**International Journal of Dermatology Research**
www.dermatologyjournal.in
Online ISSN: 2664-648X, Print ISSN: 2664-6471
Received: 20-11-2021, Accepted: 06-12-2021, Published: 21-12-2021
Volume 3, Issue 1, 2021, Page No. 12-14

# The utility of laboratory monitoring among patients with acne vulgaris receiving different doses of oral isotretinoin

**Elena Zanganeh[1], Seyedali Seyedmajidi[2], Shahin Hajiebrahimi[1], Anahita Ahmadi[1], Seyed Ashkan Hosseini[3], Mehdi Alimadadi[1], Mohammadreza Seyyedmajidi[1*]**

[1] Golestan Research Center of Gastroenterology and Hepatology (GRCGH), Golestan University of Medical Sciences, Gorgan, Iran
[2] Dental materials research center, Health research institute, Babol University of Medical Sciences, Iran
[3] Mashhad University of Medical Sciences, Mashhad, Iran

**Abstract**

**Background and study aim:** Adverse events of isotretinoin are in mucocutaneous and hepatic tissues, alterations in lipid levels and teratogenicity. This study was aimed to evaluate the alterations in aminotransferases and serum lipids in patients using different doses of oral isotretinoin.

**Patients and methods:** 300 patients with moderate to severe acne were enrolled and randomized to receive isotretinoin for 24 weeks in three groups: 40 mg daily (group A: continuous conventional dose), 20 mg daily (group B: continuous low dose) or 40 mg daily for one week out of every 4 weeks (group C: intermittent dose). Baseline liver enzymes and lipid profile were done and repeated at 4,12 and 24 weeks after starting.

**Results:** There were no statistical differences in the patients in sex, age and body mass index (BMI) in three groups. Only in group A, there was a non-significant increase in serum triglyceride (p=0.17) and non-significant decrease in HDL after 12 weeks of treatment (p=0.36). Both AST and ALT increased non-significantly after 4 weeks of treatment in this group (p=0.09). No difference was seen in serum lipids and liver aminotransferases during the study in group B and C.

**Conclusion:** The results showed that use of oral isotretinoin for the treatment of acne did not lead to permanent and significant change in serum lipids, ALT and AST levels and these alterations did not require treatment to be interrupted. Laboratory monitoring is not necessary among patients receiving intermittent or continuous low dose of oral isotretinoin.

**Keywords:** intermittent; low or conventional dose; oral isotretinoin; serum lipids; liver aminotransferases

## Introduction

Acne vulgaris is the most common dermatological disorder affecting approximately 85% of individuals 12-24 year of age [1]. It is a chronic inflammatory disease of pilosebaceous unit, characterized by comedones, papules, pustules, nodules and scarring [2]. *Propionibacterium acnes* contributed to inflammation of this condition. Treatment depends on the type and severity of acne and includes topical and oral compounds. Topical medications are retinoids, benzoyl peroxide and antibiotics while isotretinoin, antibiotics and cyproterone are used oral compounds [3].

13-*cis*-retinoic acid or Isotretinoin has been approved by the Food and Drug Administration for the treatment of severe nodulo-cystic acne since 1982. Most acne patients are treated for a short course, approximately 6 months, and total cumulative dose for a full course is 120-150 mg/kg [4]. Isotretinoin reduces sebaceous gland size up to 90% by decreasing proliferation of basal sebocytes, suppressing sebum production and inhibiting sebocytes differentiation. It also causes reduction in microbial flora which persists even after discontinuation of therapy [5, 6]. Isotretinoin is also used for the treatment of cornification, rosacea, Gram-negative folliculitis, chemoprevention of skin neoplasms, psoriasis and myelodysplastic syndromes [4]. Although isotretinoin is an effective and generally well-tolerated drug, it has broad side effects. Many of them, especially those that are mucocutaneous, are fairly predictable and dose related [7, 8]. The most common are dryness of skin, lips, mouth and nasal mucosa. Other are facial or body rash, itching, peeling of palms and soles, photosensitivity, epistaxis, bleeding and inflammation of gums, easily injured skin and fatigue. There may be some redness, dryness or irritation of eyes. There have been reports of depression and suicidal attempts [9]. Isotretinoin may also increase serum levels of liver aminotransferases and lipid changes, including increased triglyceride, total cholesterol and low-density lipoprotein (LDL) cholesterol levels and reduced levels of high density lipoprotein (HDL) cholesterol [10-12].

This study was aimed to evaluate the prevalence of alterations in aminotransferases and serum lipids in patients using different doses of oral isotretinoin in order to confirm the need for laboratory monitoring of the adverse reactions.

