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Long-term isotretinoin use does not cause parenchymal liver change: Ultrasonographic study in 50 patients

Habibullah Aktas[1] | Goksen Ertugrul[1] | Muharrem Parlak[2] | Mehmet Unal[3]

[1]Faculty of Medicine, Department of Dermatology, Karabuk University, Karabuk, Turkey

[2]Faculty of Medicine, Department of Radiology, Karabuk University, Karabuk, Turkey

[3]Faculty of Medicine, Department of Dermatology, Selçuk University, Konya, Turkey

Correspondence
Mehmet Unal, Faculty of Medicine, Department of Dermatology, Selçuk University, Konya, Turkey.
Email: dr.munal1101@gmail.com

Abstract

The effect of isotretinoin on liver enzymes and lipid profile is reported as rare and reversible. However, possible parenchymal liver changes have not been demonstrated so far. The aim of this study was to evaluate the ultrasonography findings of the liver in patients receiving long-term isotretinoin therapy. We examined ultrasonographic findings of the liver together with serum alanin aminotransferase (ALT), aspartate aminotransferase (AST), and total cholesterol and triglyceride levels in 50 consecutive patients who have taken isotretinoin 10–40 mg daily for at least 6 months between January and December 2017. Of 50 patients examined, 40 were female, 10 were male. Mean age of the patients was 24.8 years. Five patients aged between 42 and 62 were found to have Grade 1 hepatosteatosis. Despite a moderate elevation, serum ALT, AST, and total cholesterol and triglyceride levels were in normal range in these five patients. Moreover, one patient had elevated ALT, and one another patient had elevated triglyceride level although both have normal liver ultrasonographic findings. Isotretinoin did not cause parenchymal liver changes as well as serum ALT, AST, and total cholesterol and triglyceride levels in patients who take it 10–40 mg daily for at least 6 months.

KEYWORDS

acne, isotretinoin, liver

1 | INTRODUCTION

Isotretinoin, a vitamin A derivative is currently the most effective drug in the treatment of acne vulgaris and has been used worldwide for over 30 years. Although it is generally accepted as safe, a number of side effects related to isotretinoin use have been reported (Prevost & English, 2013). Since isotretinoin has potential to increase the serum lipid levels, it can indirectly contribute to lipid accumulation in the hepatocytes leading to hepatosteatosis. Hepatotoxicity, although very rare, is a worrying issue in the patients taking isotretinoin. It is recommended that liver enzymes and serum lipids be checked at regular intervals during the treatment course (Kızılyel, Metin, Elmas, Çayır, & Aktaş, 2014).

Liver ultrasonography (LUSG) is a helpful diagnostic and noninvasive tool for detecting possible liver pathologies such as steatosis or other parenchymal changes before any biochemical abnormalities occur (Khodadoostan, Shariatifar, Motamedi, & Abdolahi, 2016). The determining of healthy liver tissue by sonographic findings together with normal values of liver enzymes and lipids provide the physician and patients more compatible treatment course, which would increase the treatment success.

In this study, we evaluate the LUSG findings of patients who have been taking isotretinoin for at least 6 months and try to establish a more detailed liver map regarding long-term isotretinoin use.

2 | METHOD

The study was a retrospective study conducted between January and December 2017 in patients on isotretinoin treatment with the diagnosis of acne vulgaris, acne rosacea and oily skin in Dermatology Outpatient Clinic of Karabuk Training and Research Hospital, a tertiary center in Northern Turkey. The data were obtained from the hospital

files of patients. Fifty patients with at least 10 mg of isotretinoin per day for at least 6 months were included in the study. Patients who had previously been diagnosed with an internal disease, patients who used regular medication on any topic, and patients with alcohol use were excluded from the study. All patients included in the study had no additional disease other than skin diseases requiring isotretinoin therapy.

LUSG findings, serum alanin aminotransferase (ALT) and aspartate aminotransferase (AST) levels and lipid profiles were screened in patients who completed 6 months of isotretinoin treatment. LUSG was done by the same radiologist. Informed consent was taken from the patients and ethical approval was taken in our university council (3.1.2018/1-6). The study has been performed in accordance with the principles of the Helsinki Declaration.

