ORIGINAL ARTICLE

A Prospective Cohort Study of Laboratory Abnormalities During Isotretinoin Treatment For Acne Vulgaris

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Abstract

Background

Acne vulgaris is a chronic inflammatory condition of the pilosebaceous unit. Isotretinoin is used to treat moderate to severe acne that is resistant to antibiotics and topical agents. However, it may cause alterations in lipids and liver enzymes.

Methods

A total of 129 patients with acne vulgaris (moderate to severe facial acne) treated with isotretinoin were recruited between May 2020 and July 2021 from the dermatology clinics at Hospital Serdang and Hospital Kuala Lumpur. Of these, 120 patients with complete data of lipid panel (total cholesterol, low density lipoprotein cholesterol [LDL], triglycerides [TG], and high density lipoprotein cholesterol [HDL]) and hepatic panel (alanine transaminase [ALT] and aspartate transaminase [AST]) levels at baseline, and in three subsequent follow-up visits (i.e., one, three, and six months) were included in the analyses. Abnormalities were graded according to standard laboratory values and their severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE)grading system.

Results

Of the 120 study participants, 83% were female and 37% were male between the ages of 15 and 36 years. We observed a significant increase in median values at baseline and at the six-month follow-up for total cholesterol ($p<0.0001$), triglycerides ($p<0.0001$), LDL ($p<0.0001$), ALT ($p<0.0001$), and AST ($p<0.0001$). We observed a significant correlation between body mass index and the HDL ($r^2=-0.26$, $p=0.01$) and ALT ($r^2=0.383$, $p=7.9x10\text{-}06$) levels. Based on the CTCAE grading system, almost all study participants with abnormal results had grade 1 abnormalities. Only one patient had a grade 2 abnormality in ALT, which required treatment discontinuation.

Conclusion

Low dose isotretinoin therapy for acne vulgaris may cause mild and non-progressive elevation of LDL, total cholesterol, and liver transaminases which do not require treatment withdrawal in most cases.

Key words: *Acne vulgaris; Isotretinoin; Lipid profile; liver transaminases*

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Introduction

Acne vulgaris is the formation of comedones, papules, pustules, nodules, and/or cysts as a result of obstruction and inflammation of pilosebaceous units (hair follicles and their accompanying sebaceous glands).[1] Acne vulgaris can be classified as non-inflammatory (characterized by comedones) and inflammatory (characterized by papules, pustules, nodules, and cysts).[2]

An estimated 9.4% of the global population is affected by acne, making it the eighth-most prevalent disease worldwide.[3-5] Approximately 80% of people are affected by acne between the onset of puberty and 30 years of age.[4] In the local scenario, a study conducted among medical students aged 19-25 years at Hospital University Kebangsaan Malaysia between 2011 and 2012 showed that the prevalence of acne was 68.1%, with a comparable ratio of males to females (1:1.1).[6]

Isotretinoin or 13-cis-retinoic acid (i.e., a synthetic analogue of vitamin A) is recommended for the treatment of severe inflammatory acne of the nodulocystic or conglobate types and for cases of acne vulgaris with evidence of resistance to previous treatments with antibiotics or topical medication. Isotretinoin acts on the sebaceous glands by binding to specific retinoid receptors, modifying gene transcription.[7] It reduces the activity and size of the gland, decreasing the quantity of sebum it produces and reducing the number of Cutibacterium acnes.[7] It produces a significant reduction in comedogenesis by decreasing hyperkeratinization.[8]

Isotretinoin also may cause clinical side effects and laboratory changes, the most important being teratogenicity.[9] Mucocutaneous side effects include cracked lips, dryness of the skin and nasal mucosa, skin redness, eye dryness, and eye irritation.[3,10]

Isotretinoin treatment may increase liver transaminases (alanine aminotransferase, ALT and aspartate aminotransferase, AST), serum triglycerides (TGs), and low-density lipoproteins (LDL) cholesterol and reduce the level of high-density lipoprotein (HDL) cholesterol.[10,13] Abnormalities in serum lipid levels were common during isotretinoin therapy, while abnormalities in transaminase levels were less common and generally mild.[13] High levels of TGs and low levels of HDL cholesterol are risk factors for coronary heart disease and ischaemic stroke.[13] Isotretinoin causing drug-induced pancreatitis through hypertriglyceridemia has been reported but is rare.[14]

There are very limited data on changes in the liver enzymes and lipid levels among isotretinoin users in Malaysia. Laboratory monitoring of serum lipids and liver function tests are also at the discretion of the physician, and there is wide variation in the type and frequency of monitoring that is performed. The aim of this study was to evaluate alterations in lipid parameters (i.e., total cholesterol, TG, LDL, HDL) and liver transaminases (i.e., AST and ALT) in acne vulgaris patients treated with low dose isotretinoin.

