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The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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The WJCC is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for WJCC as 1.534; IF without journal self cites: 1.491; 5-year IF: 1.599; Journal Citation Indicator: 0.28; Ranking: 135 among 172 journals in medicine, general and internal; and Quartile category: Q4. The WJCC's CiteScore for 2021 is 1.2 and Scopus CiteScore rank 2021: General Medicine is 443/826.

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Retrospective Study

Optimal laboratory testing protocol for patients with acne taking oral isotretinoin

Yu Jeong Park, Hui Young Shin, Woo Kyoung Choi, Ai-Young Lee, Seung Ho Lee, Jong Soo Hong

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Abstract

BACKGROUND

Isotretinoin is a widely prescribed drug for various dermatological conditions, especially acne. Blood tests are routinely performed to monitor its side effects. However, the optimal testing schedule remains controversial.

AIM

To evaluate the laboratory monitoring tests and schedules of patients with acne taking isotretinoin to determine the most efficient testing regimen.

METHODS

We retrospectively reviewed electronic medical records from the Dermatology Department of Dongguk University Ilsan Hospital from 2005 to 2020 for patients prescribed isotretinoin for acne who underwent monthly blood tests.

RESULTS

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and triglyceride (TG) levels significantly changed between 5 and 6 mo when the total prescription period and dose variables were considered altogether. The high-density lipoprotein level also significantly changed between 5 and 6 mo. However, low-density lipoprotein (LDL) and total cholesterol levels significantly changed between 1 and 2 mo.

CONCLUSION

We recommend testing AST, ALT, and TG levels once every 5 to 6 mo. We also suggest testing LDL and total cholesterol levels during the first and second months.

Key Words: Acne vulgaris; Isotretinoin; Clinical laboratory techniques; Vitamin A; Liver

function test; Lipid panel

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Core Tip: Isotretinoin is a widely prescribed drug for various dermatological conditions, especially acne. Blood tests are routinely performed to monitor its side effects. However, the optimal testing schedule remains controversial. This study investigated the optimal blood test type and frequency for patients taking isotretinoin for acne. This article will contribute to Asian-specific isotretinoin laboratory guidelines and further studies.

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INTRODUCTION

Oral isotretinoin is a natural vitamin A metabolite (a retinoid) approved for use in 1982 by the United States Food and Drug Administration to treat acne vulgaris[1-4]. Isotretinoin inhibits sebaceous cell proliferation, differentiation, and lipid synthesis *in vivo*[1]. It also suppresses acne by reducing inflammation caused by *Propionibacterium acnes* and hyperkeratosis of the hair follicle sebaceous gland system [1].

Isotretinoin is a very effective treatment for acne. However, side effects such as teratogenicity, hyperlipidemia, pancreatitis, and leukopenia are possible and require periodic laboratory monitoring[1-10]. The 2016 laboratory monitoring guidelines in the US do not recommend routine monitoring of the complete blood cell count (CBC) during oral isotretinoin administration for acne[1,5,6]. However, the United States and European guidelines recommend monitoring serum lipid profiles and liver function enzymes[1]. Specifically, they recommended performing a liver and lipid panel before treatment, 1 mo after treatment, and every 3 mo thereafter[1].

In Korea, isotretinoin doses and routine laboratory monitoring protocols vary, which has likely contributed to the increase in unnecessary hospital visits, thus increasing medical expenses, which is detrimental to the finances of the national health insurance. In Korea, although the adverse effects of isotretinoin therapy for acne are known, a cohort study analyzing laboratory changes at a single institution does not exist, nor do Asian-specific guidelines regarding isotretinoin dose and monitoring protocols.

This study retrospectively investigated hematological monitoring tests and intervals for patients taking isotretinoin for acne at a single institution to determine the most effective protocol.

