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Original Research Article

A retrospective evaluation of acne patients treated with isotretinoin

Fusun Eser Aksu*

Department of Dermatology, Kahramanmaraş Necip Fazıl City Hospital, Kahramanmaraş, Turkey

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***Correspondence:**
Dr. Fusun Eser Aksu,
E-mail: drfusunaksu@gmail.com

ABSTRACT

Background: Although systemic isotretinoin offers more effective alternatives for treatment, as the drug has several side-effects, physicians are hesitatant to recommend the drug. The aim of this research was to retrospectively evaluate the effectiveness, side-effects and validity of systemic isotretinoin treatment on patients with acne, to thereby present experimental data relevant to future usage by patients suffering from acne.
Methods: Patients diagnosed with acne in the Dermatology Polyclinic of the Medical Faculty of KSU between January 2004 and September 2008 was identified from the polyclinic records. Patient data were retrieved from the archives and recorded in the pre-prepared format. A retrospective evaluation was made of the safety and effectiveness of isotretinoin treatment, and the clinical and laboratory test side-effects.
Results: A total of 241 patients were prescribed systemic isotretinoin treatment and started treatment. Of these, 129 of these patients attended regular follow-up examinations and completed the treatment. Systemic isotretinoin was determined to be effective on acne during a treatment period of 23.47±4.5 weeks with a total average dose of 113.73±22.4 mg. There were no serious laboratory test or clinical effects of an intolerable level tolerated which would lead to termination of the treatment.
Conclusions: Systemic isotretinoin treatment is effective and safe for acne vulgaris patients with nodulocystic and papulopustular types of lesion. However, it is essential that the laboratory parameters of hepatic function tests and the lipid profile are checked regularly.

Keywords: Acne, Dermatology, Isotretinoin

INTRODUCTION

Systemic isotretinoin is the only agent effective on all the basic etiological factors of acne pathogenesis. It has been used in the treatment for more than 20 years, especially in cases of nodular and nodulocystic acne.[1,2] However, the usage has recently come into question for the treatment of low and moderate level acne which does not respond to long-term, conventional treatments of although systemic isotretinoin offers more effective treatment than other medications, the possible side effects make physicians hesitant to recommend isotretinoin.[1] The aim of this study was to evaluate the demographic characteristics, treatment adaptation, effect on the patient and side-effects observed in patients treated with systemic isotretinoin and to thereby contribute to the development of future treatment methods.[3-5]

METHODS

Patients diagnosed with acne in the Dermatology Polyclinic of the Medical Faculty of KSU between January 2004 and September 2008 was identified from the Dermatology Polyclinic records. The data of age, gender, weight, type of lesion, location, recommended dose, and total cholesterol, triglyceride, AST and ALT values pre-treatment and at 1, 3 and 5 months post-treatment, clinical success and side-effects, treatment

periods, reasons for terminating treatment, relapse times, were recorded on the pre-prepared forms.

Complete healing was accepted as patients whose acne lesions healed totally and who reached the average total dose. The safety and effectiveness of isotretinoin treatment, and the clinical and laboratory test side-effects were evaluated through analysis of the above-mentioned data.

RESULTS

Of the total 28,432 patients referred to the Dermatology Polyclinic of the Medical Faculty of KSU within the specified period, 3,072 (10.8%) were diagnosed with acne and 241 (7.8%) of these patients were prescribed systemic isotretinoin treatment. Treatment was not completed by 112 patients who did not attend regular appointments. The reasons for termination of treatment were unknown in 49 patients, 18 patients did not want to continue the treatment and 45 did not attend follow-up appointments even though they had started the treatment.

Increased anxiety was noted in 2 of the 18 patients who requested to stop the treatment, increased triglyceride was determined in 1 patient (360 mg/dl), elevated ALT (less than twice the normal level), muscle-joint pain in 1, headache in 2, acronyx in 2 patients and 8 patients were afraid of the possible side effects of the treatment. The average total dose of systemic istretionin was determined as 113.73±22.4 mg/kg during the treatment period of 23.47±4.5 weeks. Of the 129 patients who completed the treatment, full recovery was determined in 124 (96.2%) and partial recovery in 5 (3.8%).

Table 1: Mucocutaneous side effects during the treatment.

