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ORIGINAL ARTICLE

Monitoring Serum Lipid Profile and Liver Transaminase Levels During Isotretinoin Therapy

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ABSTRACT

Objective: Isotretinoin is generally chosen as the first line treatment of nodulocystic acne. Close laboratory monitoring is a general practice for many dermatologists to be on the safe side due to the laboratory side effects of isotretinoin. We aimed to determine the laboratory side effects of oral isotretinoin and optimal frequency interval for laboratory monitoring during isotretinoin treatment.

Materials and Methods: One hundred patients who were under oral isotretinoin therapy were included in the study; serum lipid levels along with liver transaminase levels were recorded at the baseline, 1-, 3- and 6- months of the therapy.

Results: We found that there might be slight elevations in serum aspartate transaminase and lipid levels during isotretinoin therapy ($p<0.05$, for all). However, statistically significant elevations were observed within the first month of isotretinoin therapy.

Conclusions: Frequent laboratory monitoring might not be necessary for all acne patients undergoing isotretinoin therapy. Patients should be screened at the first month of the therapy and then, the intervals can be extended.

Keywords: Acne vulgaris, isotretinoin, medical therapy

INTRODUCTION

Oral isotretinoin has been widely used by dermatologists since its approval by the US Food and Drug Administration (FDA) for the treatment of severe nodulocystic acne in 1982 [1]. However, many dermatologists do not feel comfortable when prescribing isotretinoin due to its clinical and laboratory side effects such as teratogenicity, hyperlipidemia and associated pancreatitis, leukopenia, thrombocytopenia, and transaminitis [2]. Although laboratory abnormalities are not observed very frequently, close laboratory monitoring is still a general practice for being on the safe side. In this study, we aimed to assess the side effects of isotretinoin on the laboratory parameters, and to detect the optimal frequency interval of laboratory monitoring for patients.

MATERIALS AND METHODS

One-hundred patients who started on oral isotretinoin therapy for acne vulgaris between January 1, 2018 and March 28, 2018 were retrospectively evaluated. Patients who have

received oral isotretinoin for at least 6 months were enrolled into the study. Liver transaminase levels (alanine aminotransferase [ALT], aspartate transaminase [AST]) and serum lipid profile (total cholesterol [T-CHOL], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C] and triglyceride [TG]) were recorded for the baseline, 1-, 3- and 6- months of the therapy using electronic medical records. Patients who have higher levels than reference limits for liver transaminases and serum lipid profile at the baseline were excluded. Baseline laboratory levels of ALT, AST, T-CHOL, LDL-C, HDL-C and TG were compared with the 1st, 3rd and 6th month levels of same parameter. Comparisons for all parameters were also made between 1st, 3rd and 6th month levels. Reference limits were shown in Table 1. All patients took isotretinoin at a dose of 20, 30 or 40 mg daily at their first course or repeated courses. This study was approved by the Ethics Committee of the Hacettepe University and is registered under the following number 2020/18-19.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.23.0. (IBM Corp., Armonk, NY). Data were presented as means ± standard deviations (SDs) or medians (ranges) when appropriate. The demographic features of the study population were analysed using descriptive statistics. Categorical variables were expressed as frequencies and percentages. Generalised estimating equations (GEEs) were used to compare consecutive data of repeated measurements, including the baseline and 1-, 3- and 6-month ALT, AST, T-CHOL, LDL-C, HDL-C and TG levels. The level of statistical significance was set at $p<0.05$.

RESULTS

A total of 100 patients (25 male; 75 female) with a mean age of 22.39 ±4.70 years (range: 9 - 38 years) were enrolled into the study. The consecutive data of the mean ALT, AST, T-CHOL, LDL-C, HDL-C and TG levels are shown in Table 1. Baseline AST, T-CHOL, LDL-C and TG levels were found to be statistically lower than 1st, 3rd and 6th month levels ($p<0.001$, for all). There were no significant differences in AST, T-CHOL, LDL-C and TG between 1st, 3rd and 6th month levels ($p>0.05$, for all). The baseline HDL-C level was statistically higher than 1st month level ($p<0.001$) but there were no differences between baseline, 3rd and 6th month levels ($p>0.05$, for all). Figures 1 and 2 show the changes of laboratory parameters in relation to monthly intervals of isotretinoin treatment.