MATERIALS AND METHODS

Study period and population

This retrospective study analyzed medical records obtained from Dongguk University Ilsan Hospital's electronic medical records database. We included patients who visited the dermatology outpatient department at this hospital from 2005 to 2020 and were prescribed isotretinoin for acne based on the Korean standard classification of disease codes L700 (acne vulgaris), L701 (acne conglobata), and L709 (acne, unspecified). Among them, patients who had not taken isotretinoin for > 1 mo or had irregular laboratory monitoring instead of terminating laboratory monitoring at 1-mo intervals because side effects were excluded from the analysis. For example, patients who underwent laboratory testing at 2 mo after the first dose, or those who underwent laboratory testing at 1st month and 4th month sporadically, rather than serial laboratory monitoring, were excluded.

Data on age, sex, prescription dose, prescription period, and underlying disease were collected. Patients who underwent monthly laboratory monitoring for aspartate aminotransferase (AST), alanine aminotransferase (ALT), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol levels were included. Meanwhile, patients with irregular laboratory testing intervals during isotretinoin administration were excluded from the study.

The Institutional Review Board of Dongguk University Ilsan Hospital approved this study (IRB No. DUIH 2022-05-002).

Blood testing

All blood tests were performed in US units. Normal AST levels were 10-40 units/L for men and 9-25 units/L for women. Normal ALT ranges were 10-55 units/L for men and 7-30 units/L for women. Furthermore, the normal range (men and women) for the TG level was 40-200 mg/dL. Finally, HDL levels \geq 40 mg/dL, LDL levels \leq 100 mg/dL, and total cholesterol levels $<$ 200 mg/dL were considered normal.

Outcomes

Laboratory values for AST, ALT, TG, HDL, LDL, and total cholesterol levels were identified for each patient and were categorized by month of therapy for those performed while the patient was receiving isotretinoin. The tendency of the laboratory values to change was determined through the graph slope of the median value.

Statistical analyses

Independent variables (*e.g.*, sex, total prescription date and dose, daily average prescription dose, underlying disease type, and monthly interval per blood test) were analyzed by repeated-measures analysis of variance. Significance was set at $P < 0.05$.

RESULTS

Patient demographics

Among the 112 patients with acne, 30 were included in the analysis according to the exclusion criteria. Nineteen (63.3%) were male, and 11 (36.7%) were female. The average age was 22.8 years. The total number of prescription days was 60-180 d, with a mean of 140 d. The total prescribed dose was 600-3600 mg, with a mean total of 1825.4 mg. The lowest daily dose was 5 mg/d, and the highest daily dose was 20 mg/d; the average daily dose was 13.2 mg.

In total, 23 patients had no underlying diseases. However, one patient had androgenetic alopecia, one had asthma, one had Crohn's disease, one had ulcerative colitis, one had seborrheic dermatitis, and two had urticaria (Table 1).

Monthly blood test abnormalities

Blood tests were performed for 30 patients 1 mo after taking isotretinoin (Table 2). Overall, 2 (7%) patients had abnormal AST levels, 2 (7%) had abnormal HDL levels, 21 (70%) had abnormal LDL levels, and 6 (20%) had abnormal total cholesterol levels. All the patients had normal ALT and TG levels.

Blood tests were performed after 2 mo of isotretinoin administration ($n = 26$). Overall, 2 (8%), 1 (4%), 2 (8%), 19 (73%), and 4 (15%) patients had abnormal AST, ALT, HDL, LDL, and total cholesterol levels, respectively. All the patients had normal TG levels.

Blood tests were performed after 3 mo of isotretinoin administration ($n = 21$). Overall, 4 (19%), 1 (5%), 1 (5%), 14 (67%), and 5 (24%) patients had abnormal AST, ALT, HDL, LDL, and total cholesterol levels, respectively. One (5%) patient had an abnormal TG level.

Blood tests were performed 4 mo after isotretinoin administration ($n = 20$). Overall, 1 (5%), 1 (5%), 14 (70%), and 3 (15%) patients had abnormal AST, ALT, LDL, and total cholesterol levels, respectively. All the patients had normal HDL and TG levels.

