Original Investigation
Orijinal Araştırma

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The correlation of age, gender and drug dose with side effects of isotretinoin in patients with acne vulgaris

Akne vulgaris nedeniyle isotretinoin kullanan hastalarda ilaç yan etkilerinin yaş, cinsiyet ve ilaç dozu ile ilişkisi

Dursun Türkmen

Malatya Training and Research Hospital, Clinic of Dermatology, Malatya, Turkey

Abstract

Background and Design: Acne vulgaris is a chronic inflammatory disease of pilosebaceous unit. Oral isotretinoin is the most effective agent that has been used for many years in acne treatment. The purpose of our study was to determine the side effects of the isotretinoin and to examine the correlation between these side effects, and age, gender and drug dose.
Materials and Methods: One hundred forty nine patients with moderate or severe acne vulgaris (age between: 14-34 years) using isotretinoin were included. Eight patients discontinued treatment for various reasons. Daily isotretinoin dose was started as less than 0.5 mg/kg/day. A cumulative dose of at least 120 mg/kg was targeted in all patients. The patients were assessed in terms of side effects on a monthly basis.
Results: Of the 141 patients who have completed the treatment, 106 (75.2%) were female and 35 (24.8%) were male. Cheilitis was seen in 100%, xeroderma in 66%, photophobia in 44.7%, mild epistaxis in 42.6%, and xerophthalmia in 36.9% of the patients. Lumbar pain was seen in 41.1%, myalgia in 29.1%, arthralgia in 19.1%, headache in 13.5% of the patients. Serum lipid levels increased in 20.6% of the patients, while liver enzyme levels increased in 7.8% of the patients. Myalgia and lumbar pain was more common in females (p=0.045, p=0.019, respectively). Patients who received higher than 0.5 mg/kg/day dose had more xerosis, myalgia and triggering acne complaints (p=0.004, p=0.001, p=0.012, respectively). Myalgia were found to be more common in patients who were older than 20 years old (p=0.003).
Conclusion: Because the use of isotretinoin is a long-lasting treatment method, patient compliance is of paramount importance. Knowing how frequent side effects will occur in different patients groups and informing the patients beforehand will increase patients' confidence towards to physician and minimize the compliance problems.
Keywords: Acne vulgaris, isotretinoin, side effects, myalgia, epistaxis

Öz

Amaç: Akne vulgaris, pilosebase ünitenin kronik enflamatuvar bir hastalığıdır. Oral izotretinoin akne tedavisinde uzun yıllardır kullanılan en etkili tedavi ajanıdır. Çalışmamızda ilacın yan etkilerini tespit etmeyi ve bunların yaş, cinsiyet ve ilaç dozu ile bağlantısını araştırmayı amaçladık.
Gereç ve Yöntem: Çalışmamızda, yaşları 14-34 arasında değişen, izotretinoin kullanan, 149 orta veya şiddetli akne vulgarisli hasta yer aldı. Sekiz hasta çeşitli sebeplerle tedaviye devam etmedi. Günlük izotretinoin dozu 0,5 mg/kg'nin altında başlandı. Tüm hastalarda en az 120 mg/kg kümülatif doz hedeflendi. Hastalar yan etkiler açısından aylık olarak değerlendirildi.
Bulgular: Tedaviyi tamamlayan 141 hastanın 106'sı (%75,2) kadın, 35'i (%24,8) erkekti. Hastaların %100'ünde keilitis, %66'sında kseroderma, %44,7'sinde fotofobi, %42,6'sında hafif burun kanaması, %36,9'unda göz kuruluğu görüldü. Bel ağrısı hastaların %41,1'inde, kas ağrısı %29,1'inde, eklem ağrısı %19,1'inde ve baş ağrısı %13,5'inde görüldü. Serum lipit düzeyleri hastaların %20,6'sında, karaciğer enzim düzeyleri ise hastaların %7,8'inde yüksekti. Kas ağrısı ve bel ağrısı kadın hastalarda daha yüksekti (sırasıyla; p=0,045, p=0,019). İlaç dozu 0,5 mg/kg/günün üzerinde olan hastalarda kseroderma, kas ağrısı ve akne tetiklenmesi daha fazlaydı (sırasıyla; p=0,004, p=0,001, p=0,012). Yirmi yaşından büyük hastalarda kas ağrısı daha fazlaydı (p=0,003).
Sonuç: İzotretinoin tedavisi uzun süreli bir tedavi olduğu için hasta uyumu önem arz etmektedir. Hangi hasta grubunda hangi yan etkilerin ne sıklıkta olduğunu iyi bilmek ve hastaları önceden bu konuda bilgilendirmek hastanın hekime olan güvenini arttıracaktır ve uyum problemini minimuma indirecektir.
Anahtar Kelimeler: Akne vulgaris, izotretinoin, yan etkiler, kas ağrısı, epistaksis

