

The efficacy, safety and tolerance of azithromycin pulse therapy in papulopustular acne in Iraqi patients.

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Mazin Hamed, Ahmed Abdul-Aziz*, Abdulla Salah**

Tikrit University, College of Medicine, Department of medicine ,dermatology*.

Tikrit teaching hospital**

Abstract

Objective: to assess efficacy, safety, and tolerance of azithromycin in acne. *Methods:* open-label non-comparative therapeutic study of 500 mg of azithromycin thrice weekly for 8 weeks in treatment of moderate-sever papulopustular facial acne in Iraqi patients. Patients were examined by two dermatologists and a full count of lesions, we used special grading system of papulopustular acne .The lesions were counted at the beginning of the treatment (baseline, day 1) and at weeks (2,4,8). The difference between the number of lesions at baseline and in subsequent visits was used to evaluate the efficacy of therapy. A difference equal to or greater than 50 % was considered "good-excellent", 20 – 50% "moderate," and < 20 % "poor".No topical therapy was associated. All patients were also evaluated at 2 months, post-treatment follow-up visit. 74 patients were enrolled (11-27 years) with moderate-sever papulopustular acne. (72%) had excellent response, (12%) moderate response, (16%) poor response. The pustular inflammatory acne responded more dramatically, while the comedonal lesions more resistant. No serious side effects were noticed. After the 8th week, patients advised to stop azithromycin and followed up for 2 months. *Conclusions:* azithromycin pulse therapy is safe, effective and tolerable antibiotic for mild-moderate inflammatory acne with very few side effects.

Introduction

Acne vulgaris is a common inflammatory disorder of the pilo-sebaceous follicles. It is a multifactorial disease and its pathophysiology centers on the interplay of follicular hyperkeratinization, colonization with *Propionibacterium acnes* (PA), increased sebum production, and inflammation. This disease has a high prevalence, occurring mainly in adolescence. Although the peak of prevalence is around the 17th year of life, acne lesions can appear earlier and are not uncommonly observed in the age group ranging from 12 to 14 years, in which the condition is under reported⁽¹⁾

Antibiotic therapy has long been found useful in the management of moderate-to-severe acne vulgaris. Mechanisms of action include suppressing growth of PA, reducing the production of inflammatory mediators, and acting in immunomodulation⁽²⁾. Commonly prescribed antibiotics include tetracyclines, doxycycline, minocycline, limecycline and erythromycin⁽³⁾.

Azithromycin is an orally administered macrolide that has a wide spectrum of activity.

It is characterized by rapid and extensive uptake from the circulation into intracellular compartments following oral administration and by a long half-life (t_{1/2} 50h). The drug remains in the tissues for prolonged periods, from 2 to 4 days, at levels higher than the minimum inhibitory concentration for many common pathogens^(4, 5), making azithromycin a promising alternative to conventional antibiotics.

This pharmacokinetics allow for shorter dosing schedules because of prolonged tissue levels. The efficacy of azithromycin for the treatment of skin and soft tissue infections in adults and children is well established. The unique pharmacokinetics of azithromycin makes it a suitable agent for the treatment of acne⁽⁶⁾.

We performed open-label, non-comparative study, using an 8-weeks pulse-therapy regimen in patients who were not currently using any other topical or systemic treatment.

Patients and methods

The primary focus of this open-label non-comparative therapeutic study was to assess

the efficacy, safety, tolerability and compliance of 500 mg of azithromycin thrice weekly (once on every other day) for 8 weeks in the treatment of moderate-sever papulopustular facial acne in Iraqi patients.

This study enrolled 74 patients from the out-patient dermatology clinic at Tikrit teaching hospital during the period from July 2008 to April 2009. Patients were examined by two dermatologists and an assessment was made, including a full count of papular and pustular lesions, we used special grading system of papulopustular acne⁽⁷⁾ (table 1). The lesions were counted at the beginning of the treatment (baseline, day 1) and at weeks (2,4,8). The difference between the number of lesions observed at baseline and the number seen in subsequent examinations was used to evaluate the efficacy of therapy. A difference equal to or greater than 50 percent was considered "good-excellent", between 20 and 50 percent "moderate," and less than 20 percent "poor" (table 2).