Blood tests were performed after 5 mo of isotretinoin administration ($n = 18$). Overall, 1 (6%), 11 (61%), and 5 (28%) patients had abnormal HDL, LDL, and total cholesterol levels, respectively. All the patients had normal AST, ALT, and TG levels.

Blood tests were performed after 6 mo of isotretinoin administration ($n = 10$). Overall, 1 (8%), 1 (8%), 7 (54%), and 3 (23%) patients had abnormal AST, ALT, LDL, and total cholesterol levels, respectively. All the patients had normal HDL and TG levels.

Monthly changes per blood test

Table 3 and Figure 1 present the monthly changes per blood test in detail.

AST: The AST level did not change when only AST values were included in the analysis. However, the AST level significantly changed between 5 and 6 mo of isotretinoin use when the prescription period and dose were included in the analysis (Figure 1A).

ALT: Although Figure 1B indicates that the median value of ALT tended to increase over a longer period of use, no significant change in ALT levels was observed when only the blood test values were considered. However, significant changes were observed between 5 and 6 mo of isotretinoin administration when the prescription period and dose were included in the analysis.

TG: Figure 1C presents that the median value of TG tended to increase over a longer period of use; significant changes were observed between 5 and 6 mo of isotretinoin administration. Significant

Table 1 Overall patients' characteristics

Characteristics	Mean (min-max)	n (%)
Age	22.8 (15-38)	30 (100)
Sex	Male	19 (63)
	Female	11 (37)
	Total	30 (100)
Total prescription days	339.1 (230-1216)	
Total prescription dose (mg)	4029.7 (230-10495)	
Daily prescription dose (mg/d)	13.2 (8.01-20)	
Underlying disease	None	23 (77)
	Androgenetic alopecia	1 (3)
	Asthma	1 (3)
	Crohn's disease	1 (3)
	Ulcerative colitis	1 (3)
	Seborrheic dermatitis	1 (3)
	Urticaria	2 (6)

Table 2 Number of patients with a laboratory abnormality by month of therapy

Laboratory	Month 1 (total number: 30), n (%)	Month 2 (total number: 26), n (%)	Month 3 (total number: 21), n (%)	Month 4 (total number: 20), n (%)	Month 5 (total number: 18), n (%)	Month 6 (total number: 13), n (%)
AST	2 (7)	2 (8)	4 (19)	1 (5)	0 (0)	1 (8)
ALT	0 (0)	1 (4)	1 (5)	1 (5)	0 (0)	1 (8)
TG	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)
HDL	2 (7)	2 (8)	1 (5)	0 (0)	1 (6)	0 (0)
LDL	21 (70)	19 (73)	14 (67)	14 (70)	11 (61)	7 (54)
Total cholesterol	6 (20)	4 (15)	5 (24)	3 (15)	5 (28)	3 (23)

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

changes in the prescription period and dose were also observed between 5 and 6 mo after including the dependent variable.

HDL: Generally, the median value of HDL in [Figure 1D](#) tended to decrease, and a significant change was observed between 5 and 6 mo of isotretinoin administration when only the blood test values were considered. However, this effect disappeared after including the dependent variable.

LDL: Although [Figure 1E](#) demonstrates that the median value of LDL tended to increase over a longer period of use, the LDL level did not change when we included only the LDL values in the analysis. However, the LDL level significantly changed between 1 and 2 mo of isotretinoin use when the prescription period and dose were included in the analysis.

Total cholesterol: Although [Figure 1F](#) presents that the median value of total cholesterol tends to increase over a longer period of use, the total cholesterol level did not change when we included only the blood test values in the analysis. However, a significant change was observed between 1 and 2 mo of isotretinoin use when the prescription period and dose were included in the analysis.