Table 1. Consecutive data on ALT, AST, T-CHOL, LDL-C, HDL-C and TG levels.

	Baseline	1th month	p_1	3th month	p_3	6th month	p_6	pα	pβ	p_γ
ALT (< 50 U/L)	15.30 ± 7.32 (6-42)	16.45 ± 11.63 (5-76)	0,939	15.77 ± 13.53 (7-132)	1.00	15,31 ± 9,41 (6-62)	1.00	1.00	1.00	1.00
AST (< 50 U/L)	18.99 ± 4.27 (10-33)	21.85 ± 6.38 (14-52)	**<0.001**	21.69 ± 8.55 (13-94)	**<0.001**	21,69 ± 6,57 (7-46)	**<0.001**	1.00	1.00	1.00
T-CHOL (< 200 mg/dL)	163.26 ± 30.45 (72-241)	173 ± 29.16 (88-227)	**0.001**	171.88 ± 30.80 (102-238)	**0.003**	179,4 ± 34,35 (75-241)	**<0.001**	1.00	0.121	0.062
LDL-C (< 130 mg/dL)	101.53 ± 21.74 (59-150)	110.98 ± 21.61 (56-167)	**<0.001**	111.65 ± 23.00 (65-181)	**<0.001**	114,76 ± 24,72 (53-178)	**<0.001**	1.00	0.088	0.417
HDL-C (>50 mg/dL)	51.80 ± 13.13 (28-119)	50.15 ± 12.42 (29-110)	**0.016**	49.37± 10.39 (33-84)	0.065	49,73 ± 12,22 (29-113)	0.069	1.00	1.00	1.00
TG (<150 mg/dL)	80.75 ± 37.75 (28-194)	93.14 ± 38.13 (21-211)	**<0.001**	98.08 ± 47.47 (23-260)	**<0.001**	97,76 ± 47,75 (26-268)	**0.001**	0.802	1.00	1.00

Data are presented as means ± standard deviations (minimum-maximum).

$p<0.05$, statistically significant and in bold

p_1 : p value between baseline and 1st month

p_3 : p value between baseline and 3rd month

p_6 : p value between baseline and 6th month

pα : p value between 1st month and 3rd month

pβ : p value between 1st month and 6th month

p_γ : p value between 3rd month and 6th month

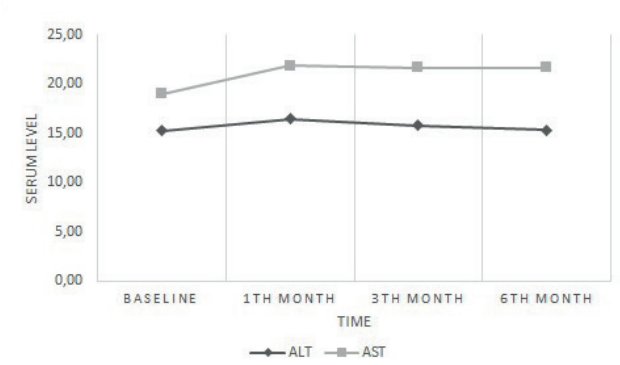

Figure 1. Changes in the mean ALT and AST levels during 6 months follow-up.

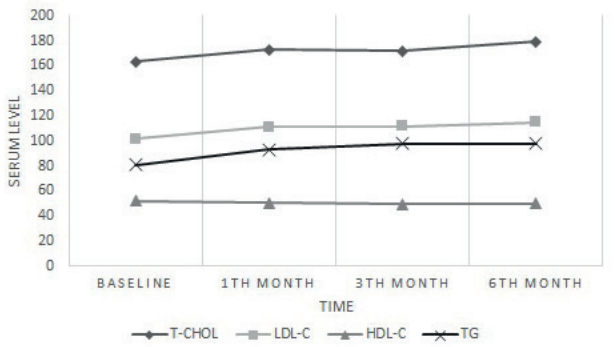

Figure 2. Changes in the mean T-CHOL, LDL-C, HDL-C and TG levels during 6 months follow-up.