Materials and Methods

This was a prospective cohort study conducted between May 2020 and July 2021 in the dermatology clinics of Hospital Kuala Lumpur and Hospital Serdang.

Using the two population means formulae, paired t-test (published mean of ALT at three months=18.2 (±4.59), published mean of ALT at six months=23.3 (±20.23), α-value=0.05, power of statistical test=80%, confidence level=95%, four follow-up visits, and consideration of 20% dropout rate), the calculated sample size was 117 study participants. A total of 129 eligible study participants diagnosed with acne vulgaris (moderate to severe) who did not respond to combined therapy (i.e., topical, and systemic treatment) were screened and recruited. Of these, 120 participants completed the study.

Participants were briefed about the study and their written consent was obtained by the clinicians. Acne vulgaris patients with the

following conditions were excluded from the study: i) pregnant or planning for pregnancy, ii) history of hypersensitivity reactions to isotretinoin, iii) pre-existing liver disease, iv) hematological disorders, or v) receiving isotretinoin therapy for conditions other than acne.

The severity of acne in the study participants was assessed and determined using the Comprehensive Acne Severity Scale criteria.[2] A standardized data collection form was used to collect sociodemographic data as well as the laboratory biochemical tests of lipid profile (i.e., total cholesterol, TG, LDL, and HDL) and liver transaminases (i.e., ALT and AST) at recruitment (baseline). Patients were followed up at three different visits, i.e., at one month, three months, and six months. At each follow-up visit, the patients were assessed by their treating clinicians, and the isotretinoin dose was adjusted, whenever necessary, according to the standard clinical practice at both study sites.

Blood was also drawn from patients to quantify lipid profile and liver transaminases. Outcomes were recorded based on standard laboratory values and their severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0 grading system.[16]

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the Malaysian Good Clinical Practice Guidelines. Ethical approval was obtained from the Medical Research and Ethics Committee of the Malaysian Ministry of Health [KKM/NIHSEC/P20-925(12)].

Descriptive statistics were performed to describe the characteristics of the study population and data set. Numerical values were presented as mean and standard deviation (SD) or median and interquartile range (IQR), while categorical variables were presented as absolute number and percentage. The Friedman test, a nonparametric alternative to the one-way ANOVA with repeated measures, was used to test for median differences in lipid profiles and liver transaminases between different clinical visits. The Spearman correlation test was performed to investigate the correlation between lipid profile and liver transaminases and ody mass index (BMI). Results with $p<0.05$ were considered statistically significant. All data analyses were performed using IBM SPSS Statistics for Windows version 21.0.

Results

Nine study participants defaulted follow-up, hence excluded from the data analyses. Of the 120 remaining participants, 83 (69.2%) were female and 37 (30.8%) were male, with ages ranging between 15 and 36 years. Of the 120 participants, 36 (30%) were overweight and obese, while only three individuals (2.5%) had comorbidities. Eighty-six patients (71.7%) were diagnosed with moderate acne and 34 (28.3%) with severe acne, with the mean duration of acne being 6±4.20 years.

All the study subjects were treated with low doses of isotretinoin ranging from 0.2 to 0.4 mg/kg, with daily doses of between 10 to 30 mg daily, which is the standard clinical practice at the study sites (see Table 1). Our data showed that 89.2%, 65%, and 80.8% of participants were treated with the lowest isotretinoin dose of 10 mg daily at baseline, which was continued at first and third months of follow-up, respectively till 6th month of treatment (Table 1).

