

Efficacy and Safety of Combined Isotretinoin and Azithromycin for Treatment of Severe Nodulocystic Acne

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ABSTRACT

Background: A combination of azithromycin & isotretinoin has been used for treatment of Severe nodulocystic acne before, however, an optimal scheduled doses regimen of such combination remained to be elucidated.

Objectives: To evaluate the effectiveness, safety and tolerability of using a new combination of fixed low doses of isotretinoin and azithromycin in an alternative days regimen in treatment of severe nodulocystic acne in Iraqi patients.

Patients and Methods: A prospective open-labeled clinical study in which 54 young adult and adolescent patients with severe nodulocystic acne were recruited for the study at the Department of Dermatology in Basra General Hospital during from May-October 2015. The patients were received a combination of fixed dose of isotretinoin 20 mg thrice weekly and 500 mg azithromycin given orally thrice weekly on alternating days and one day off for 12 weeks. The participants was assessed before, during and after treatment. The calculation of percentage and scoring of reduction of acne lesions was also carried out.

Results: There was a marked reduction in the inflammatory lesions at the first 4 weeks of the treatment, with a significant clearance of 38.4% of the papular lesions, 63.5% of pustular and 43% of the nodular lesions. At the end of the study, there was a significant reduction in the number of the inflammatory lesions, with the clearance of 76% of the papules, 96% of the pustules and 86% of the nodules. The most frequent adverse effects reported was dryness of face and lips.

Conclusion: Fixed dose of azithromycin 500 mg combined with isotretinoin 20 mg on alternating day regimen proved to be effective, safe & well tolerated regimen for treatment of severe nodulocystic acne with high score of patient satisfaction.

Keywords: Isotretinoin, Azithromycin, Acne

فعالية وامان عقاري الايزوتريتينوين والازثرومايسين الفموي كعلاج لمرض حب الشباب الشديد التكييسي عند المرضى العراقيين
الخلفية: بالرغم من فعالية عقاري الايزوتريتينوين والازثرومايسين كعلاج لمرض حب الشباب الشديد التكييسي الا ان تحديد الجرعة المناسبة لكلا العقارين بحاجة الى توضيح وتحديد اكثر.

اهداف البحث: تقييم فعالية وامان عقاري الايزوتريتينوين والازثرومايسين بجرع ثابتة ومحددة كعلاج لمرض حب الشباب الشديد التكييسي عند المرضى العراقيين.

طريقة اجراء البحث والمرضى: دراسة مستقبلية غير مقارنة شملت ٥٤ مريضا مصابا بمرض حب الشباب الشديد التكييسي، اجريت الدراسة في مستشفى البصرة العام للفترة من مايس ولغاية تشرين الاول ٢٠١٥. اعطي المرضى جرع ثابتة من الايزوتريتينوين ٢٠ ملغم ثلاث مرات اسبوعيا بالتناوب مع الازثرومايسين ٥٠٠ ملغم ثلاث مرات اسبوعيا. تم تقييم الاستجابة للعلاج شهريا بواسطة حساب نسبة اختزال اعداد الآفات الجلدية مع تسجيل اي اثار جانبية مصاحبة.

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النتائج: كان هناك اختزال واضح في اعداد ونسب الآفات الجلدية ابتداءً من نهاية الشهر الاول لبدء العلاج حيث انخفضت نسبة الحطاطات الى ٣٨.٤ % ونسبة البثور الى ٦٣.٥ % والتكيسات بنسبة ٤٣%. في نهاية الدراسة كان هناك انخفاض بنسبة ٧٦% في الحطاطات، ٩٦% بنسبة البثور و ٨٦% بنسبة التكيسات. كان جفاف الجلد والشفتين هي الآثار الجانبية الأكثر تسجيلًا.