3 | STATISTICAL ANALYSIS

For analysis of data, the package program SPSS 24.0 (Statistical Package for the Social Sciences Inc., Chicago, IL) was used. Normal distribution fitness analyzes were performed with the Kolmogorov Smirnov test. Chi-square test was used to compare categorical data. For comparing continuous data, Student's *t* test was used for variables with normal distribution and Mann–Whitney *U* test was used for non-normal distribution. A *p* value <.05 was considered significant for all analyzes.

4 | RESULTS

Forty (80%) of 50 participants were female and 10 (20%) were male, aged between 13 and 62 years. The mean age was 24.8 years. The average daily isotretinoin dose was 10 mg, 20 mg, and 30 mg for 24, 20, and 6 patients, respectively.

LUS was normal in 43 patients, but Grade 1 hepatosteatosis was detected in five patients, hepatomegaly and hemangiomas in one patient and hemangiomas in one patient. Serum liver enzymes and lipid profile were in normal range in all these seven patients (Table 1).

Only, in one patient; ALT (59 U/L) and in one patient; triglyceride increase (541 mg/dL) were observed at the end of the study. Other 48 patients had normal serum liver enzyme and lipid levels. Mean ALT, AST, cholesterol, and triglyceride levels were 16 U/L, 22 U/L, 178 mg/dL, and 116 mg/dL, respectively. Mean age of five patients with Grade 1 hepatosteatosis were 50.8 years (min: 42 and max: 62 years) and their ALT, AST, cholesterol, and triglyceride levels were also in normal range. But, ALT, AST, cholesterol, and triglyceride levels of patients with Grade 1 hepatosteatosis were a little higher compared to patients who have normal LUS ($p < .05$). A total of 43 patients with normal LUS findings had a mean age of 21.5, which is very much lower compared to patients with abnormal LUS ($p < .05$).

Particularly, mean ALT level seemed very different between two ultrasonography finding group. It was 24.2 U/L in patients with Grade 1 hepatosteatosis while 15.1 U/L in patients with normal LUS findings ($p < .05$).

5 | DISCUSSION

Although isotretinoin has been described as safe in several studies, there is a reality that it is still used with concern. One of these concerns is the hepatic side effect that makes the patients and families worried (Vieira, Beijamini, & Melchiors, 2012). In fact, many studies have reported that isotretinoin is also safe for liver health despite alterations in liver enzymes. However, in a paper, a case of autoimmune hepatitis related to oral isotretinoin was reported, and personal stories published in newspapers, magazines and internet blogs (Guzman Rojas et al., 2016).

Patients taking isotretinoin should be followed by regular check-up of liver function tests and lipid profile (Hansen et al., 2016). In one article, it was reported that monitoring of hepatic side effect while on isotretinoin was inadequate, and basically the essential test should be GGT and creatinine kinase level (Webster, Webster, & Grimes, 2017).

Since isotretinoin has potentially rising effect on blood lipids; hepatosteatosis may be an important problem for isotretinoin users. Taylor and Mitchison reported a young male with fatty liver after isotretinoin treatment in 1991 in which the patient had used desiccated liver pills for weightlifting purposes and also he had no initial liver sonography test (Taylor & Mitchison, 1991). To our knowledge, there is no published fatty liver case related to isotretinoin apart from that case in the literature, so far.

LUSG is a noninvasive method for diagnosis of liver diseases, sometimes before significant clinical symptoms. Hepatosteatosis can be detected in the ultrasonography before an increase in liver transaminases. Although LUS is not a golden technique in diagnosing hepatosteatosis (Obika & Noguchi, 2012), it can provide a rapid, cost-effective, noninvasive, and considerable screening with normal liver

TABLE 1 Age, liver anzyme, lipid profile, and daily dose distribution according to LUS results

Liver USG	Mean age (year)	ALT (U/L)	AST (U/L)	Cholesterol (mg/dL)	Triglyceride (mg/dL)	Average daily dose (mg)
Grade 1 hepatosteatosis *n* = 5	50.8	24.2	25.8	188.6	145	12
Normal *n* = 43	21.5	15.1	21.3	177.2	112.4	17.2
Coincidental lesions *n* = 2	19	13	26	182.5	122	10
Total number *n* = 50	24.8	16	22	178	116	16.4

Abbreviations: ALT, alanin aminotransferase; AST, aspartate aminotransferase; USG, ultrasonography.

enzyme levels for patients on long-term isotretinoin use, because serum hepatic enzyme levels may be normal during hepatosteatosis.

