Research Article

Efficacy of isotretinoin alone and its combination with azithromycin in moderate to severe acne vulgaris: a comparative study

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Abstract

Introduction: Acne vulgaris is a multi factorial disease and represents a spectrum of disease severity from a couple of comedones and pustules to severe nodulocystic acne. Treatment therefore must be tailored with the goal of preventing physical and/or psychological morbidity. Isotretinoin is indicated for the treatment of acne vulgaris, however to minimize its adverse effects and improve the efficacy, it may be combined with antibiotics such as Azithromycin. **Objective:** A study was carried out to evaluate and compare the efficacy of isotretinoin alone and combination therapy with azithromycin for the treatment of moderate to severe acne. **Methods:** 120 patients of 15-25 years of age with moderate to severe acne vulgaris were enrolled at random. The lesions were classified on the basis of Pillsburry, shelly and Klingman grading system. 60 patients were treated with oral isotretinoin 0.5 mg/kg daily dose and remaining 60 patients were treated with same dose of isotretinoin along with oral azithromycin 500 mg/day for 3day/week. The number of lesions was calculated on day one and at biweekly interval thereafter for three months. The number of lesions observed on day one and the number detected in subsequent examination were used to evaluate the efficacy of therapy. **Results**: 91.66% (n=55) of the patients showed significant clinical improvement with combination treatment as compared to isotretinoin alone showing only 73.33% (n=44) clinical improvement. **Conclusion**: Isotretinoin itself provides significant relief but combined treatment with Azithromycin seems to be more effective.

Keywords: Acne, Azithromycin, Combination therapy, Isotretinoin.

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INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit that is seen primarily in adolescent with significant psychological and social impact. The four major factors responsible for Acne vulgaris are, increased sebum production, abnormal cornification of pilosebaceous duct, abnormality of the microbial flora and inflammation. Choice of treatment modalities depends mainly on the severity of acne and includes topical and systemic therapy. Commonly used topical agents are benzoyl peroxide, erythromycin, clarithromycin, clindamycin, tazorotene and retinoic acid etc. In systemic therapy commonly used drugs are Isotretinoin, Azithromycin, Doxycycline, Minocycline, Dapsone, Zinc sulphate and Clofazimine etc. Isotretinoin is indicated for cases of moderate to severe acne, unresponsive to conventional therapy. However the side effects caused by it, an idea of low dose isotretinoin therapy for Acne vulgaris is attractive and has been practiced by various authors[1,2,3,4] Azithromycin is one of the antibiotics that has been recently prescribed for treatment of acne and is at least as effective as doxycycline and minocycline[5,6,7,8.] Mechanisms of its action include suppressing growth of Propionibacterium. acne, reducing the production of mediators of inflammation, and acting on immunomodulation[9]. Although oral Isotretinoin continues to be the mainstay of acne therapy, Combination therapy with Azithromycin

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has been an essential part of dermatologists regimen for treating acne nowadays. However, only few studies are available in literature on combinational therapy, and its comparison with low dose isotretinoin in moderate to severe acne vulgaris. Hence a study was undertaken to compare the efficacy of Isotretinoin alone and its combination with Azithromycin.

MATERIAL AND METHOD

The present study was carried out in the Department of Dermatology, Venereology and Leprosy, of a Tertiary Care Center and Hospital, Jaipur. 120 patients attending OPD and diagnosed as a case of moderate to severe acne vulgaris from December 2012 to November 2013 were included in the study.

Inclusion Criteria

- Age above 15 years and of both sexes
- Patients having moderate to severe acne vulgaris
- A written consent for participation in the study

Exclusion Criteria

- Age less than 15 yrs
- Patients having mild facial acne vulgaris, papulopustular rosacea
- Married female, Pregnant women and women who intend to become pregnant during the course of treatment, lactating mothers.
- History of macrolide sensitization, having polycystic ovary.
- Presence of renal or hepatic derangement, pre-existing hyperlipidemia, past history of photosensitivity, allergic reaction to the prescribed drugs.
- Presence of a systemic disease.