الاستنتاجات: ان عقاري الازثروميسين بجرعة ٢٠ ملغم ثلاث مرات اسبوعيا بالتناوب مع الازثروميسين بجرعة ٥٠٠ ملغم ثلاث مرات اسبوعيا علاجًا فعالًا وامينا لمرض حب الشباب الشديد التكييسي

INTRODUCTION

Acne is a chronic inflammatory disease of the pilosebaceous units. It is characterized by seborrhea, the formation of opened and closed comedons, erythematous papules, pustules and in more severe cases nodules, deep pustules and pseudo cysts. In some cases, it is accompanied by scarring.^[1] The sites of predilection are the face, upper trunk, and upper arms. Acne vulgaris is a disease of adolescents with 90% of all teenagers being affected by some degree. It may begin in the twenties or thirties, or may persist for many years.^[2] In general, there are four major principles governing the therapy of acne: correcting the altered pattern of follicular keratinization, decreasing sebaceous gland activity, decreasing follicular bacterial population & producing an anti-inflammatory effect^[1,3]. Moderate to severe acne resistant to topical antibiotic or acne which covers a large portion of the body surface may be best treated with systemic antibiotic.^[4] Azithromycin, a macrolide antibiotic has been reported to be a safe and effective alternate treatment of moderate to severe inflammatory acne.^[5] The drug bind irreversibly to a site on 50S subunit of the bacterial ribosome, thus inhibiting the translocation steps of protein synthesis. They may also interfere at other steps, such as transpeptidation.^[6] Oral isotretinoin is indicated for 'severe forms of acne resistant to adequate courses of standard therapy with systemic antibacterial and topical therapy & because of its adverse effects, the dose is commencing more cautiously with 0.5 mg/kg for the first month and then to increase as tolerated up to 1.0 mg/kg for a further 12–16 weeks.^[7,8] The

treatment of severe nodulocystic acne is often difficult & in most instances the disease required combined therapy with a high risk of scarring & other disfiguring complications. Recently, the synergistic effect of combination of low dose isotretinoin & pulsed oral azithromycin was used to treat moderate to severe acne with successful results^[9], however, an optimal scheduled doses with a more convenient regimen that increases patient compliance & adherence to treatment protocol & minimizes the risks of dose related adverse effects is needed, therefore, we sought to evaluate the efficacy, safety and tolerability of using a combination of fixed doses of isotretinoin and azithromycin in an alternating days regime for treatment of severe nodulocystic acne in Iraqi patients.

PATIENTS AND METHODS

A prospective, open-labeled, clinical study designed to assess the efficacy, safety and tolerability of a suggested new combination of a fixed dose of isotretinoin 20 mg thrice weekly (taken at Saturday, Monday & Wednesday) and 500mg azithromycin given orally thrice weekly (on Sunday, Tuesday & Thursday) on alternating days and day off (Friday) for 12 weeks in the treatment of severe nodulocystic acne in adolescent and young adult Iraqi patients. A total of 54 young adult and adolescent patients with severe nodulocystic acne patients with grade 4 and 5 acne according to the US FDA global score.^[10] Those who completed the study period were included in this trial, their ages ranged from 15-29 years with a mean age 20.9 ± SD 3.4 years. Eligible patients

were informed about the nature of the study and a written informed consents were obtained from them.

US FDA global acne score system: ^[10]

- 0 = Normal, clear skin with no evidence of acne vulgaris
- 1 = Skin is almost clear: rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
- 2 = Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulo-cystic lesions)
- 3 = Non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be one small nodulo-cystic lesion
- 4 = Inflammatory lesions are more apparent: many comedones and papules/pustules, there may or may not be a few nodulo-cystic lesions
- 5 = Highly inflammatory lesions predominate: variable number of comedones, many papules/pustules nodulo-cystic lesions.

