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RESEARCH ARTICLE

THE EFFECT OF FIXED LOW DOSE ISOTRETINOIN ON LIVER AMINOTRANSFERASES IN ACNE VULGARIS

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ABSTRACT

Objectives: The objective of our follow-up study is to evaluate liver enzymes in acne patients treated with isotretinoin.
Setting: Dermatology outpatient clinics, MIMS, Mandya.
Participants: we included the patients diagnosed with moderate to severe acne. All patients were treated with low dose isotretinoin and followed-up in our outpatient clinics 20 weeks. Patients were subjected to an interview questionnaire which included data on age, gender, previous treatment and liver enzymes.
Primary outcome: Blood analyses were repeated in the follow-up visits baseline, 4,8,12,16,20 weeks.
Results: AST, ALT of 40 patients aged 15-40 years receiving isotretinoin for moderate to severe acen were monitored before, during and every month interval for 4 months. Pretreatment values of mean AST and ALT levels are 12.58±3.58 and 10.76± 2.70 repectively. Values of AST and ALT were increased from the baseline. There is statistically significant increase in the levels at second, third and fourth month. The values were increased two times the upper limit upto grade 2.
Conclusion: The present study showed statistically significant increase in liver aminotranferase, the increase was >two times the upper limit of normal.

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INTRODUCTION

Acne is an extremely common dermatological disorder affecting around 79-95% of the adolescents. Acne is a chronic inflammatory condition that develop in the pilosebaceous unit and the comedones form the primary lesion (Vieira *et al*., 2012). Acne is one of the common complaint in dermatological clinic. Although self-limiting in majority of cases, it has significant psychological effect on patients (Schmitt *et al*., 2011). People with acne have social, psychological and emotional disability more when compared with other illnesses (Layton *et al*., 1997). Oral isotretinoin is the only drug that affects most of the pathogenic factors of acne and is considered to be the effective drug for severe nodulocystic acne. Oral isotretinoin is currently the most effective acne treatment, with long term remission rates (Ahmadvand and Javanbakht, 2006). Isotretinion, first generation retinoid is regarded as a major therapeutic advance in dermatology and is now used for the treatment of moderate to severe acne.

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Isotretinoin is indicated for severe acne that are unresponsive to conventional treatment. The classical recommended dose is 0.5-1.0mg/kg/day for 4-8months (Amichai *et al*., 2006). Many adverse reactions as been reported. As the side effects are dose related the idea of low dose isotretinoin therapy for acne is attractive. Laboratory alterations due to hepatic and hematologic toxicity as well as dyslipidemias is known. Statistically insignificant discreet elevations in the results of the tests occur with almost all patients (Brito *et al*., 2010). There are study about the efficacy of the low dose isotretinoin. Study related to know the effects on liver fuctions with the conventional regimen are done. To date there is no study to evaluate the effect of low dose continuous isotretinoin therapy on the liver aminotransferase. The purpose of this study was to evaluate the alteration in liver aminotransferases before, during and after low dose continuous oral isotretinoin therapy.

MATERIALS AND METHODS

A total of 40 patients attending the department of dermatology, Mandya Institute of Medical Sciences, were included in the study. The study was approved by the institutional ethical committee. Eligible patients included males and females aged >15yrs and older with moderate to severe acne. Children below

the age of 12 years were not included in the study due to the risk of systemic toxicity. To be included in the study all sexually active female patients of childbearing potential had to use effective contraception 1month before the onset of therapy and 3 months after the treatment Reason for exclusion was any other use of systemic or topical therapy for acne vulgaris, any abnormalities in the laboratory assessment at baseline, known hypersensitivity to isotretinoin, parabene in isotretinoin capsules. All patients were included after written informed consent. After recording detailed demographic data(which included age , sex, age of onset of the disease, duration of disease etc.), the patients were examined under good illumination and were finally graded into mild , moderate and severe on the basis of the severity as described below (Indian acne grading).

- Mild disease: Few to several papules/pustules with no nodule
- Moderate disease: several to many papules/pustules with few to several nodules
- Severe disease: Numerous and /or extensive papules/pustules with many nodules.

The baseline hematological, biochemical investigations that were carried out included heamoglobin estimation (Hb), total and differential leukocyte counts (TLC,DLC), total bilirubin, serum glutamate oxaloacetate transaminase and serum glutamate pyruvate transaminase (SGOT, SGPT). The selected patients were assigned to receive 20mg of isotretinoin daily for 16wks. the patients were followed up every 2 weeks for the first month and subsequently every four weeks. The study evaluation visits were performed at baseline, at weeks 4,8,12,16 and the end of the treatment.

RESULTS

A total of 40 patients with the age group of 15-30yrs were included in the present study. The demographic data and severity of acne is summarized in the table 1.