Table 3 Significant monthly change points for each blood test and their relationship to the dependent variable

Blood test	Variable	1-2 mo	2-3 mo	3-4 mo	4-5 mo	5-6 mo
AST	Sex	0.221	0.761	0.769	0.467	0.743
	Prescription days	0.721	0.341	0.584	0.777	0.020
	Prescription dose	0.588	0.310	0.369	0.980	0.029
	Total	0.523	0.434	0.868	0.311	0.153
ALT	Sex	0.296	0.362	0.174	0.912	0.927
	Prescription days	0.699	0.055	0.345	0.262	0.016
	Prescription dose	0.948	0.081	0.527	0.314	0.021
	Total	0.580	0.261	0.689	0.709	0.126
TG	Sex	0.818	0.357	0.538	0.858	0.313
	Prescription days	0.801	0.681	0.823	0.718	0.008
	Prescription dose	0.730	0.355	0.876	0.883	0.009
	Total	0.788	0.501	0.529	0.536	0.024
HDL	Sex	0.552	0.999	0.747	0.498	0.190
	Prescription days	0.475	0.227	0.579	0.922	0.323
	Prescription dose	0.632	0.190	0.528	0.950	0.083
	Total	0.521	0.232	0.716	0.611	0.018
LDL	Sex	0.464	0.524	0.510	0.715	0.445
	Prescription days	0.015	0.869	0.325	0.747	0.786
	Prescription dose	0.006	0.918	0.167	0.842	0.835
	Total	0.052	0.338	0.140	0.755	0.746
Total cholesterol	Sex	0.469	0.348	0.373	0.576	0.336
	Prescription days	0.066	0.761	0.310	0.869	0.761
	Prescription dose	0.019	0.576	0.095	0.925	0.710
	Total	0.104	0.228	0.076	0.698	0.427

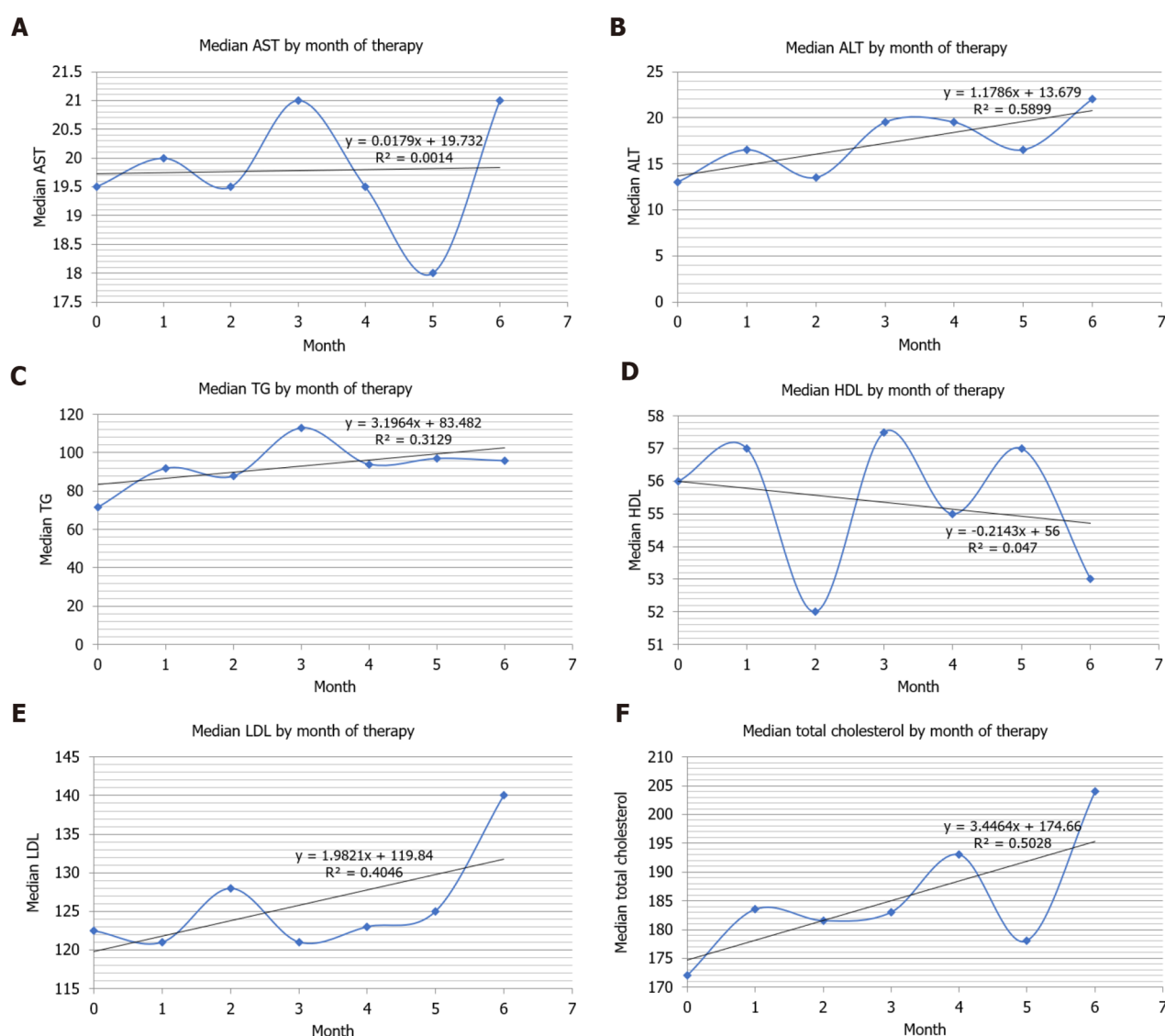
P-values of < 0.05 were considered statistically significant. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