The patients records were studied to compile the diagnostic and clinical data including a detailed history, age of onset, sex, duration of the disease, type of skin, and relation of the disease with diet, cosmetics used, secondary infection, premenstrual flare, pregnancy, solar radiation, stress and seborrhea was taken. History of similar disease or other skin disease in the family was recorded. Informed consent using purposive sampling technique was taken. In this prospective, comparable, time-bound study, the patients were divided into two groups of 60 patients each at random for purpose of treatment as follows:

(a) Group-A, treated with Oral Isotretinoin (0.5mg/kg/day) dose,
(b) Group-B, treated with Oral Isotretinoin (0.5mg/kg/day) and Azithromycin (500mg/day, in 3days a week) dose.

Initial-assessment of acne of the patient under good natural light was done using grading system as per Pillsburry, Shelly and Klingman (1956) as follows:

Grade 1 (mild): Comedones, occasional papules.
Grade 2 (moderate): Comedones, papules, few pustules.
Grade 3 (severe): Pustules, some nodules and abscess.
Grade4 (cystic): Mainly cysts and abcesses with or without widespread scarring.

Baseline investigations including complete blood cell counts, liver function tests, lipid profile and urine pregnancy test were done before starting the patient on isotretinoin and follow up investigations were carried out at the end of first and third month of treatment. Along with above drugs all patients advised not to apply any topical medicament or to undergo any beauty procedures, such as chemical peels, bleaches, facials, laser therapy and phototherapy during study period. Only topical rinse-off cleansers were allowed during follow-up.

Periodic Assessment

The response to treatment was evaluated on follow up at two weekly intervals. The efficacy of the drugs was assessed by lesion counts at each visit. The number of lesions were calculated on day one of the treatment and thereafter at biweekly intervals for three months. The difference between the number of lesions observed at baseline and the number detected in subsequent examinations was used to evaluate the efficacy of the therapy. On each follow up visit the response of Isotretinoin and Isotretinoin with Azithromycin were recorded according to type of lesions (grading) and reduction in the number of lesions on follow up at two week intervals as follows:

(a) Reduction more than 90%, as excellent response.
(b) Reduction between 60-90%, as good response.
(c) Reduction between 30-60%, as fair response.
(d) Reduction less than 30%, as poor response.

The adverse effects of Isotretinoin and Isotretinoin with Azithromycin were recorded. The results were evaluated and compared in following parameters like inital response, duration of treatment, and adverse effects. Also the laboratory results were evaluated in the beginning at the end of one month and on completion of treatment. The results of group-A and B were be analysed and compared for the improvement at the end of 1st, 2nd and 3rd months. The data was analysed by student "t" test, Paired "t" test and by Chi Square Test.

OBSERVATION AND RESULTS

One hundred twenty adolescent patients were enrolled. Two groups of 60 patients each i.e Group-A and Group-B, were formed. In Group-A, 42 males (70%) and 18 females (30%) were enrolled, while in Group-B, 43 males (71.66%) and 17 females (28.34%) were enrolled at random. The age ranged from 15 to 25 years in both

groups. All suffering from moderate to severe cystic acne. In Group-A, moderate acne (n=9), severe acne (n=26), cystic acne (n=25) and in Group-B, moderate acne (n=10), severe acne (n=26), cystic acne (n=24) cases. **Table-1** represents the demographic data and disease characteristics. The results in **Table-2** reflects that forty four patients (73.33%) in Group-A and fifty five patients (91.66%) in Group-B showed improvement within 12 weeks, with a significant reduction in their inflammatory papulo-pustular lesions. Maximum clearance was observed at the end of 12 weeks. In Group-A, 15 showed "excellent response", 25 showed "good response" 4 showed "fair response", 15 showed "poor response" and one patient had "no response". In Group-B, 17showed "excellent response", 31 showed "good response" 7 showed "fair respone", and 5 showed "poor response", characterized by slow clearance with new eruptions. Pustular lesions showed a major degree of clearance, but comedones persisted for longer period. All sites showed almost equal degree of clearance. Adverse effects, such as chelitis, xerosis, erythema of face, redness of eyes, dryness of mouth, insomnia, headache were more common in Group-A patients, with significant reduction in Group-B patients. These patients were advised to use the antacid after meal and vitamin-E daily. This successfully alleviated the symptoms. All patients completed the 12 weeks study period.