At every check-up we assessed the clinical response to azithromycin, any adverse events, and patient tolerance.

The exclusion criteria were pregnancy, a history of macrolide sensitization and retinoid therapy. Patients with relapsing acne previously treated with antimicrobials such as doxycycline, minocycline, and erythromycin were eligible to be enrolled in the study after a six-month wash-out period. No topical therapy was associated. Patients were advised not to undergo any beauty procedures, such as chemical peels, bleaches during the study period.

All patients were also evaluated at 2 months, post-treatment follow-up visit.

Results

At this open therapeutic trial 74 patients were enrolled (34 males, 40 females) all of them were teenagers and adolescents (ages 11-27 years) with moderate-sever papulopustular acne. About 20 of them defaulted after the first visit for unknown reasons and another 4 patients after the second visit. The response was relatively low in the second visit but more prominent at the third visit and later on (fig. 1). Of the 54 patients who were seen after 2 weeks

18(33.3%) patients achieved good-excellent response, 24(44.4%) patients had moderate response, 12 (22.2%) patients had poor response. At the second visit 35(64.8%) had excellent response, 11(20.3%) moderate response and 8 (14.8%) poor response. At the third visit 4 patients defaulted, 50 completed the study, of them 36(72%) had excellent response, 6(12%) moderate response, 8(16%) poor response (table 3). The pustular inflammatory acne responded more rapidly and dramatically, while the comedonal lesions show more resistance. The response was noticed at equal ratios at different sites of the face. No serious side effects were noticed. Post-inflammatory hyperpigmentation seen in 4 (7.4%) patients, acne scarring (both old and new) was seen in some patients.

Six patients reported to have early flair during the course of therapy with eruption of new pustules which later on subsided. The response rate was initially slow but accelerated with continuation of therapy. After the 8th week, patients advised to stop azithromycin and followed up for 2 months, only four patients (8 %) developed few papules and pustules on the face (relapse).

Discussion

Acne is multifactorial disease primarily of teenagers with follicular plugging and inflammation. It is the most common skin disease; affecting almost every individual during puberty.⁽⁹⁾

Despite the initially high default (expected in our community and circumstances, and this could be partially explained by the delayed response of acne lesions), the response rate and compliance of our patients was encouraging. But the compliance was much improved in those who continued treatment and noticed a desirable response. Also the easy dosing schedule and the higher tolerability of the drug contributed to this compliance. The use of mobile phone for communication had helped us greatly in follow up and to encourage patients continue treatment. The side effects reported were few (gastric upset, abdominal pain, diarrhea and headache) and fortunately, no serious reaction reported. Our patients achieved a lower response (72%

excellent&12%moderate) than that reported by Federico who reported a good-excellent response of 90.4% after 4 weeks of therapy⁽⁸⁾ and slightly higher than Singhi who reported a response of 70.25 %⁽¹⁰⁾. Gruber et al⁽¹¹⁾ compared azithromycin with minocycline and observed a satisfactory clinical response (70-75%) with both the drugs. These findings suggest that azithromycin is a better alternative in patients with moderate to severe acne and has no serious side effects. This study showed that azithromycin has greatest advantage over other systemic antibacterials in acne because it is long acting drug and can be used in single dose three times weekly, no other acne drug has this property. Another advantage is the relatively long disease-free period after discontinuation of therapy which may be explained by the fact that azithromycin persists in tissues for long period^(4,5). The drawback of this study is that it is open-labeled non comparative, but it threw alight to the tolerability, efficacy and safety of this drug in acne, since till now it is not so widely used in Iraq and we expect the chance of *Propionibacterium acnes* resistance to be much lower than to other systemic antibacterials used for acne. The stability of azithromycin in gastric acid may be responsible for the low incidence of gastrointestinal disturbances which is very troublesome in the tetracyclines. Photosensitivity not reported in any patient, though we used the drug during summer season. This is another advantage of azithromycin over other antibacterials used in acne. Proper patient selection is mandatory as patients with inflammatory acne responded better than those with comedonal acne because the mode of action of azithromycin is mainly antibacterial and anti-inflammatory, but not keratolytic. Further studies are required to identify the optimum dose and duration of therapy and to compare the efficacy of the drug with other systemic antibacterials.