Side-effect	Roaccutane® users (n:114)	Zoretanin® users (n:15)	Total (n:129)	Rate (%)
Cheilitis	114	15	129	100
Skin dryness	40	10	50	38.8
Epistaxis	18	6	24	18.6
Dryness and itching in hands	29	12	41	31.8
Burning, stinging in eyes	13	6	19	14.7
Erythema and desquamation on face	40	5	45	34.9
Photosensitivity	1	2	3	2.3
Acronyx	2	2	4	3.1
Light sensitivity in eyes	2	-	2	1.6
Hair loss	2	-	2	1.6

Table 2: Other side-effects during the treatment.

Side-effect	Roaccutane® users (n:114)	Zoretanin® users (n:15)	Total (n:129)	Rate (%)
Headache	3	2	5	3.9
Fatigue	1	3	4	3.1
Muscle-joint pain	2	1	3	2.3
Depression	2	-	2	1.6
Constipation	-	2	2	1.6

Table 3: The comparison of serum triglyceride, total cholesterol, AST and ALT values at pre-treatment and 1 month post-treatment.

	Pre-treatment		1 month post-treatment		P
	N	Average	N	Average	
Triglyceride (mg/dl)	129	85.09±49.71	129	98.00±57.64	0,00
Total cholesterol (mg/dl)	129	146.97±31.22	129	157.60±35.84	0.00
AST (U/L)	129	20.32±4.66	129	22.80±6.67	0.00
ALT (U/L)	129	35.57±8.24	129	35.53±9.82	0.95

Of these 129 patients, 27 (21%) were referred again because of recurrence 23.77±13.1 months after the treatment. Conventional acne treatment was recommended for 24 (89%) and systemic isotretinoin treatment was applied again to 3 (11%) patients. The most common mucocutaneous side-effect seen in all the 129 patients was cheilitis (Table 1). Headache, fatigue, muscle-joint pain, depression and constipation were observed as non-cutaneous side-effects (Table 2). Of the 129 patients who have completed the treatment, 114 were determined to have used Roaccutane® and 15 patients to have used Zoretanin®, as preparates of isotretinoin. As the number of patients using Zoretanin® was so much lower than the number of patients using Roaccutane®, it was not possible to make a statistical comparison of the two medications in respect of the clinical side-effects and laboratory values. The frequencies of the side-effects related to the medications are shown in Tables 1 and 2.

Table 4: The comparison of serum triglyceride, total cholesterol, AST and ALT values at 1 and 3 months post-treatment.

	1 month post-treatment		3 months post-treatment		P value
	N	Average	N	Average	
Triglyceride (mg/dl)	129	98.00±57.64	129	108.02±63.64	0.02
Total cholesterol (mg/dl)	129	157.60±35.84	129	160.74±38.93	0.20
AST (U/L)	129	22.80±6.67	129	23.02±5.38	0.72
ALT (U/L)	129	35.53±9.82	129	35.58±10.19	0.95

Serum triglyceride, total cholesterol, AST and ALT levels before treatment and at 1, 3 and 5 months post-treatment are shown in Tables 3-5. A statistically significant increase was determined in the triglyceride value after 1 month of treatment compared to the pre-treatment value (Table 3).

The increase was observed to continue at a lower level of statistical significance in the comparison of 1 and 3-month values (Table 4). No statistically significant difference was determined between the 3 and 5-month values of triglyceride (Table 5).

A statistically significant increase was determined in the total cholestorol levels at 1 and 3 months post-treatment compared to the pre-treatment values (Table 3).

The changes in total cholesterol values at 3 and 5 months post-treatment were not statistically significant (Tables 4 and 5). A statistically significant increase was determined in the AST level at 1 month post-treatment compared to the pre-treatment value (Table 3). No statistically significant change was determined in the AST level in the comparison of the values at 1-3 months and 3-5 months (Tables 4 and 5).

Table 5: The comparison of serum triglyceride, total cholesterol, AST and ALT values at 3 and 5 months post-treatment.

	3 months post-treatment		5 months post-treatment		p value
	N	Average	N	Average	
Triglyceride (mg/dl)	116	108.00±63.6	116	109.20±69.5	0.65
Total cholesterol (mg/dl)	116	160.2±38.1	116	158.3±34.4	0.40
AST (U/L)	116	23.1±5.3	116	23.6±8.4	0.41
ALT (U/L)	116	35.8±9.8	116	35.7±10.2	0.15