A total of 107 patients received 10 mg daily during the first month. At the second follow-up, the dose was increased to 20 mg daily in 28 (26%) of the patients for the subsequent 2 months. At the third follow-up, the treatment dose was reduced back to 10 mg daily in 14 (50%) of the 28 patients for the final 3 months. These adjustments were based on the clinical responses and the biochemical test results (i.e., lipid profile and liver transaminase).

Table 1. Patient characteristics and isotretinoin doses on repeated follow-up

Variables (n=120)		Mean±SD	n (%)
Age 15-25 26-29 30-36		23±5.0	 96 (80) 13 (11) 11 (9)
Sex Male Female			 37 (30.8) 83 (69.2)
Ethnicity Malay Chinese Indian Others			 110 (91.7) 6 (5.0) 2 (1.7) 2 (1.7)
Body Mass Index (kg/m^2) Healthy (18.5-24.9) Overweight (25.0-29.9) Obese (≥30.0)		22.9±3.96	 84 (70.0) 29 (24.2) 7 (5.8)
Comorbidities Absent Present			 117 (97.5) 3 (2.5)
Severity of acne Moderate Severe			 86 (71.7) 34 (28.3)
1st treatment with isotretinoin 2nd treatment with isotretinoin			118 (98.3) 2 (1.7)
Duration of acne (years)			6 ± 4.20
Isotretinoin dose (mg) at 1st month (1st visit)	10		107 (89.2)
	20		12 (10.0)
	30		1 (0.8)
Isotretinoin dose (mg) at 2nd and 3rd month (2nd visit)	10		78 (65.0)
	20		41 (34.2)
	30		1 (0.8)
Isotretinoin dose (mg) at 4th-6th month (3rd visit)	10		97 (80.8)
	20		22 (18.3)
	30		1 (0.8)

Lipid profile and liver transaminase

Our data demonstrated significantly higher levels of the total cholesterol, TG, and LDL, but not the HDL, at the six-month follow-up when compared with the baseline. Likewise, a significant increasing trend was observed in the liver transaminases, i.e., ALT and AST as shown in Table 2.

We further compared the incidence of abnormal laboratory parameters (i.e., lipid profiles and liver transaminase) at baseline and in each follow-up visit. Since the majority of our patients (n=107) were prescribed the lowest dosage (10mg) of isotretinoin at baseline, our analysis of the incidence of abnormal laboratory parameters included only these study participants. In addition, we investigated whether dose adjustment at different clinical visits affects the incidence of abnormal laboratory parameters. Interestingly, we observed a significant increase in the incidence of abnormal LDL from 65.4% to 81.3% ($p<0.05$) (see Table 3).

Table 2. Effects of oral isotretinoin on repeated measures of lipid profiles and liver transaminases

Laboratory variable	Baseline Median (IQR)	1st month Median (IQR)	3rd month Median (IQR)	6th month Median (IQR)	*p-value*
Total cholesterol	4.8 (1)	4.9 (1)	5.1 (1)	4.9 (1)	<0.001
Triglycerides	0.8 (0.5)	0.8 (0.5)	0.9 (0.5)	0.9 (0.5)	<0.001
LDL	2.98 (0.9)	3.1 (0.8)	3.1 (0.7)	3.1 (0.7)	<0.001
HDL	1.4 (0.4)	1.4 (0.3)	1.4 (0.4)	1.4 (0.4)	0.656
ALT	12 (10)	12 (9)	14 (11)	15 (12)	<0.001
AST	18 (5)	19 (6)	20 (7)	20 (6)	<0.001

Although increasing trends of abnormal incidence were observed for total cholesterol, TGs, HDL, ALT and AST, these were however nonsignificant. We further observed that, of the 28 participants prescribed with an increment of isotretinoin dosage at the 1st-month follow-up visit (from 10 mg daily to 20 mg daily), half of these participants (n=14, 50%) were adjusted to the initial starting dosage of 10 mg at the 3rd month by the treating clinicians based on the clinical observations and laboratory findings (see Table 3).