Address for Correspondence/Yazışma Adresi: Dursun Türkmen MD, Malatya Training and Research Hospital, Clinic of Dermatology, Malatya, Turkey
Phone: +90 530 223 69 55 E-mail: dursunturkmen44@gmail.com **Received/Geliş Tarihi:** 27.08.2019 **Accepted/Kabul Tarihi:** 21.04.2020
ORCID: orcid.org/0000-0001-9076-4669

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Introduction

Acne vulgaris is a chronic inflammatory disease of pilosebaceous unit. It is the most common skin disease which influences almost 85% of the population between 12-14 years of age. Although acne vulgaris is a self-limiting disease, it should be treated since it can leave scars and cause psychological problems[1]. Isotretinoin, approved by the Food and Drug Administration in 1982, is the most effective treatment agent used for many years in the treatment of severe acne, it is the only agent that suppresses sebum production, provides long-term remission and is effective against all factors that play a role in acne pathogenesis[2-7]. The conventional standard dose recommended for isotretinoin is 0.5-1 mg/kg/day for the first 16-32 weeks until a target cumulative dose of 120 mg/kg[8]. Side effects of isotretinoin are known, but there is no much data on age, sex, and drug dose relationship. The purpose of my study was to find out common side effects of the isotretinoin and to examine the association between these side effects and age, gender and drug dose.

Materials and Methods

Patients with moderate and severe acne vulgaris who did not benefit from other acne treatments and did not receive any topical or systemic treatment for acne during the past year were included in our study. A total of 149 patients between the ages of 14 and 34 years between July 2017 and July 2019 were included in the study. The study was conducted in line with the Declaration of Helsinki. Ethics board approval was taken from Malatya Clinical Researches Ethics Board (approval number: 2018/27, date: 27.03.2018) and written consent was taken from all participants in the study. Female patients were informed about contraception, as required. Before the beginning of treatment, the patients were given leaflets which included information about the drug. All patients and their family members were informed about common side effects. During the treatment period, patients were assessed monthly, possible side effects were examined and the patients were re-informed about the emerging side effects. Daily isotretinoin dose was started as less than 0.5 mg/kg. During the follow-up, isotretinoin was given to 39 patients (27.7%) as less than 0.5 mg/kg/day, while 102 patient (72.3%) was given 0.5-1.0 mg/kg/day. At least a cumulative dose of 120 mg/kg was targeted in all patients. Before the treatment started, routine biochemistry, lipid profile, hemogram tests were studied in all patients and beta-human chorionic gonadotropin test in female patients. Patients who had a normal baseline blood tests results underwent blood tests in every two months. Patients who had an abnormal baseline blood tests results underwent blood tests monthly.

Statistical Analysis

SPSS (SPSS for Windows, Version 22.0, SPSS Inc, U.S.A) program was used for statistical assessment. Continuous variables were given as numbers and percentages, while categorical variables were given as means ± standard deviations. Chi-square test was used for the comparison of categorical variables. A p-value less than 0.05 level was accepted as statistically significant.