DISCUSSION

The results of this study showed full recovery in 96.2% and partial recovery in 3.8% of the cases treated with systemic isotretinoin. These rates are concordant with findings in literature. In a study by Al-Khawajah of 262 cases treated with isotretinoin at a dose of 0.6-0.75 mg/kg/day for 16-35 weeks (cumulative total dose; 75-146 mg/kg), full recovery was determined in 90.4% and partial recovery in 3.8% of the patients.[2] In a study by Erdem et al, full recovery was reported in 90% and partial recovery in 3.8% of a total of 50 cases with acne

treated with isotretinoin (dose; 0.5-1 mg/kg/day, duration; 14-26 week, total cumulative dose 75-110 mg/kg).[3] In a study by Sarıcaoğlu et al, isotretinoin treatment (0.5-1 mg/kg dose, average cumulative dose; 100 mg/kg) was administered to 21 nodular/ nodulocystic cases with acne and full recovery was reported in 90.47% of the cases.[4]

The current recommended dose for isotretinoin treatment for patients with acne is 0.5–2 mg/kg.[5] A cumulative dose of at least 120 mg/kg has been reported to minimize the risk of relapse and provide the best long-term remission.[6] In the current study, the initial dose of isotretinoin treatment was 1-1.5mg/kg/day in 3 cases and 0.5-1 mg/kg/day in 126 cases, and isotretinoin (the average total dose; 113.73±22.4 mg/kg) was administered for 23.47±4.5 weeks. Cumulative and daily dose are known to have a great effect on the rate of relapse. The relapse rate has been reported as 22% with a treatment protocol of a dose of 1 mg/kg/day and 39% with a treatment protocol of a dose of 0.5 mg/kg.[7] In the current study, 21% of the cases who completed the treatment were referred again after 23.77±13.1 months because of relapse. Conventional acne treatment was applied to 24 patients and systemic isotretinoin was administered again to 3 patients. The average cumulative dose of the cases with relapse was 112 mg/kg. Layton et al reported clinical recovery (at least 85%) in all of 88 cases to whom a similar dose regimen was applied. In that study the rate of relapse was 39% and most of these relapses occured within 3 years of the isotretinoin treatment.[8]

Side-effects in isotretinoin treatment are mostly mucocutaneous side-effects. The most common dose-related side-effect is dryness of the skin and mucosa as the basic principle of isotretinoin is to reduce the volume of the sebaceous glands and decrease sebum production. The dryness is generally treatable and reversible. The most common side effect overall, which is seen in more than 90% of cases, is cheilitis. Xerosis, dermatitis, localized degloving, skin atrophy and fragility have been reported to be observed in more than 50% of patients treated with isotretinoin, generally in the first month of treatment. Dryness in the nasal mucosa and epistaxis can be seen in one third of patients. Brittle nails, xerostomia and thirst are less frequently reported side-effects and very occasionally alopecia might be seen.[9,10]

In the current study, no mucocutaneous side-effect developed of a severity to terminate the treatment. The rates of side-effects in the current study are consistent with other studies in literature.[9] Other side-effects in the neuropsychiatric system and musculoskeletal system were not of a level to necessitate terminating the treatment in the current study (Table 2). The most common complaints related to the musculoskeletal system are myalgia and arthralgia, generally seen in patients with a high level of physical exercise and a history of trauma.[12,14] Rates of fatigue have been reported as 5%-7% and headache as 10%-15%.[9,13] Chia et al reported that isotretinoin does not result in depression, but that on the contrary, both traditional acne and isotretinoin treatments reduce depressive symptoms.[15] In a retrospective analysis of 20,895 acne cases, Jick et al stated that depression and suicide rates in one third of the cases were equal in those using both oral antibiotic and isotretinoin.[16] In a study by Çikim et al of 94 cases, remission of depression was determined in all except 1 case (1%). The treatment of the patient with depression was terminated.[17]

In the current study, a statistically significant increase was determined in the triglyceride value at the end of the first month of treatment compared with the pre-treatment values. When the values at the end of the first month were compared with those at the end of the third month, the increase was seen to continue, albeit at a lower level of statistical significance. No statistically significant increase was determined between the values at the end of the third month and the end of the fifth month. Similarly, a statistically significant increase was determined in total cholesterol values at the end of the first month of treatment compared with the pre-treatment values, but no significant increase was seen from the first to third month or from the third to fifth month (Table 3 and 4). None of the increases in the lipid value were of a level to affect the continuation of treatment. An increase in triglyceride level is the most commonly seen side-effect of isotretinoin. Zane et al determined an increase in triglyceride levels in 44% and increased total cholesterol levels in 31% of a total of 13,772 patients.[18] In another study, isotretinoin was administered to 94 acne patients at a dose of 0.5-1 mg/kg/day and increased triglyceride was determined in 8.5% of the patients. The triglyceride levels returned to normal within 1-2 months with a reduction of the isotretinoin dose and dietary adjustments and no case required termination of the treatment.[17]