Table 1: Demographic profile and group characteristics

Total enrolled patients(n=120)	Group-A(n=60)	Group-B(n=60)
Treatment prescribed to patients	Isotretinoin(0.5mg/kg/day)for 12 weeks	Isotretinoin(0.5mg/kg/day)plus Azithromycin 500mg/day for 3 days a week dose for 12 weeks
Sex distribution		
Male	42(70%)	43(71.66%)
Female	18(30%)	17(28.34%)
Age distribution(15-25yrs)		
15-20yrs	34(56.77%)	17(28.33%)
20-25yrs	26(43.44%)	43(71.64%)
Regional distribution		
Urban	48(80%)	47(78.33%)
Rural	12(20%)	13(21.67%)
Disease duration		
< 1yrs	20(33.33%)	18(30%)
1-3yrs	30(50%)	29(48.33%)
>3yrs	10(16.64%)	13(21.64%)
Severity of acne		
Moderate	9(15%)	10(16.67%)
Severe	26(43.33%)	26(43.33%)
Cystic	25(41.67%)	24(40%)
Type of skin		
Oily	38(63.33%)	29(48.33%)
Dry	11(18.33%)	11(18.33%)
Normal	11(18.33%)	20(33.34%)
Relationship to occupation		
Student	45(75%)	38(63.33%)
Housewife	4(6.67%)	9(15%)
Service/Business	11(18.33%)	13(21.67%)
Relationship to Family		
Present	29(48.33%)	22(36.66%)
Absent	31(51.67%)	38(63.34%)
Relationship with personality disorder		
Shame	36(60%)	35(58.33%)
Anger	35(58.33%)	34(56.66%)
Lack of confidence	21(35%)	23(38.33%)
Impair social contact	32(53.33%)	35(58.33%)
History of previous treatment		
Oral	14(23.33%)	16(26.66%)
Topical	10(16.66%)	8(13.34%)
Oral + Topical	9(15%)	19(31.66%)
No treatment	27(45%)	17(28.33%)

Table 2: Clinical response to treatment as a percentage reduction in lesion count in Group-A and Group-B patients at 12weeks of treatment

Clinical response to treatment	Group-A	Group-B
Excellent response	15(45%)	17(28.33%)
Good response	25(41.66%)	31(51.66%)
Fair response	4(6.66%)	7(11.66%)
Poor response	15(25%)	5(8.22%)
No response	1(1.67%)	None
Adverse effects		
Cheilitis	33(55%)	15(25%)
Xerosis	26(43.33%)	18(30%)
Erythema	7(11.67%)	4(6.67%)
Gastrointestinal disturbances	None	6(10%)
Laboratory Investigations		
Levels of serum cholesterol and triglycerides	Raised(5%)	Not significant(4%)
Levels of serum liver enzymes	Elevated (4%)	Less elevated(2%)

Figure 1: Before treatment

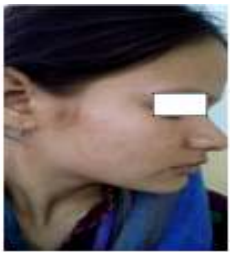

Figure 2: After treatment (Group-A)

Figure 3: Before treatment

Figure 4: After treatment (Group-B)

DISCUSSION

Acne vulgaris is a common dermatological problem that mostly affects adolescents. The disorder has serious psychosocial impact on the sufferers. The choice of the proper treatment is determined by the severity and extent of the problem. In moderate-to-severe acne, systemic treatment is required in most cases, using antibiotics, hormonal therapy, and oral retinoids[10,11,12]. As a first line of systemic treatment in adolescence most researchers recommend the use of oral retinoids. Isotretinoin has revolutionized the treatment of acne. A number of workers have also indicated high efficacy of azithromycin, because of its unique pharmacologic properties. 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[13,14]. The present study was undertaken to compare efficacy of treatment with Isotretinoin alone and Isotretinoin in combination with Azithromycin, in moderate to severe acne vulgaris. Two groups of 60 patients each i.e. Group-A (Isotretinoin alone) and Group-B (Isotretinoin with Azithromycin) were formed and regular treatment was given for 12 weeks and response was noted at every 2 weeks for next 12 weeks.

