. Side effects were found in 15% of the patients in doxycycline group including abdominal pain and vomiting and 5% of patients in azithromycin group including nausea (16). Efficacy of the medications in this study was similar to ours (79%) and also the reported adverse events were almost like our findings in the twogroups in terms of type (gastrointestinal and dermatologic). Knaggs et al in 2011 studied the effect of azithromycin and doxycycline in 40 patients for 2 months. Twenty five patients received 100 mg/day doxycycline and fifteen patients received 250 mg azithromycin every other day. Therapeutic effect in both groups was almost 71%. Patient's satisfaction for treatment was 70% in doxycycline group and 82% in azithromycin group. Side effects in doxycycline group included skin rashes in 10% of the patients while in azithromycin skin rashes were found in 4% (17). Treatment period was 2 months in this study while it was 3 months for our study. Patient's satisfaction level in our study was 95% for azithromycin and 93.3% for doxycycline. In a study in 2012 Speroff et al compared azithromycin 500 mg every other day with doxycycline 200 mg daily on 80 patients in two groups of 40 patients each containing 20 male and 20 female patients. Therapeutic effect of the drugs after four months was 81.1% in azithromycin group and 76% in doxycycline group and the difference was not statistically significant. Treatment side effects in doxycycline group included skin rash and photosensitivity in 18% and headache in 5%. In azithromycin group dermatologic (skin rash) and neurologic adverse effects were found in 10% and 2%, respectively (18). In consistent to our study, patients in this investigation were equally assigned to the two groups and the number of male and female patients in the two groups was similar. Frequency of neurologic side effects was 5% in doxycycline group and 2% in azithromycin group in this study; however, no cases of neurologic complications were seen in our study.

Ellis and Krach in a study compared the effect of 250 mg/day azithromycin and 100 mg/day doxycycline in treatment of acne for a three-month period. Therapeutic response was similar and nearly 78.5% in both groups and persisted for 3 months after treatment discontinuation. Nausea and vomiting was reported in four patients in doxycycline group and two patients in azithromycin group. Photosensitivity was seen in four patients in doxycycline group but not azithromycin group. Patients in this study were 15 to 28 years old (19), while in our study they were 15-31 years old. Therapeutic effect in this study was close to our results (78.5%).

Mean improvement of acne in our study according to the global acne grading system was 74% in both study groups highlighting the high efficacy of both of these drugs. Quantitative evaluation of the acne according to GAGS scale was performed at the end of each month of treatment and

showed higher efficacy of azithromycin in comparison to doxycycline during the first two months in acne treatment, although at the end of the three-month period the effect of the both drugs was almost similar.

Subjective evaluation of the two treatment regimens asked from patients showed that nearly 94% assessed therapeutic effect moderate to good reflecting their satisfaction. Therefore, azithromycin is a long acting drug with minor side effects and high patient compliance. On the other hand,

it costs more than older antibiotics which is a compliance limiting factor in patients from lower economic levels. Results of the presents study and previous investigations demonstrated that azithromycin, a long acting macrolide, can be an acceptable alternative for the classic doxycycline in treatment of inflammatory acne and given the long half-life and low complications, it has higher patient compliance while its short-term effects are better than doxycycline.

Table.1 Frequency of gastrointestinal side effects in the study population

	Gastrointestinal side effects	
Type of therapy	Yes N (%)	No N (%)
Doxycycline	7 (11.7%)	53 (88.3%)
Azithromycin	2 (3.3%)	58 (96.7%)
Total	9 (7.5%)	111 (92.5%)

As shown on the table, gastrointestinal side effects are more frequently seen with doxycycline (11.7%) than azithromycin (3.3%).

Table.2 Frequency of dermatologic side effects in the study population

	Dermatologic side effects	
Type of therapy	Yes N (%)	No N (%)
Doxycycline	3 (5%)	57 (95%)
Azithromycin	1 (1.7%)	59 (89.3%)
Total	4 (3.3%)	116 (96.7%)

According to the table, dermatologic adverse effects of doxycycline (5%) is higher than azithromycin (1.7%), however. No patients demonstrated neurologic side effects.

Table.3 Comparison of patients' evaluation about their treatment in the two groups

	Patients' evaluation			
Type of therapy	No improvement	Mild improvement	Moderate improvement	Good improvement
Doxycycline	2 (3.3%)	2 (3.3%)	24 (40%)	32 (53.3%)
Azithromycin	1 (1.7%)	2 (3.3%)	27 (45%)	30 (50%)
Total	3 (2.5%)	4 (3.3%)	51 (42.5%)	62 (51.7%)

Accordingly patients' evaluation of treatment is moderate to good in 95% of patients in azithromycin group and 93.3% of patients in doxycycline group and the difference isn't significant.

Table.4 Comparison of mean final score of the patients at the end of first,
second and third months of treatment

	Baseline	First month	Second month	Third month
Doxycycline	24.35	17.27	11.60	6.52
Azithromycin	24.92	15.9	9.88	6.15

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