

# Beneficial Effect of Isotretinoin Gel As Adjunctive Treatment to Oral Azithromycin in the Management of Facial Acne Vulgaris.

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## ABSTRACT:

### BACKGROUND:

Acne is a multifactorial disease with multiple pathogenic factors, hence combination therapies are needed. Combination therapies using agents with complementary mechanisms of action increasingly are recognized as an effective strategy for treating acne.

### OBJECTIVE:

The rationale of utilizing topical retinoids with azithromycin in treating facial acne vulgaris will be highlighted, particularly in relation to improvement.

### METHODS:

A randomized, clinical trial was carried out at the outpatient Department of Dermatology and Venereology, Baghdad Teaching Hospital between April 2007 and August 2008.

A total of 48 patients with moderate to severe papulopustular acne vulgaris were allocated to two groups, azithromycin and azithromycin plus isotretinoin gel, both groups received Azithromycin for two months. Azithromycin 250 mg was prescribed every day for one month and every other day for the following month. Patients in second group were instructed to apply Isotretinoin gel 0.05% once daily over a 3 months treatment period. The clinical assessment was done by counting the number of inflammatory lesions in three occasions: baseline, two months and three months.

### RESULT:

After two months, both groups showed a statistically significant difference from the baseline in reducing inflammatory lesions and improving acne. Adding topical isotretinoin gel produced a higher percentage of reduction in their lesional counts, but differences between the two groups were not statistically significant. After three months, regression in the percentage of reduction of the lesional count from 57.7% to 32.4% in the first group. While in the second group the reduction was maintain in 69.8%.

### CONCLUSION:

Adding topical 0.05 per cent isotretinoin gel to oral azithromycin enhances and maintains the rate of improvement of facial acne vulgaris.

**KEY WORDS:** acne vulgaris, azithromycin, isotretinoin gel

## INTRODUCTION:

Acne vulgaris is an exceptionally common, chronic, and recurring disease. It is a disease of the pilosebaceous unit, involving abnormalities in sebum production, follicular epithelial desquamation, bacterial proliferation, and inflammation<sup>(1)</sup>. The major therapeutic agents are topical and systemic retinoids, antimicrobial agents, and systemic hormonal drugs.

Retinoids, first shown in the 1970s to be of value for treating acne, are derivatives of vitamin A that prevent comedone formation by normalizing desquamation of follicular epithelium. They are effective in both the treatment of inflammatory lesions and in the prevention of the formation of

comedones<sup>(2)</sup>. A topical retinoid should be the foundation of treatment for most patients with acne, because retinoids target the microcomedon, the precursor to all acne lesions. They may produce local irritation, increased sensitivity to sunlight, and exacerbation of inflammatory lesions<sup>(3)</sup>.

Systemic antibiotics used in acne vulgaris have both antimicrobial and anti-inflammatory properties. They reduce *P. acnes* within follicles, thereby inhibiting production of bacterial-induced inflammatory cytokines.<sup>(4)</sup> Tetracycline and erythromycin suppress leukocyte chemotaxis<sup>(5)</sup> and bacterial lipase activity<sup>(6)</sup> while minocycline and doxycycline inhibit cytokines and matrix metalloproteinases thought to contribute to inflammation and tissue breakdown.<sup>(7)</sup> The main systemic antibiotics used in acne vulgaris are

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tetracycline, doxycycline, minocycline, and erythromycin. Azithromycin is an orally administered antibiotic that has a wide spectrum of activity. It belongs to the azalide group of antibiotics and is closely related structurally to macrolides like erythromycin. It is more tissue stable, penetrates deeply into tissue and has a higher terminal half-life than erythromycin.

Many clinical studies showed that oral Azithromycin is effective and safe therapeutic in treating acne vulgaris. It is at least as effective as tetracycline or doxycycline in the treatment of acne<sup>(8) (9)</sup>.

Combination therapy is often employed when patients have a mixture of comedonal and inflammatory acne lesions. Because adequate clinical studies are lacking, it is difficult to compare various combination therapies.

The aim of the study is to evaluate the usefulness of adding topical 0.05 per cent isotretinoin gel to oral azithromycin in acne treatment.

### **PATIENTS AND METHODS:**

This study was conducted at the Out-Patients Department of Dermatology and Venereology, Baghdad Teaching Hospital in the period between April 2007 and August 2008.

A total of 46 patients with moderate to severe papulopustular acne vulgaris were included in the study. Women were excluded if they were pregnant, nursing, or planning a pregnancy

A full face count of papular and pustular lesions was done for each patient. The number of lesions was calculated at the beginning of the treatment (baseline, day 1), after two months and after three months. The difference between the number of lesions observed at baseline and the number seen in after two months and three months was used to evaluate the efficacy of the 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"<sup>(10)</sup>.

Patients were randomly assigned to receive azithromycin plus topical isotretinoin 0.1 percent gel, or Azithromycin alone. Isotretinoin is applied once daily in the evening after facial cleansing. Patients were requested to avoid excessive exposure to UV light.

Azithromycin 250 mg (Azitromed. Mediterranean Pharmaceutical Industries, Syria) was prescribed every day for one month and every other day for the following month. Patients in both groups were instructed to take Azithromycin for two months only. Patients in second group were instructed to apply isotretinoin gel 0.05% (Isotrex gel. Stiefel

Laboratories Ireland) once daily at night over a three months treatment period.