DISCUSSION

Oral isotretinoin has revolutionized acne treatment and has become the standard treatment[8]. However, it can cause systemic side effects, including leukopenia, hyperlipidemia, and hepatotoxicity[1-9]. Moreover, most patients require long-term use. Thus, periodic blood tests are necessary to ensure patient safety; however, no consensus on dose and frequency has been established to date[1-6,9].

Since 2006, many studies have argued that only few patients have abnormal laboratory test results[6]. Thus, the frequent monitoring of isotretinoin treatment has little value. For example, a 2016 retrospective study including 515 patients in the United States who received isotretinoin for acne treatment has reported that 2.4% of patients developed leukopenia but they did not require treatment discontinuation, and a clinically non-significant number of patients (1.6%) developed thrombocytopenia [2]. This evidence suggests that routine CBC tests are unnecessary, which has been supported by other authors, such as Barbieriet *et al*[6]. Furthermore, Hansen *et al*[2] evaluated patients who received the maximum daily dose of isotretinoin, reporting that liver function and lipid profile monitoring was unnecessary unless the patient had specific risk factors. The 2016 United States and European guidelines also include these recommendations[1]. However, Barbieri *et al*[6] have reported that many clinicians still perform monthly blood tests, creating a cost burden for patients and the health insurance system.

Here, significant changes in AST, ALT, and TG levels in terms of total prescription period and isotretinoin dose were observed between 5 and 6 mo. Isotretinoin is metabolized in the liver and has an approximately 14 h half-life in the blood[8]. The primary metabolite 4-oxo-isotretinoin has a half-life of almost 28 h[8,10]. Therefore, it would take between 5 and 6 mo to significantly accumulate in the body



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Figure 1 The tendency of blood test levels to change while taking isotretinoin. A: Aspartate aminotransferase; B: Alanine aminotransferase; C: Triglycerides; D: High-density lipoprotein; E: Low-density lipoprotein; F: Total cholesterol. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

and affect blood test results. This result is consistent with those of other previously reported studies[11, 12]. In addition to liver levels, vitamin A derivatives have the potential to increase lipid levels because they accumulate in fat[13]. As lipid accumulation and elimination take a long time, changes may occur between 5 and 6 mo. Therefore, the contraceptive period of another vitamin A derivative, alitretinoin, is 1-3 years because of this fat accumulation[13]. Therefore, we recommend testing LDL, total cholesterol, liver function, and lipid levels before treatment and 1-2 mo after starting isotretinoin. Subsequently, if no abnormalities are detected, monitoring every 6 mo is sufficient.