In a large retrospective study containing 3,525 patients, no severe side effect occurred for cutting the therapy (Brzezinski, Borowska, Chiriac, & Smigielski, 2017). Another study from Australia by Rademaker showed that not even a single patient of 1,743 patients who used various dosages of isotretinoin during 6-year follow-up did not stop taking the drug due to any severe adverse effect except two pregnancies (Rademaker, 2010).

In our study, liver ultrasonography was performed in addition to monthly checking serum liver enzymes and lipid profile in 50 patients receiving isotretinoin. The ultrasonographic findings of the patients were completely normal except for seven patients This result is not surprising since acne vulgaris, the most common indication of oral isotretinoin, is seen in younger patients. The mean age of the 50 patients with our study was 24.8, while the mean age of 43 patients with normal ultrasonography was 21.5, a much lower value.

Mean age of three males and two females patients with hepatosteatosis were a 50.8 years (min: 42 and max: 62 years), which is much higher than mean age of other 43 patients with normal LUS. These results suggest that isotretinoin may cause a tendency to hepatosteatosis in elderly patients. However, there is already a tendency to hepatosteatosis in older people without needing use of isotretinoin or other drugs. (Daryani et al., 2010). Since patients with hepatosteatosis already used lower doses compared to patients with healthy liver, the possibility of isotretinoin to cause fatty liver in those patients is low.

Reportedly, the most common biochemical side effects of isotretinoin are hyperlipidemia and increase in liver transaminases. These are generally mild and reversible, and observed in 10–25% of the patients (Bauer, Ornelas, Elston, & Alikhan, 2016; Zane, Leyden, Marqueling, & Manos, 2006). Those patients whose tests found risen were followed by cutting isotretinoin, and rechecking the values. Unlikely, our study did not find such a great abnormality in serum liver enzyme levels and lipid profile.

In our patients, enzyme and lipid levels were normal except for only two patients after 6 months, one with ALT 59 U/L and the other with triglyceride 541 mg/dL. This can be explained by lower dose which our patients have taken.

In a study investigating hepatotoxicity risk in 11 cases with Gilbert syndrome, who use isotretinoin for their acne, surprisingly not only an effective and safe outcomes regarding acne signs were obtained, but also bilirubin levels were found to be decreased in the patients during isotretinoin use (Fernández-Crehuet et al., 2014).

Acne ,indeed, has significant association with metabolic syndrome. Metabolic syndrome is closely related to hyperlipidemia and so hepatosteatocytosis. (Stefanadi et al., 2018; Uzuncakmak, Akdeniz, & Karadag, 2018). Surprisingly, our patients did not reveal an abnormal hepatosteatocytosis on liver sonography except a few relatively older patients who could already be expected to have fatty liver.

Our main limitation is that we have no pretreatment liver ultrasonography results, but retrospective design of our study did not let us have such a knowledge. Since it is unreasonable that isotretinoin could correct a possible parenchymal liver disorder, identification of normal liver sonography in patients using long-term isotretinoin suggests that patients initially have healthy liver.

In addition, there could have been higher number of patients in the study. Our results, however, encourage both patients and physicians for a good harmony throughout the treatment. Our sonographic findings showed further evidence about safety of isotretinoin for patients needing it for long time.

In conclusion, we found that patients on isotretinoin treatment for at least 6 months, had normal liver ultrasonographic findings along with normal serum liver enzymes and blood lipid profile. It is clear that these data obtained from this study are valuable for patients needing long-term use, but having some concerns about hepatotoxicity.

ORCID

Habibullah Aktas https://orcid.org/0000-0001-9239-1659
Mehmet Unal https://orcid.org/0000-0002-8964-3314

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