Statistical analyses were used in all parameters. Paired- T test was used to compare the mean of lesional count change resulting from treatment P- Values of less than 0.05 were considered significant.

Patients were seen regularly every two weeks for three months to assess the response of treatment and recording the side effects.

### **RESULTS:**

Patient's data:

Forty-eight patients with moderate to severe papulopustular acne vulgaris were included in the study to assess the therapeutic value of adding topical 0.05 per cent Isotretinoin gel to oral azithromycin.

Eight patients defaulted from the study for unknown reasons. Forty patients completed the study, their ages ranged between 15-26 years with a mean of  $18.8 \pm 2.5$  years, with 20 patients in each group as follows: Group treated with azithromycin alone, it included 12 females and 8 males, their ages ranged from 15-25 years with a mean  $\pm$ SD of  $18.3 \pm 2.1$  years. The second group treated with azithromycin plus Isotretinoin gel, it consisted from 11 females and 9 males, their ages ranged from 15-26 years with a mean  $\pm$ SD of  $19.4 \pm 2.9$  years.

Comparison between the two groups regarding their ages, lesional count before therapy showed that there was no statistical significant difference.

The assessment of mean  $\pm$ SD of lesional count before and after treatment was as follow: group treated with azithromycin only, the mean base line was  $24.7 \pm 5.2$  reduced to  $10.4 \pm 5.4$  reaching 57.7% as a percentage of reduction after two months. After three month the mean of the lesional count was  $16.7 \pm 7.2$ , while in the second group the mean base line was  $26.1 \pm 5.5$  reduced to  $7.2 \pm 5.3$  reaching 72.3% as a percentage of reduction after two months. After three months the mean of the lesional count was  $8.3 \pm 5.9$ .

After two months, both groups showed a statistically significant difference from the baseline in reducing inflammatory lesions but differences between the two groups were not statistically significant. The clinical assessment of the patient's response to treatment in the two groups is shown in table (1). After three months the comparison between the two groups revealed a regression in the percentage of reduction of the lesional count from 57.7% to 32.4% in the first group. While in the second group the reduction was maintain in 69.8%.

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Few adverse events were considered to be treatment-related. An irritant dermatitis occurred in three patients using Isotretinoin gel but was well tolerated by them. Four patients had gastrointestinal disturbances in the form of heartburn and nausea.

### DISCUSSION:

Acne is an extremely common skin condition, and despite not directly endangering life it can have a devastating physical and psychological effect on the lives of vulnerable adolescents.

In acne vulgaris, most therapeutic combinations were superior to monotherapy. However there is no fixed regimen for every patient and the determination of this combination depend on the physician experience and the clinical state of the patient. Tolerance of drug and compliance of patient are also acting as limitation factors.

Many combinations can be suggested and further studies are needed to reach the optimal therapy for each acne patient.

This study confirmed that Azithromycin alone is a safe and effective treatment for acne vulgaris. Patient compliance was excellent and only four patients had gastrointestinal disturbances in the form of heartburn and nausea. The results in this clinical trial were agreeable with the previous studies<sup>(8)(9)(11)</sup>.

Combination therapy using retinoids plus antibacterial can treat existing acne lesions faster than the individual agents alone and can also prevent the development of new lesions. Retinoids have not only the typical potent comedolytic activity but also anti-inflammatory effects. When added to antibacterial therapy, topical retinoids demonstrate faster and significantly greater reduction of inflammatory acne lesions and comedones than antibacterial alone<sup>(12)</sup>. This study showed that adding topical isotretinoin 0.1 percent gel further enhance the improvement and increases

the percentage of reduction of leisonal count when evaluated after two months.

Topical retinoids, as isotritinoin 0.1 percent gel, normalize desquamation of the follicular epithelium, whereas antibiotics, as Azithromycin, inhibit the growth of P. acnes and the production of free fatty acids. So, therapeutic combination of both remedies decreases comedogenesis, bacterial growth, and inflammation, thus targeting three of the four pathogenic factors associated with acne.

Systemic antimicrobial agents currently used for the reduction of inflammatory papules and cysts require frequent administration and are sometimes associated with uncomfortable side-effects contributing to a decrease in compliance. Hence maintaining the improvement, achieved by antibiotic, by other means is needed and topical retinoids seem to be a good option. Isotretinoin gel 0.05% can be used alone for long-term maintenance to prevent the reemergence of comedones and inflammatory acne lesions and to spare the use of antibiotics, thus helping to reduce the risk of bacterial resistance.

Several controlled studies have provided clinical evidence about the efficacy of adapalene gel 0.1% monotherapy for maintenance<sup>(12)(13)</sup>. These studies show that topical retinoid therapy maintains or achieves further improvement after an initial combination regimen involving a topical retinoid plus antibiotic. In contrast, vehicle or no treatment is associated with a significant rate of relapse. This study showed that isotritinoin 0.1 percent gel as a topical retinoid monotherapy behave similarly in maintaining the improvement when compared to no treatment group.

This study demonstrates a clinical benefit of continued treatment with isotritinoin 0.1 percent gel, as an initial drug combined with antibiotic and as a maintenance therapy for acne.

**Table (1): The assessment of the patient's response to treatment in the two groups after two months therapy.**

Group	Good Response		Moderate Response		Poor Response		Total	
	No.	%	No.	%	No.	%	No.	%
Azithromycin	10	50	8	40	2	10	20	100
Azithromycin+ Isotritinoin gel	13	65	6	30	1	5	20	100

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