Results

There were a total of 149 patients included in the study. We stopped treatment in two patients (one due to sacroileitis and one due to elevated liver enzymes). Six patients discontinued treatment because they were concerned about the various side effects of the drug [epistaxis (2), elevated liver enzymes (1), elevated lipids (1), excessive xerosis (1), irritability (1)]. One hundred and forty-one patients were checked regularly until the end of treatment.

Of the 141 patients who have completed the treatment, 106 (75.2%) were females and 35 (24.8%) were males. The ages of the patients were between 14 and 34 years (20.9±4.7). 60 (42.6%) patients had only face involvement, 69 (48.9%) patients had face and body involvement, 10 (7.1%) patients had face, body and scalp involvement. In 26 (18.4%) of the patients, a first degree relative had history of isotretinoin use (Table 1). In the six-month follow-up, complete recovery was found in 127 (90.1%) patients, while partial recovery was found in 14 (9.9%) patients and the treatment was prolonged.

Of the mucocutaneous side effects, cheilitis was seen in all (100%) patients. Xeroderma was seen in 93 (66%) patients, photophobia in 63 (44.7%) patients, mild epistaxis in 60 (42.6%) patients, and xerophthalmia in 52 (36.9%) patients. In addition, 62 (44%) patients were found to have an increase in acne severity in the first 45 days of the treatment (Table 2).

Table 1. Demographic characteristics of the study patients (n=141)

	Number	Percentage
Gender		
Male	35	24.8
Female	106	75.2
The use of isotretinoin in the family		
Yes	26	18.4
No	115	81.6
Site of acne		
Face	60	42.6
Face and body	69	48.9
Face, body and scalp	10	7.1
Face and scalp	1	0.7
Body	1	0.7
Drug dose		
<0,5/kg/day	39	27.7
≥0,5/kg/day	102	72.3
Recovery month		
Partial recovery	14	9.9
Complete recovery 1st month	3	2.1
Complete recovery 2nd month	11	7.8
Complete recovery 3rd month	35	24.8
Complete recovery 4th month	50	35.5
Complete recovery 5th month	16	11.3
Complete recovery 6th month	12	8.5

Table 2. Mucocutaneous side effects in patients receiving isotretinoin

	Number	Percentage
Cheilitis	141	100
Xerosis	93	66
Exacerbation of acne lesions	62	44
Photophobia	63	44.7
Mild epistaxis	60	42.6
Xerophthalmia	52	36.9
Hair loss	11	7.8

Table 3. Systemic side effects in patients receiving isotretinoin

	Number	Percentage
Lumbar pain	58	41.1
Myalgia	41	29.1
Arthralgia	27	19.1
Headache	19	13.5
Psychological side effects	34	24.1
Decreased appetite	23	16.3
Increased appetite	8	5.7
Nausea	2	1.4
Weakness	1	0.7
Shortness of breath	1	0.7
Chest pain	1	0.9
Slight elevation in liver enzymes	11	7.8
Elevation in lipids		
Slight	28	19.9
> Two times	1	0.7

Systemic side effects were less frequent than mucocutaneous side effects. Of the systemic side effects, lumbar pain was seen in 58 (41.1%) patients, myalgia in 41 (29.1%) patients, psychological side effects such as stress and nervousness in 34 (24.1%) patients, arthralgia in 27 (19.1%) patients, headache in 19 (13.5%) patients, decreased appetite in 23 (16.3%) patients, increased appetite in 8 (5.7%) patients. Of the biochemical parameters, mild elevation of total cholesterol and/or triglyceride was seen in 28 (19.9%) patients. In one (0.7%) patient, total triglyceride increased more than two fold and it returned to normal when the drug dose was decreased. Liver enzyme levels increased in 11 (7.8%) patients (Table 3). Systemic side effects were mild and they returned to normal with a decreasing the dose of drug in patients have completed the treatment.