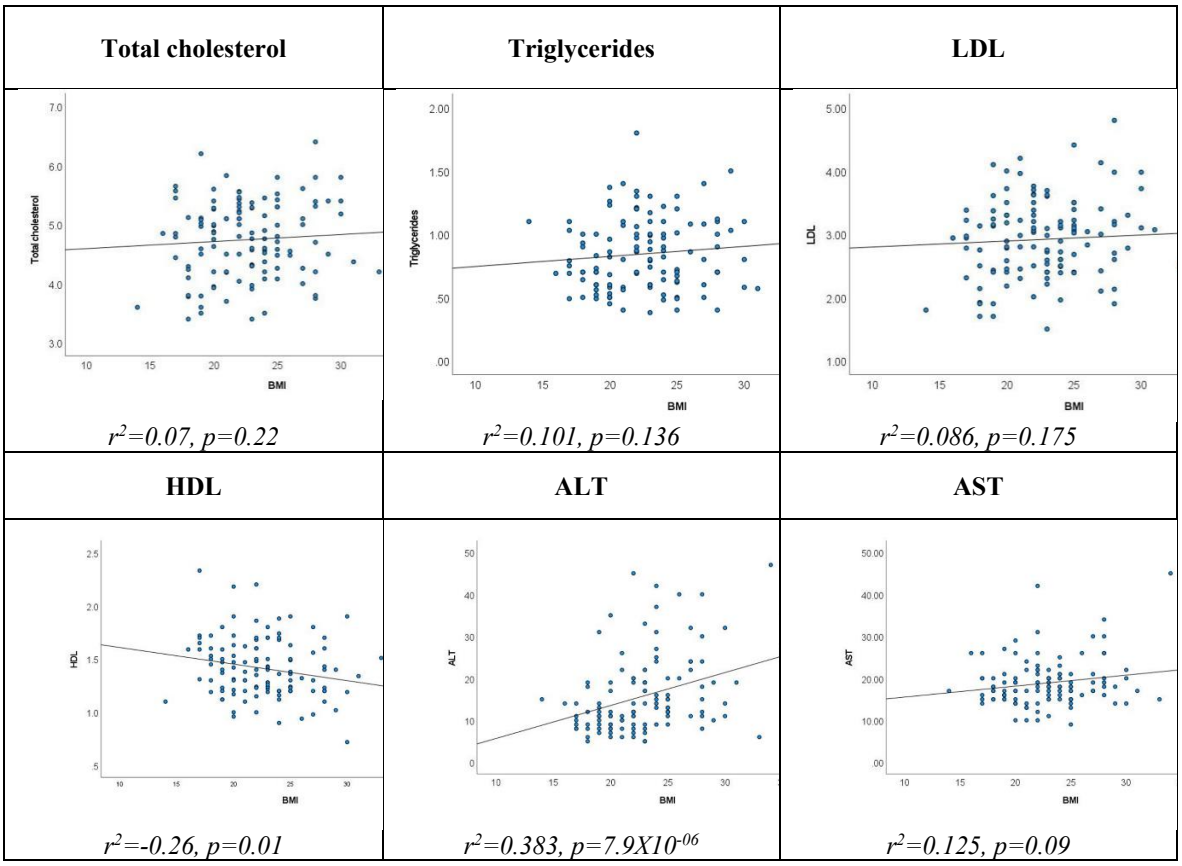
We then investigated the relationship between body mass index (BMI) and the baseline laboratory parameters, i.e., lipid profile and liver transaminases, which were quantified. Our data showed a significant negative correlation between BMI and HDL level ($r^2=-0.26$, $p=0.01$), indicating the higher the BMI of the participants in this study cohort, the lower the HDL level. On the other hand, we observed a positive correlation between BMI and ALT ($r^2=0.383$, $p=7.9X10^{-06}$).

Table 3. Incidence of acne vulgaris patients with abnormal levels of lipids and liver transaminase parameters