Age of Onset

Patients were of 15 to 25 years age group as acne is most commonly seen in adolescents. In a study by Bork BM *et al* in 1984, most of the patients belonged to 16-23 years of age group, which is comparable to our study. Difference in the age group with the different authors may be explained on the basis of geographical and racial distribution.

Sex Distribution

In Group-A, 70% (42 patients) were males and 30% (18 patients) were females, while in Group-B 71.66% (43 patients) were males and 28.34% (17 patients) were females. Bloch and Hamilton in 1964 also noted that males had more common and more severe form of acne as compared to the females and attributed it to more androgen secretion by males.

Duration of Disease

In Group-A , 33.33% had disease duration less than 1 year, 50% had disease duration from 1 to 3 years and 16.64% cases had disease for more than 3 years. In Group-B, 30% had disease duration less than 1 year, 48.33% had disease duration from 1 to 3 years and 21.64% cases had disease for more than 3 years. Most of the patients had duration of 1-3 years. These patients were mainly males and had severe acne which may be the reason for early consultation.

Occupation

Most of the patients were students (75%), followed by business and service class (18.33%) and housewife (6.67%) in Group-A. In Group-B 63.33% were students, followed by business and service class (21.67%) and then housewife (15%). It may be due to large student

population in and around the area of study and common age group for acne patients.

Type of Skin

In the present study most of the patients (63.33% in Group-A and 48.33% in Group-B) had oily skin. Excessive oiliness has been related to hyperplasia and increased secretions of the sebaceous glands in a study done by Klingman AM and Shelly. Both males and females acne patients averagely secreted more sebum than normal subjects. The levels of secretion correlate well with the severity of acne (Burton JL, Shuster S 1971).

Distribution of the Acne

In our patients face was involved in all cases (100% in both Groups) followed by back (40% in Group-A and 36.66% in Group-B), neck (35% in Group-A and 25% in Group-B) and chest (28.33% in Group-A and 26.66% in Group-B). Tauff A, Cunliffe WJ, Damabel FT also reported that face being the most common site (99%) for acne and to lesser extent on the back (60%) and chest (15%). Kile and his associates found surface lipids were significantly greater in patients with acne over the face. Pauchi and Strauss also noted that output of sebum on the forehead was quantitatively more than other body areas. As face is the presenting body part. Patient are more conscious, therefore such cases make a bulk amongst acne group. This is well depicted in our study by 100% involvement of face.

Regional Distribution

Most of the patients belonged to urban area (80% in Group-A and 78.33% in Group-B) as compared to rural area (20% in Group-A and 21.67% in Group-B) in our study. Pandey SS, Kaurp, Singh G (1980) also concluded that acne was found more common in urban boys than in their rural counterparts. It may be due to the fact that urban patients are more aware and conscious about their look and report early for treatment. It may also be due to easy availability of dermatological services in urban area. The management of acne may require modification of major etiological factors. The available medications have varying effects on each of these factors. Antibiotics have their role in acne vulgaris mainly by their antibacterial and anti-inflammatory effects. Although Isotretinoin has revolutionized the treatment of acne, however the present study revealed that when combined with Azithromycin it gives better results i.e. 91.66%(55 cases) showed improvement at the end of 12 weeks in Group-B, whereas 73.33%(44cases) showed improvement in Group-A. The P-value comes out to be 0.008, which is highly significant. The adverse effects, such as Chelitis (55% in Group-A and 25% in Group-B), Erythema (11.67% in Group-A and 6.67% in Group-B), Gastrointestinal disturbances(None in Group-A and 10% in Group-B), Dry skin (43.33% in Group-A and 30% in Group-B) etc. were reported. These however subsided with use of antacid and vitamin-E. It is evident from present study that the combination therapy of low dose Isotretinoin and oral Azithromycin is more effective in moderate to severe acne and has a reasonably acceptable results, and low adverse -effects profile. Few other studies have been published on the effective use of combination of Isotretinoin with azithromycin in treating acne in adolescent population[15,16,17]. Our study is in agreement with these studies where the authors have clearly presented their opinions about Isotretinoin in combination with Azithromycin, making it suitable for the treatment of acne[18,19,20,21]. This study further confirms that combination is safe, effective, and tolerable treatment regimen with lesser side effects and good compliance.