The main exclusion criteria were: uses of topical acne treatment in the last three months, history of macrolides sensitization, pregnant patients & those patients who had an abnormal laboratory tests findings at the baseline. Only topical rinse-off cleaners were allowed during follow up period. Married women were advised to avoid any oral medications & to undertake strict contraceptive measures whilst on treatment. Baseline investigations included: complete and differential blood counts, liver function test, renal function test, complete lipid profile and urine pregnancy test for married females were done & were repeated every month for the whole duration of treatment. The efficacy of the combination treatment was assessed by counting the number of inflammatory and non-inflammatory acne lesions at the involved sites (face, upper chest, upper back and shoulders)

initially at the baseline visit and at 4 weekly intervals for 12 weeks. The response to treatment was assessed by the following parameters:

- 1- Counting the mean number of acne lesions at different treatment periods and estimating the significance of difference between these means by paired t-test using SPSS version 17.
- 2- Calculation and comparison of the percentage of reduction in the number of inflammatory lesions before and at the end of the trial (12 weeks)
- 3- Grading the response according to the percentage of total reduction in inflammatory lesions as follows: $\geq 80\%$ = excellent, 60%-79%= good response, 40% - 59% = moderate & $< 40\%$ = poor

Any adverse effects were reported at each visit. The degree of patient satisfaction was also assessed at the end of the trial by using 4 points satisfaction scale as follows:- 3: very satisfied, 2:satisfied, 1: slightly satisfied, 0: unsatisfied.

RESULTS

The ages of participants were ranged from 15 to 29 years (20.9 years, ± 3.4 years); male to female ratio was 0.89:1; the mean duration of the disease was 2.9 ± 1.6 years. Considering the clinical response to treatment, there was a marked and significant reduction in the number of comedons and the inflammatory lesions during the first 4 weeks of the treatment in which the mean number of popular lesions was reduced from 22.69 at the baseline to 14.48, similarly postural, nodular, cystic and comedon lesions were also reduced significantly from baseline 16.57, 10.69, 4.58 and 15.09 to 6.50, 5.61, 3.04 and 10.1 respectively, (Table-1) ($P < 0.05$). There were clearance of 38.35% of the popular, 63.48% of the postural, 43.18% of the nodular, 35.63% of the cystic and 36.1% of the comedonal lesions at the end of first month of the treatment. At the end of the trial, there was further marked and significant reduction in the

number of lesions compared to baseline, with the clearance of 76% of the papules, 95.8% of the pustules, 86.2% of the nodules, 85.4% of the cysts and 79.6% of the comedons. (Table-1).

Table 1. Mean number & percentage of the reduction of inflammatory lesions at baseline, during & the end of the trial.

Duration	Papules No. (%)	Pustules No. (%)	Nodules No. (%)	Cysts No. (%)	Comedons No. (%)
Baseline	22.69 (100.0)	16.57 (100.0)	10.69 (100.0)	4.58 (100.0)	15.09(100.0)
4 weeks	14.48* (38.35)	6.50* (63.48)	5.61* (43.18)	3.04* (35.63)	10.1* (36.1)
8 weeks	7.85* (65.34)	2.33*(88.34)	3.06* (70.9)	1.32* (74.47)	5.36* (66.25)
12 weeks	5.50* (76.0)	1.02* (95.8)	1.43* (86.2)	0.64* (85.4)	3.84* (79.6)

* P<0.05 Significant when compared with the baseline

Grading the response to treatment at the end of the trial, there was a remarkable clearance of the inflammatory lesions in the majority of the patients and 92.6% of them showed good to excellent response, 7.4% moderate response and none of our patients showed poor response to treatment (Table-2). All the involved sites including face, chest, back and shoulders were responded equally to the treatment leaving behind either trace of pigmentation or atrophic scarring (Fig 1,2,3,4,5&6). Adverse effects were reported in all patients and these include: dryness of the face and lips in 53 (98.1%), chellitis in 33 (61.1%) mild abdominal pain in 16 patients (29.6%) and diarrhea in 3 (5.6%) (Table-3).

Table 2. Scoring the response according to percentage of total reduction of the inflammatory lesions

Percentage of reduction	Number of patients	Percentage
≥ 80% reduction (excellent)	25	46.3
60%-79% reduction (good)	25	46.3
40%-59% reduction (moderate)	4	7.4
< 40% reduction (poor)	0	0%

Table 3. Adverse reaction s of azithromycin and isotretinoin therapy(at the end of 12 weeks)

Adverse reactions	Number of patients	Percentage
Dryness of face & lips	53	98.1
Cheilitis	33	61.1
Mild abdominal pain	16	29.6
Diarrhea	3	5.6

N.B: more than one side effect may be seen in the same patient.