The effect on serum lipid level of systemic isotretinoin and acitretin treatment was investigated by Coşkun in a study of 40 patients. Cholesterol and triglyceride serum levels were observed to increase in a retinoid-dependent manner. Serum lipid levels were determined to be specifically dose-dependent affected, with a statistically significant effect determined at doses >0.4 mg/kg. The effect of the average total dose on lipid values was evaluated as significant and long-term, low-dose retinoid treatment was therefore recommended.[19] Several different studies have demonstrated that there may be increases in cholesterol and triglyceride levels as a result of isotretinoin treatment.[9,18,20,21] Berstad et al applied isotretinoin at a dose of 1 mg/kg/day to 60 patients for 20 weeks and determined an increase of 17% in triglyceride levels.[22] In a study by Lestringant et al, isotretinoin at a dose of 0.2-1.6 mg/kg/day was administered to 140 patients, and a significant increase in triglyceride and cholesterol levels was reported in the sixth week.[23]

In a study by Amichai et al, an increase of 20% above the normal value was determined in the lipid parameters of 4.2% and a decrease of 2-fold normal values in liver

enzymes of 4.8% of 638 patients who were treated with isotretinoin.[24] In another 6-month study of 83 patients treated with 0.5 mg/kg/day isotretinoin, Ghalamkarpour et al reported no significant change in liver enzyme levels and cholesterol levels and statistically significant increases in triglyceride levels.[25]

In the current study, a statistically significant increase was determined in AST values at the end of the first month of treatment compared with the pre-treatment values, but no statistically significant increase was determined in the comparison of the values at the end of the first month and the third month and the end of the third month and the fifth month. No statistically significant change was determined in ALT levels during the treatment (Table 3 and 5). Although, together with a slight liver transaminase increase, short-term liver toxicity has been reported in 15% of patients who have used isotretinoin, with the continuation of treatment, there have been no reports of liver toxicity and mortality related to isotretinoin treatment.[18,26]

Liver injury resulting from retinoids occurs in reaction to an acute toxic event. Liver toxicity caused by retinoids has been seen at very low levels related to isotretinoin.[20] During isotretinoin treatment, there may be temporary increases in serum transaminases in approximately 20% of patients, but severe and permanent liver toxicity is lower than 1%.[26] While some studies have reported no changes in liver function tests during isotretinoin treatment, others have shown that an increase, especially in AST levels, can be determined at the end of first month.[1,9,11,27] Changes in liver fuction tests are generally seen in AST and ALT values. It has been stated that the increases in these tests are generally close to the the upper limit of the normal range and the increase in values above normal is very slight. The probability of developing liver toxicity is lower in patients with normal pre-treatment liver enzyme values.[20]

In a study by Michealson et al, isotretinoin at a dose of 0.5 mg/kg/day for 3 months was administered to 90 patients and significant increases were determined in AST and ALT values. The AST value in 1 case and the ALT value in 2 cases exceeded the normal range and those abnormal AST and ALT values were stated to be rare.[28] Schulips et al treated 28 patients with isotretinoin at a dose of 0.5 mg/kg/day and significant increases in the ALT and AST values were determined.[29] In contrast, Barth et al reported no significant changes in liver function tests in a series of 200 patients treated with isotretinoin at a dose of 1 mg/kg/day.[20]

In the current study, as the number of patients using Zoretanin was much lower than that of those using Roaccutane®, it was not possible to make a statistical comparison of the clinical side-effects of these two medications. However, when the proportional rates of clinical side-effects were compared, a higher rate was determined in patients using Zoretanin®. There is a need for large-scale, randomized studies to provide further information on this subject. In addition, although both of these medications have the same agents, other different contents could be considered to contribute to this effect. Roaccutane® includes titanium dioxide and canthaxanthin as excipients while Zoretanin® includes DL-alpha-tocopheryl, butylated hydroxyanisole, disodium edetate, titanium dioxide, ponceau 4R (cochineal red A) and black iron oxide.

CONCLUSION

The results of this study demonstrated that no liver toxicity or increases in lipid values were observed which were severe enough to warrant terminating the full-time isotretinoin treatment. It was also noted that the systemic isotretinoin treatment applied to patients with acne is generally very successful. Physicians should bear in mind that the increases in total cholesterol, glyceride and ALT in the first months of treatment are not a cause for great concern as they do not continue. Nonetheless, the control of these parameters should not be neglected.

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