Table 1. Age, Sex and Grades of participants

	N(%)	Mean age	Moderate	Severe
Male	13(32.5%)	23.4	6	10
Female	27(67.5%)	19.2	15	9

The initial mean acne scores were 80.26% and 88.26% in male and females respectively. During the follow up there were significant decrease in total acne load in both sex.

Table 2. Grading of acne

Grade of acne	Week 0	Week 4	Week 12	After 4months
0	-	-	7%	7%
1	-	12%	80%	90%
2	58%	62%	13%	3%
3	42%	26%	-	-

Mucocutaneous side effects were noted in 62.5% of patients. Cheilitis was the commonest side effects noted. Other side effects are less common and shown in Table 3.

Table 3. Adverse events with isotretinoin

Cheilitis	20
Xerosis	10
Eye and nasal dryness	8
Hairloss	5
Menstrual irregularities	2
Irritation and redness	4

Measured baseline value of SGOT in continuous low dose therapy group were12.58± 3.58, then after at 4wks, 8wk, 12wk, 16wk and at the end of the treatment were 30.96± 6.50, 61.60± 9.35, 89.22± 14.02, 101.34± 14.21 respectively. There was increase in SGOT at all the intervals compared with baseline. Measured baseline value of SGPT in continuous ow dose therapy group were 12.58± 3.58 then after at 4wks, 8wk, 12wk, 16wk and at the end of the treatment were 30.96± 6.50, 61.60± 9.35, 89.22± 14.02, 101.34± 14.21 respectively. There was significant increase in LDL at all the intervals compared with baseline.

Table 4. Liver enzyme levels at different week compared with baseline

Duration	SGOT	SGPT	P value
Baseline	12.58± 3.58	10.76± 2.70	<0.001
4th week	30.96± 6.50	27.76± 5.19	<0.001
8th week	61.60± 9.35	53.76± 7.38	<0.001
12th week	89.22± 14.02	81.02± 8.92	<0.001
16th week	101.34± 14.21	91.38± 10.70	<0.001

DISCUSSION

Retinoid have gained wide range clinical use in recent years. Isotretinoin since its introduction has led to an extensive modification in the treatment regimens of acne vulgaris. The FDA recommends isotretinoin for treating severe nodulocystic acne that is unresponsive to conventional therapy. However American Academy of Dermatology (AAD) guidelines for acne treatment encourage isotretinoin use for less severe acne patients. The most important advantage is, its effect on all four pathogenic factors affecting the acne. However, retinoid therapy is usually complicated by dose dependent side effects. Some of the side effects can compromise the patients compliance and necessitate dose reduction or treatment discontinuation with conventional therapy. In conventional dosage, the use of isotretinoin has been limited not only by the occurrence of mucocutaneous adverse effects, Teratogenicity and depression with suicidal ideation, but also by the biochemical abnormalities such as hyperlipidemia and impaired liver function test. Low dose isotretinoin has few side effects. Mandekou - Lefaki *et al* in his study achieved excellent results in 68% and good results in 31% who received low dose isotretinoin[8]. Hermes *et al* treated 94 patients with initial dose of 10mg/day with a variable increase according to side effects, reaching a mean dosage of 0.43 mg/kg, and reported very good results in 62.8% and good results in 31.9% of the patients (Hermes *et al*., 1998). The results of the present study showed that the mean age of the women was greater than the age of men, possibly because acne usually affects men at puberty due to harmone changes, but women at adulthood affected. Oral treatment with isotretinoin for three months or longer induces alterations in triglyceride, AST and ALT levels. Although various studies have confirmed these results, the magnitude of

the alterations has varied greatly between studies (Zane *et al*., 2006; Júnior *et al*., 2009; Michaëlsson *et al*., 1986; Altman *et al*., 2002; Tallab *et al*., 2004; Bener *et al*., 2009 and Bershad *et al*., 1985). The present study showed statistically significant increase in liver aminotranferase, the increase was >two times the upper limit of normal in some of the patients. The increase was started from the 8th week onwards above the normal range, but when compared with the baseline the values was increased from 4 week and the increase was progressive. In situations such as this, Altman *et al*. suggest interrupting treatment due to the risk of developing liver disease. The increase in the levels of aminotransferase was from normal to grade 2 levels. This slight increase in the liver enzymes is due to the multitude of factors influencing. The increased level of ALT and AST found in the present study show the importance of having the patients monitored by the multidisciplinary team. The study was done to see the changes or the alternation occurring with the daily use of the isotretinoin on the liver enzymes.

Conclusion

The results show that in the patient evaluated in the study, the use of the low dose isotretinoin for the treatment of acne led to increase in serum ALT, AST levels. Although these alterations did not require treatment to be interrupted, they may increase the patient's risk of developing liver disease. So for this reason rigorous monitoring of liver function test is required to minimize the inherent risk treatment with the drug. Despite the low dose of ISO used for treatment, proper clinical and laboratory evaluation and monitoring are mandatory.

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