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Table (1): Severity grading of inflammatory acne. (Hapif)

<i>Severity</i>	<i>Papule /pustule</i>	<i>Nodules</i>	<i>Additional factors of severity</i>
Mild	Few-several	None	Psychosocial circumstances
Moderate	Several-many	Few-several	Occupational difficulty
Severe	Numerous	Many	Inadequate therapeutic response

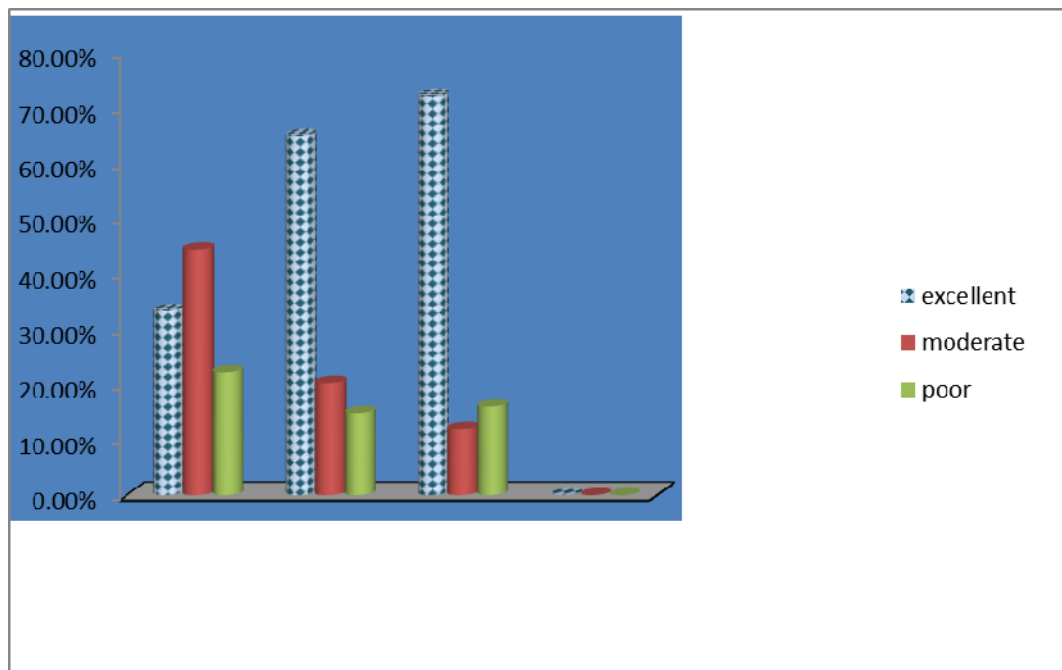
Table (2): Grading scale of acne response to evaluate efficacy of therapy.

Grade of response	% of reduction of acne
Excellent(good)	> 50
Moderate	20-50
Poor(irresponsive)	<20

Table (3): Response to treatment as a percentage of reduction in mean lesional count.

Response to treatment	Poor (Less than 20 %)	Moderate (20-50 %)	Good-excellent (More than 50%)
Week 2	22.2%	44.4%	33.3%
Week 4	14.8 %	20.3 %	64.8%
Week 8	16 %	12 %	72%
Follow up after 2 months	Only 4patients relapsed (8%)		

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2weeks 4weeks 8weeks
Fig 1 the response rate at the three visits