DISCUSSION

Oral isotretinoin is considered as the most effective treatment available for severe acne. It is preferred by many dermatologists in severe cystic, nodular, or other actively scarring acne types [3]. Since the introduction of the drug for acne treatment, laboratory monitoring widely varied among prescribers without any standardized guidelines. The frequency of laboratory monitoring and the type of laboratory workup that should be performed during isotretinoin treatment have been recently changed as more data on the drug's side effect profile have been published.

Liver function tests, including ALT and AST, are routinely performed in acne patients receiving isotretinoin therapy. Many studies reported elevations in liver function tests, but these elevations were not associated with irreversible hepatic sequelae [2,4]. In the literature, mild to moderate ALT levels have been detected in up to 8.9% of asymptomatic patients. Fatty liver disease, as a result of obesity, and alcohol intake were identified as risk factors for elevated AST and ALT levels [4]. In our study, we found statistically significant elevation in AST levels, whereas there was no statistically significant elevation in ALT levels. The degree of elevation in AST levels was mild and no deviations from the reference range were observed. AST and ALT are enzymes that are not-specific for liver and they can be found in muscle and other tissues including red blood cells. Elevated muscle enzymes, including creatine kinase (CK), have been reported in many studies due to the intake of oral isotretinoin [5,6]. CK elevations greater than five times of normal can be a sign of rhabdomyolysis, which can lead to renal damage [7]. Webster et al.[8] claimed that AST elevation was usually accompanied by CK elevation, suggesting a muscle (rather than liver) source for the AST. They reported that ALT was less strongly paired with CK but there was still some overlap. Although we did not test CK to correlate it with AST and ALT in our study, we thought that the elevation of AST may be associated with muscle damage, not with liver damage. Therefore, Gamma glutamyltransferase (GGT), which is a liver specific enzyme, might be preferred for monitoring liver functions. Additionally, slight increase in AST level in the first month of treatment and its stability in the following months suggested that frequent follow-up was not required.

Serum lipid elevations are well known laboratory abnormalities seen in isotretinoin therapy [4]. Barbieri et al.[9] reported high TG levels (>500 mg/dL) in fewer than 1% of patients who were screened. High TG levels (>800 mg/dL) might be a risk factor for the development of acute pancreatitis but the few reported cases in the literature illustrate that pancreatitis is not likely caused by hypertriglyceridemia because elevations were mild to moderate in those patients, it occurs idiosyncratically more commonly than due to the hypertriglyceridemia, itself [10,11]. Therefore, screening the lipid profile might not be preventive for the development of acute pancreatitis. In our study, T-CHOL, LDL-C and TG were found to be statistically elevated on the 1st, 3rd and 6th month of therapy compared to the baseline but the following elevations were not statistically significant after the 1st month when compared with each other. This data might support that monitoring the serum

lipids is adequate just for the first month of therapy and there is no need for repeated tests. When examining the lipid and enzyme parameters, we did not take the variable doses of isotretinoin into account. This might be the limitation of the study.

Extending the monitoring intervals can reduce overcrowding in hospitals, especially under pandemic conditions. Thus, by not monitoring patients frequently, we can also treat patients who want to receive isotretinoin treatment during the pandemic period but are reluctant to come to the hospital very often.

In conclusion, mild elevations that are within the reference ranges might be expected in serum AST, T-CHOL, LDL-C, and TG levels during isotretinoin therapy, and the elevations are usually observed on the first month of therapy. There might be no need for close monitoring of AST, T-CHOL, LDL-C, and TG levels after the first month of therapy.

Author contribution

Study conception and design: DG, and EB; data collection: DG and EB; analysis and interpretation of results: DG, NA, BYA, SEE, SD, GEL, AK and EB; draft manuscript preparation: DG and EB. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Ethics Committee (Protocol no. 2020/18-19/2020).

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Conflict of interest

The authors declare that there is no conflict of interest.

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