## Patients and methods

This is a prospective and observational study was carried out in 300 outpatients between January 2017 and December 2019 (3 years). According to global acne grading system [13], the patients had moderate to severe acne with no other medications for last three months. Patients with a history of cardiac disease,

pancreatitis, hyperlipidemia, impaired liver enzymes, diabetes, pregnant women and children were excluded. The patients with history of smoking, alcohol consumption were not enrolled. Written consent was taken from married ladies regarding contraception and side effects were explained. This research was approved by the Ethical Committee in Research Center of Gastroenterology and Hepatology. The patients randomized to receive oral isotretinoin for 24 weeks in three groups: 40 mg daily (group A: continuous conventional dose), 20 mg daily (group B: continuous low dose) or 40 mg daily for one week out of every 4 weeks (group C: intermittent dose). Baseline liver enzymes and lipid profile were done and repeated at 4,12 and 24 weeks after starting.

All the data were analyzed using Statistical Package for Social Sciences (SPSS, IBM Corp.; Armonk, NY, USA). The values were expressed as mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. The normality of distribution of data was assessed using the Kolmogorov-Smirnov test. Comparisons of categorical variables across the groups were performed using an overall chi-square test or Fisher's exact test, if required.

## Results

All patients could continue study protocols. There were 209 females (70.7%) and 91(30.3%) males. Age range was from 16-35 years. As shown in Table 1, there were no statistical differences in sex, age and body mass index (BMI) in study groups. BMI, serum lipids and liver aminotransferases during the study were shown at Table 2. Mean of BMI was not changed during the study. Only in group A (continuous conventional dose), there was a non-significant increase in serum triglyceride ($p$=0.17) but no in total cholesterol and LDL and non-significant decrease in HDL after 12 weeks of treatment ($p$=0.36). In this group, both AST and ALT increased non-significantly after 4 weeks of treatment ($p$=0.09). The aminotransferase elevations were not over double the upper limit of normal. No difference was seen in serum lipids and liver aminotransferases during the study in group B (continuous low dose) and C (intermittent dose).

## Discussion

The results of this study showed that only 40 mg daily (continuous conventional dose) of oral treatment with isotretinoin for 12 weeks but no longer induces mild elevation of triglyceride and mild reduction of HDL (both non-significant) in patients having normal lipids and BMI at baseline. The incidences of hypertriglyceridemia have varied from 25% to 44%. It also may affect total cholesterol and LDL with increases in approximately 30% of patients. HDL was decreased in 20% to 25% [14, 15]. Recent studies demonstrated that the lipid levels rarely elevate over double the upper limit of normal and are rarely enough to require cessation of treatment [16]. The most significant lipid elevations were observed in patients who already had elevated baseline laboratory values [17]. Patients who are overweight or have increased baseline triglyceride levels are at risk for hypertriglyceridemia, but normal baseline triglyceride levels do not rule out the possibility of developing these abnormalities [14]. Triglyceride levels often return to baseline within one month of cessation of the drug [18]. There are few cases of pancreatitis, and some are confounded by concomitant administration of another medication known to cause pancreatitis [19]. Although isotretinoin should be used with caution in patients with a personal or family history of pancreatitis, the chance of a patient developing pancreatitis is exceedingly rare [3]. Moreover, these considerations may explain the fact that other studies have failed to find any significant alterations in triglyceride levels or liver aminotransferases [20]. In addition, no significant increases occur with chronic treatment over long periods [21]. As in this study, increased triglyceride levels did not reach more than twice the upper limit of the normal range, a situation that would justify interrupting treatment. The studies that monitored patients after the end of treatment reported that the increase in triglyceride levels appears to be reversible in the majority of patients, suggesting that adjustments to the diet and regular physical activity would be sufficient to control triglyceride levels [20].

The present study found, only in patients using 40 mg daily (continuous conventional dose) of oral isotretinoin, statistically non-significant increases in liver aminotransferases after four-weeks treatment but no longer, they were clinically irrelevant in all of the patients. None of them had an increase in aminotransferase that was $\geq 2$ times the upper limit of normal. These levels usually normalize within a few weeks despite continuation of the drug and are usually insignificant [18]. It is rare to develop changes in liver function if it has not presented within the first 2 months. If pretreatment liver function tests are normal, the risk of hepatic disease is low [14]. Hepatitis has been associated with isotretinoin but studies have not found a causal relationship with chronic liver toxicity [18]. Isotretinoin does not affect the overall risk for cardiac disease in young healthy patients, even in those experiencing significant lipid abnormalities during isotretinoin treatment [21].

In conclusions, the results showed that use of oral isotretinoin for the treatment of acne did not lead to permanent and significant change in serum lipids, ALT and AST levels and these alterations did not require treatment to be interrupted. Laboratory monitoring is not necessary among patients receiving intermittent or continuous low dose of oral isotretinoin.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

## Acknowledgements

We wish to thank Behestan Darou company who took part in this research project to provide the drug "Isotret HEXAL®: Isotretinoin 20 mg".