Shah *et al*[3] published a study in 2018 with a similar opinion to that in our study. They also argued that patients should be tested at baseline, 2-3 mo, and a few months after reaching the peak dose; such testing protocol would be cost-effective for patients and the national insurance system[3]. The total cost for patients who underwent baseline and monthly laboratory monitoring for 6 mo was approximately \$525, compared with approximately \$225 at baseline, after 1-2 mo, and after 6 mo, with estimated savings of \$300[3].

In Korea, a liver + lipid panel (excluding direct bilirubin and gamma-glutamyl transferase tests) costs 91650 won, of which 65470 won are covered by insurance. If monthly monitoring is performed for 6 mo (including the baseline exam), the cost to the patient will be 641550 won, of which 458290 won is covered by insurance. However, testing only at the baseline, 1 mo, 2 mo, and 6 mo reduces the general rate to 366600 won, of which 261880 won is covered by insurance, which is a considerable reduction in cost.

Some studies, including those by Hansen *et al*[2] and Shah *et al*[3], have discouraged performing liver and lipid tests if the first 3 mo of monitoring indicate normal results. However, significant changes in liver function and lipid test results were observed. Furthermore, the European Medicines Agency, the United States, and other European guidelines recommend performing liver function and lipid tests (at different intervals)[1]. Therefore, minimal tests are necessary. Consequently, we recommend minimal periodic examinations once every 6 mo after reaching the peak isotretinoin dose.

Some limitations of this study are that we could not confirm isotretinoin compliance and that we only included few patients. Furthermore, if blood test abnormalities were detected, the drug may have been immediately stopped, and subsequent progress could not be confirmed.

CONCLUSION

This study investigated the optimal blood test type and frequency for patients taking isotretinoin for acne. Our results suggest performing a liver and lipid panel before beginning isotretinoin, 1 mo and 2 mo after administration, and every 6 mo thereafter if no abnormalities are detected, to save on costs. However, more frequent monitoring may be necessary if there is a family history of related adverse effects, such as hyperlipidemia, or if the patient has specific risk factors, such as obesity, viral hepatitis, and additional drug or alcohol intake. This article will contribute to Asian-specific isotretinoin laboratory guidelines and further studies.

ARTICLE HIGHLIGHTS

Research background

Isotretinoin is a widely prescribed medication for various dermatological conditions, particularly acne. Regular blood tests are performed to monitor its side effects. However, the optimal tests and their timing remain controversial.

Research motivation

Since 2006, many studies have reported that only a small proportion of patients taking isotretinoin have abnormal laboratory test results. Thus, frequent monitoring of isotretinoin treatment may be unnecessary.

Research objectives

This study aimed to evaluate the most efficient testing regimen for patients with acne taking isotretinoin.

Research methods

This retrospective study analyzed medical records obtained from Dongguk University Ilsan Hospital's electronic medical records database. Independent variables (*e.g.*, sex, total prescription date and dose, daily average prescription dose, underlying disease type, and monthly interval per blood test) were analyzed using repeated-measures analysis of variance.

Research results

Aspartate aminotransferase, alanine aminotransferase, and triglyceride levels significantly changed between 5 and 6 mo when the total prescription period and dose variables were considered altogether. High-density lipoprotein level also significantly changed between 5 and 6 mo. However, low-density lipoprotein and total cholesterol levels significantly changed between 1 and 2 mo.

Research conclusions

Liver and lipid panel should be performed before beginning isotretinoin administration, 1 and 2 mo after administration, and every 6 mo thereafter if no abnormalities are detected to save on costs.

Research perspectives

This article will contribute to Asian-specific isotretinoin laboratory guidelines and further studies.

FOOTNOTES

Author contributions: Park YJ, the first author, analyzed the data and wrote the manuscript; Shin HY and Choi WK participated in the data collection; Lee SH and Lee AY reviewed and edited the manuscript; Hong JS was the corresponding author and designed the study; all authors have read and approved the final manuscript.

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