Biochemistry Test	Baseline		1st month		3rd month			6th month		
	Normal (n, %)	Abnormal (n, %)	Normal (n, %)	Abnormal (n, %)	Dose adjustment	Normal (n, %)	Abnormal (n, %)	Dose adjustment	Normal (n, %)	Abnormal (n, %)
Total Cholesterol	79 (73.8)	28 (26.2)	72 (67.3)	35 (32.7)	Overall	65 (60.7)	42 (39.3)	Overall	65 (60.7)	42 (39.3)
					10 mg daily	48 (73.8)	30 (71.4)	10 mg daily	54(83.1)	34 (81)
					20 mg daily	17 (26.2)	11 (26.2)	20 mg daily	11(16.9)	8(19)
					30 mg daily	0 (0)	1 (2.4)	30 mg daily	0	0
TG	107 (100%)	NA	105 (98.1)	2 (1.9)	Overall	105 (98.1)	2 (1.9)	Overall	105 (98.1)	2 (1.9)
					10 mg daily	77 (73.3)	1 (50)	10 mg daily	87(82.9)	1(50)
					20 mg daily	27 (25.7)	1 (50)	20 mg daily	18(17.1)	1(50)
					30 mg daily	1 (1)	0	30 mg daily	0	0
LDL	37 (34.6%)	70 (65.4) *	25 (23.4)	82 (76.6) *	Overall	20 (18.7)	87 (81.3) *	Overall	20 (18.7)	87 (81.3) *
					10 mg daily	16 (80)	62 (71.3)	10 mg daily	17(85)	71(82)
					20 mg daily	4 (20)	24 (27.6)	20 mg daily	3(15)	16(18.4)
					30 mg daily	0	1 (1.1)	30 mg daily	0	0
HDL	28 (26.2%)	79 (73.8)	24 (22.4)	83 (77.6)	Overall	26 (24.3)	81 (85.7)	Overall	26 (24.3)	81 (75.7)
					10 mg daily	20 (76.9)	58 (71.6)	10 mg daily	22 (84.6)	66 (81.5)
					20 mg daily	6 (23.1)	22 (27.2)	20 mg daily	4 (15.4)	15 (1.2)
					30 mg daily	0 (0)	1 (1.2)	30 mg daily	0 (0)	0 (0)
ALT	105 (98.1)	2 (1.9)	112 (95.3)	5 (4.7)	Overall	100 (93.5)	7 (6.5)	Overall	100 (93.5)	7 (6.5)
					10 mg daily	73 (73)	5 (71.4)	10 mg daily	82 (82)	6 (85.7)
					20 mg daily	26 (26)	2 (28.6)	20 mg daily	18 (18)	1 (14.3)
					30 mg daily	1 (1)	0 (0)	30 mg daily	0 (0)	0 (0)
AST	106 (99.1)	1 (0.9)	116 (99.1)	1 (0.9)	Overall	106 (99.1)	1 (0.9)	Overall	106 (99.1)	1 (0.9)
					10 mg daily	77 (72.6)	1 (100)	10 mg daily	87 (82.1)	1 (100)
					20 mg daily	28 (26.4)	0 (0)	20 mg daily	19 (17.9)	0 (0)
					30 mg daily	1 (1)	0 (0)	30 mg daily	0 (0)	0 (0)

*Statistically significant increase in the incidence of abnormal level of LDL at 6th month compared with baseline

Figure 1. Correlation between baseline lipid profile and liver transaminase with BMI



Discussion

Our study explored the changes in liver enzymes (AST and ALT) and lipid profile (total cholesterol, TG, LDL, and HDL) during typical treatment with oral isotretinoin over a six-month period. This study showed a statistically significant increase in total cholesterol, LDL, TG, and liver transaminases (ALT and AST). Liver enzymes were less affected by isotretinoin therapy than lipid profiles. No significant changes were observed in HDL. Several studies evaluating the effects of isotretinoin on liver enzymes and lipids suggest that oral isotretinoin may cause changes to varying degrees, alterations in liver transaminases (AST and ALT), and lipid profiles (particularly TG, LDL, and total cholesterol).[1,4] Many studies suggest that isotretinoin use is associated with increases in TG and LDL and decreases in HDL levels.[8,10,14]

Zane et al. studied 13,772 patients with acne who received oral isotretinoin therapy between 1995 and 2002. They reported a cumulative incidence of new abnormalities in patients with normal baseline values with a frequency of 44% for TG, 31% for total cholesterol levels, and 11% for transaminase levels. Moreover, these abnormalities were generally transient and reversible.[11] Most studies show a moderate increase in serum lipids (but a decrease in HDL) in a minority of patients, usually occurring at baseline and plateauing or declining in subsequent weeks.[15]

Our study supports these findings. However, this study is limited to observation of treatment over a 6-month period, so the subsequent consequences of abnormalities in test results at the end of treatment could not be evaluated. Interestingly, most abnormalities were observed in the first 3 months of treatment, with no further changes toward the end of treatment. Of the study participants with abnormal results, almost all had grade 1 abnormalities in both lipids and liver transaminases (based on CTCAE grading). Only one patient developed a grade 2 abnormality at ALT, which required treatment discontinuation. The abnormalities

in this cohort were generally mild and did not require treatment interruption.