## References

1. Leyden JJ. A review of the use of combination therapies for the treatment of acne vulgaris. J Am Acad Dermatol,2003:49:211-7.
2. Vieira AS, Beijamini V, Melchiors AC. The effect of isotretinoin on triglycerides and liver aminotransferases. An Bras Dermatol,2012:87(3):382-7.
3. Dhaked DR, Meena RS, Maheshwari A, Agarwal US, Purohit S. A randomized comparative trial of two low-dose oral isotretinoin regimens in moderate to severe acne vulgaris. Indian Dermatol Online J,2016:7(5):378-85.
4. Rao PK, Bhat RM, Nandakishore B, Dandakeri S, Martis J,

Kamath GH. Safety and efficacy of low-dose isotretinoin in the treatment of moderate to severe acne vulgaris. Indian J Dermatol,2014:59(3):316.
5. Barbieri JS, Spaccarelli N, Margolis DJ, James WD. Approaches to limit systemic antibiotic use in acne: Systemic alternatives, emerging topical therapies, dietary modification, and laser and light-based treatments. J Am Acad Dermatol,2019:80(2):538-49.
6. Ganceviciene R, Zouboulis CC. Isotretinoin: state of the art treatment for acne vulgaris. J Dtsch Dermatol Ges,2010:8:47-59.
7. Ryan-Kewley AE, Williams DR, Hepburn N, Dixon RA. Non-antibiotic Isotretinoin Treatment Differentially Controls Propionibacterium acnes on Skin of Acne Patients. Front Microbiol,2017:25:8:1381.
8. Amichai B, Shemer A, Grunwald MH. Low dose isotretinoin in the treatment of acne vulgaris. J Am Acad Dermatol,2006:54:644-6.
9. Camera E, Ludovici M, Tortorella S, Sinagra JL, Capitanio B, Goracci L *et al*. Use of lipidomics to investigate sebum dysfunction in juvenile acne. J Lipid Res,2016:57(6):1051-8.
10. Yildirim Y, Olcucu O, Agca A, Alagoz C, Demircan A, Basci A *et al*. Evaluation of corneal topography and biomechanical parameters after use of systemic isotretinoin in acne vulgaris. J Ophthalmol, 2014, 701361.
11. Kaymak Y, Ilter N. The results and side effects of systemic isotretinoin treatment in 100 patients with acne vulgaris. Dermatol Nurs,2006:18:576-80.
12. Zane LT, Leyden WA, Marqueling AL, Manos MM. A population-based analysis of laboratory abnormalities during isotretinoin therapy for acne vulgaris. Arch Dermatol,2006:142:1016-22.
13. Doshi A, Zaheer A, Stiller MJ. A comparison of current acne grading system and proposal of a novel system. Int J Dermatol,1997:36:416-8.
14. Nickle SB, Peterson N, Peterson M. Updated Physician's Guide to the Off-label Uses of Oral Isotretinoin. J Clin Aesthet Dermatol,2014:7(4):22-34.
15. Tan AU, Schlosser BJ, Paller AS. A review of diagnosis and treatment of acne in adult female patients. Int J Womens Dermatol,2017:4(2):56-71.
16. Ertam, Barth JH, MacDonald-Hull SP, *et al*: Is it necessary to have routine blood tests in patients treated with isotretinoin? J Dermatol Treat,2006:17:214-6.
17. Oon HH, Wong SN, Aw DCW, Cheong WK, Goh CL, Tan HH. Acne Management Guidelines by the Dermatological Society of Singapore. J Clin Aesthet Dermatol. 2019 Jul;12(7):34-50.
18. Bugdayci G, Polat M, Oguzman H, Cinpolat HY. Interpretation of Biochemical Tests Using the Reference Change Value in Monitoring Adverse Effects of Oral Isotretinoin in 102 Ethnic Turkish Patients. Lab Med,2016:47(3):213-9.
19. Atiq MU, Raza A, Ashfaq A. Idiosyncratic Reaction Causing a Rare Side Effect: Isotretenoin-induced Pancreatitis. Cureus,2019:11(11): e6102.
20. Tallab T, Joharji H, Jazei M, Bahamdan K, Ibrahim K, Karkashan E. Isotretinoin therapy: any need for laboratory assessment? West Afr J Med,2004:23:273-5.
21. Krishna S, Okhovat JP, Kim J, Kim CN. Influence of ω-3 fatty acids on triglyceride levels in patients using isotretinoin. JAMA Dermatol,2015:151(1):101-2.