The most common unavoidable side effects was dryness of face and lips and & it was mild and did not necessitate cessation of treatment. No significant laboratory abnormality was reported during follow up period. Regarding patient satisfaction at the end of the treatment course (12 weeks), the results demonstrated that 36 patients were very satisfied with the treatment (66.6%), 10(18.5%) patients were scoring satisfied, 6(11.1%) patients were slightly satisfied & only 2 patients (3.7%) were unsatisfied with the results, (Table-4).

Table 4. Patients distribution according to satisfaction score

	Number of patients	Percentage of patients
Scale 3:very satisfied	36	66.6
Scale 2:slightly satisfied	10	18.5
Scale 1: satisfied	6	11.1
Scale 0:unsatisfied	2	3.7



Fig 1. Nodulocystic acne before treatment



Fig 2. Same patient in figure 1 after treatment



Fig 3. Patient with severe acne before treatment



Fig 4. Same patient in figure 3 after treatment



Fig 5. Women with sever acne before treatment



Fig 6. Patient in figure 5 after treatment

DISCUSSION

Acne is a widespread dermatological problem that affects mainly adolescents and grownups.^[11] The treatment of severe acne in many occasions is considered as a therapeutic challenge to the treating physician because of the long term use of drug therapy, the inevitable adverse effects of these drugs & the high risk of disfiguring physical & psychological scarring. However, the choice of proper treatment is also influenced by the severity of the cases, i.e. mild to moderate acne lesions are usually well controlled by topical preparations with or without additional systemic antibiotic while the treatment of severe acne including nodulocystic type with topically applied drugs are not effective, hence systemic drugs always should

be considered.^[12,13] The result of our study confirms the effectiveness and tolerability of combined oral azithromycin given orally thrice weekly on alternating days and low dose oral isotretinoin thrice weekly in the treatment of severe nodulocystic acne with minimal side effects,. The study demonstrated a good to excellent response in more than 90% of patients & with a significant reduction of the inflammatory lesions count that was observed especially in the first four weeks. Interestingly the pustular lesions were responded earlier, within the first 4 week, than other inflammatory lesions. This observation was similarly reported in other studies.^[9,14] The use of combination of low dose isotretinoin & oral azithromycin

pulses for treatment of severe acne was firstly reported by De D et al ^[9] & where found to be an effective regimen and has an acceptable side effects and low post-treatment relapse rate. In our study we demonstrated similar findings, however, we suggested that an alternating days regimen instead of fixed daily doses would be more convenient & more tolerable regimen, subsequently, this will further increases the patient's compliance and adherence to the treatment protocol and eventually will ensure a good response to treatment. The other advantage of this regimen was to use a fixed doses of both azithromycin and isotretinoin regardless the age and weight of patients depending on the extreme variability of the recommended dosing of isotretinoin for severe acne in the published literatures & it was ranging from 0.1mg/kg/day to 1.0mg/kg/day.^[15] Even more, the total cumulative dose of isotretinoin in our study was 720 mg which was much lower than the recommended conventional doses^[16,17], In addition, most of the studies demonstrated that there was no significant difference in the improvement of acne by the end of the treatment course between doses of 0.5 and 1.0 mg/kg/day^[18,19], and the low dose of isotretinoin was comparably as effective as the conventional dosing in the treatment of acne with few drug related side effects. thereby leading to improved tolerability and increased patient satisfaction.^[12,20] The therapeutic advantage of combined treatment was further supported by the well documented effectiveness & safety profile of azithromycin for acne in the published studies.^[5,21] Fewer side effects were reported by treatment regimen and mostly was related to unavoidable adverse reactions of isotretinoin and these were well tolerated & did not necessitate the cessation of treatment. In Conclusion, fixed dose of azithromycin 500mg combined with isotretinoin 20 mg on alternating days prove to be effective, well tolerated regimen for treatment for severe and nodulocystic acne with minimal unavoidable adverse reactions.

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