Although many studies have reported significant changes in total cholesterol and TG and liver transaminases, other studies have reported that these adverse effects are minimal and do not affect the course of treatment.[17] Alcalay et al studied 907 patients who had completed five to nine months of treatment. They reported that only 1.5% of patients had serum TG levels above 400 mg/dL. Serum levels of liver enzymes were not sufficiently elevated to a degree necessitating discontinuation of treatment.[18] In addition, Brito et al conducted a prospective clinical and laboratory evaluation of 150 patients treated with oral isotretinoin before initiation of therapy, one month after initiation, and every three months thereafter until completion of treatment. They found no statistically significant changes in liver transaminases, TG, or cholesterol levels.[1] In another study of 30 participants, Baxter et al also reported no significant changes in TG or cholesterol levels measured at baseline or during.[19]

All our patients received an isotretinoin dose of 0.2-0.4 mg/kg, with 89.2% (n=107) of the patients receiving an isotretinoin dose of 10 mg at baseline. In approximately 42% of the study participants, the dose was increased during the first 3 months of treatment. A statistically significant increase in abnormal LDL levels ($p<0.05$) from baseline to follow-up at month 6 was observed in most participants who received a 10 mg dose at baseline. Increasing trends in the occurrence of abnormalities were also observed for total cholesterol, TGs, HDL, ALT, and AST, but these were not significant. The low isotretinoin dose used for clinical treatment in this cohort may be a contributing factor to the mild biochemical changes and better tolerability in patients. A study by Bettoli et al. showed that a low initial dose of 0.1-0.2 mg/kg/day, or about 10 mg daily, and a gradual increase to the highest dose tolerated by the patient, is a successful way to achieve good clinical results while minimizing side effects compared with a standard dose of 0.5 mg/kg/day.[20]

Approximately 27.5%, 79%, and 74% of study participants had abnormal baseline total cholesterol, LDL, and HDL, respectively. Our data showed that 30% of the study participants fell into the overweight and obese category (BMI). This study was conducted during the Covid pandemic, in which most people had a sedentary lifestyle compared with the pre-pandemic period. This may have contributed to the unhealthy BMI and lipid abnormalities at baseline. However, changes in BMI and its correlation with blood levels were not studied during the six-month follow-up period. These participants also had a negative correlation between BMI and HDL (the higher the BMI, the lower the HDL). Significantly low HDL levels accompanied by high LDL levels and an unhealthy BMI at baseline suggest a potential risk for metabolic syndrome and cardiovascular disease. A positive correlation between BMI and ALT in this study may indicate the risk of fatty liver in participants. Close monitoring of lipid profile and liver enzyme parameters is particularly important in patients at high risk of developing metabolic syndrome.

Although our study demonstrated statistically significant increases in total cholesterol, LDL, TG, ALT, and AST, they are clinically insignificant as low-dose isotretinoin was well tolerated by the study participants. Nevertheless, lipid profiling and liver function tests should be routinely performed in all patients starting treatment with isotretinoin. This should be followed by repeat blood testing after two months. If repeat test results are normal after two months, further laboratory monitoring may not be necessary. If abnormalities are present, or a higher dose adjustment is required, more frequent monitoring is recommended.

Limitations

Low-dose isotretinoin was used in this study with most patients receiving 0.2-0.3 mg/kg. This may explain the mild changes observed in liver transaminases and lipid panels. This study was conducted in the Klang Valley area only, hence the results may not represent the whole

population of Malaysia.

Conclusion

Low-dose isotretinoin therapy for acne may cause mild and non-progressive elevation of LDL, total cholesterol, and liver transaminases which do not require the withdrawal of treatment in most cases.

Conflict of Interest Declaration

The author have no conflict of interest to declare.

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