CONCLUSION

Combination of low dose Isotretinoin with Azithromycin seems to be superior option. However, further randomized, controlled comparative trials are needed to assess this point in moderate to severe acne vulgaris.

REFERENCES

1. Bellosta M, Vignini M, Miori L, *et al.* "Low-dose isotretinoin in severe acne". *Int JTissue React 1987;*9:443-6.
2. Plewig G, Dressel H, Pfleger M, *et al.*"Low dose isotretino in combined with tretinoin is effective to correct abnormalities of acne". *J Dtsch Dermatol Ges 2004;* 2:31-45.
3. Strauss JS, Leyden JJ, Lucky AW, *et al*."A randomized trial of the efficacy of a new micronized formulation versus a standard formulation of isotretinoin in patients with severe recalcitrant nodular acne". *J Am Acad Dermatol 2001*; 45:187-95.
4. Akman A,Durusoy C,Senturk M, *et al.*"Treatment of acne with intermittent and conventional isotretinoin : A randomized, controlled multicenter study". *Arch Dermatol Res 2007;* 299:467-73.
5. Fernandez-Obregon AC. Azithromycin for the treatment of acne. Int J Dermatol. 1997; 36: 239-40.
6. Fernandez-Obregon AC. Azithromycin for the treatment of acne. Int J Dermatol. 2000; 39:45-50.
7. Kus S, Yucelten D, Aytug A. Comparison of efficacy of azithromycin vs. doxycycline in the treatment of acne vulgaris. Clin Exp Dermatol. 2005; 30:215-20.
8. Gollnick H, Cunliffe W, Berson D *et al*. Management of acne: a report from a global alliance to improve outcomes in acne. J Am Acad Dermatol. 2003; 49(Suppl 1):S1-37.
9. Tan AW, Tan HH. Acne vulgaris: a review of antibiotic therapy. Expert Opin Pharmacother. 2005 Mar; 6(3):409-18.
10. Bloch, B: Metabolism, endocrine glands and skin disease with special reference to acne vulgaris and xanthoma. Br. J. Derm symph. 1931; 43: 61-870.
11. Sulzberger, MB and Witten, VH: Hormone and acne vulgaris. Med. Clin N Amer. 1951; 35: 373-390.
12. Leider M and Rosenblum M: A Dictionary of

Dermatological words, terms and phrases, New York. Mc Graw Hill, 1968.
13. Hardy DJ, Henesey DM, Beyer JM *et al*. Comparative in vitro activities of new 14-, 15-, and 16-membered macrolides. Antimicrob Agents Chemother. 1988; 32:1710-19.
14. Neu HC. Clinical microbiology of azithromycin. Am J Med. 1991; 91(Suppl. 3A):12S-18S.
15. Duran JM, Amsden GW. Azithromycin: indications for the future? Expert Opin Pharmacother. 2000 Mar; 1(3):489-505.
16. Kapadia N, Talib A. Acne treated successfully with azithromycin. Int J Dermatol. 2004 Oct; 43(10):766-7.
17. Caputo R, Barbareschi M, Veraldi S. Azithromycin: a new drug for systemic treatment of inflammatory acneic lesions. G Ital Dermatol Venereol. 2003; 138:327-31.
18. Scheinfeld NS, Tutrone WD, Torres O, Weinberg JM. Macrolides in dermatology. Clin Derm. 2003; 21:40-9.
19. Alvarez-Elroco S, Enzler MJ. The macrolides, erythromycin, clarithromycin, and azithromycin. Mayo Clin Proc. 1999; 74:613-34.
20. Ross JI, Snelling AM, Carnegie E *et al*. Antibiotic-resistant acne: lessons from Europe. Br J Dermatol. 2003; 148:467-78.
21. Rafiei R, Yaghoobi R. Azithromycin versus tetracycline in the treatment of acne vulgaris. J Dermatolog Treat. 2006; 17(4):217-21.

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