In terms of gender differences, epistaxis was more common in males, but there was not statistically significiant difference (p>0.05), while myalgia and lumbar pain were more common in females (p=0.045, p=0.019, respectively). When the drug doses were compared, the patients who received higher than 0.5 mg/kg/day dose had more xerosis, myalgia and triggering acne than those who received less than 0.5 mg/kg/day (p=0.004, p=0.001, p=0.012, respectively). When above 20 years, respectively ≤20 years were compared, myalgia was found to be more common in patients older than 20 years (p<0.05) (Table 4). No difference regarding side effects was found between ages and genders in terms of drug dose.

Table 4. Findings of statistically significant side effects of isotretinoin according to gender, drug dose and age

		Yes number (%)	No number (%)	p-values*
Gender				
Myalgia				
Male		5 (14.3)	30 (85.7)	0.045
Female		36 (38.0)	70 (62.0)	
Lumbar pain				
Male		8 (22.9)	27 (77.1)	0.019
Female		50 (47.2)	56 (52.8)	
Dose of drug				
Xerosis	<0.5mg/kg/day	18 (46.2)	21 (53.8)	0.004
	>0.5mg/kg/day	75 (73.5)	27 (26.5)	
Myalgia	<0.5mg/kg/day	3 (7.7)	36 (92.3)	0.001
	>0.5mg/kg/day	38 (37.3)	64 (62.7)	
Exacerbation of acne lesions	<0.5mg/kg/day	10 (25.6)	29 (74.4)	0.012
	>0.5mg/kg/day	52 (51)	50 (49)	
Age				
Myalgia	Age 14-20 years	14 (18.4)	62 (81.6)	0.003
	Age ≥21 year	25 (43.1)	33 (56.9)	
*p<0.05				

Discussion

It has been well known that since isotretinoin (13-cis-retinoic acid) is a vitamin A (retinol) analogue, most of the side effects of the drug show side effects similar to hypervitaminosis A syndrome. Isotretinoin has a half-life of 22 hours and a bioefficacy of 25% and plasma concentrations increase when it is taken with food. Side effects decrease when it is taken twice a day[9]. Side effects are generally grouped into two main groups, mucocutaneous and systemic. The frequency and severity of side effects except for teratogenicity are dependent on dose and they may be controlled with supplementary treatments. These side effects are usually reversible with the discontinuation of the drug[6,10]. When severe side effects are seen, lower doses may be given and in this scenario, a longer period of treatment is required to reach the cumulative dose[11]. In our study, daily dose was given in two doses to decrease the side effects. In addition, the drug was given with meals to increase the absorption of the drug, as recommended. Although 14 of the patients who completed the treatment had a partial recovery, all other patients achieved to have complete recovery. Of the 14 patients who had only partial recovery, 11 were those who were given a high dose (>0.5 mg/kg/day) of the drug.

Mucocutaneous toxicity is the most frequent side effect and it is mostly a tolerable and dose dependent effect which responds well to treatment[2,9,12]. Cheilitis is the most frequent side effect of mucocutaneous

toxicity and it is seen in all patients who receive treatment. Absence of cheilitis is called unsuccessful treatment/accutane failure[9]. Cheilitis incidence is reported as 100% in previous studies[13,14]. In accordance of previous works, all of the patients in my study had cheilitis. Cheilitis responded well to moisturizing pomades and in severe cases, mild effective corticosteroid pomades also responded well in our study.

Xeroderma and dryness in mucosal membranes may be seen in more than half of the cases. In previous studies, frequency of xeroderma has been reported as between 47% and 85%[14-16]. In my study, frequency of xeroderma was 66% and it was higher in patients who received high dose drug. Xeroderma was seen more common in winter season in our study and it regressed with topical moisturizers and topical corticosteroids. Symptoms such as feeling of burning and stinging in the eyes due to dryness of the eye, nose and mouth mucosa, nose bleeding and dry mouth-thirst are also common during isotretinoin treatment. Gökalp[17] found that 41.3% of the 223 patients with acne vulgaris who were using isotretinoin had mucosa dryness, while 28.7% had nose bleeding. In our study, xerophthalmia and nose bleeding were found with frequencies of 36.9% and 42.6%, respectively. Xerophthalmia regressed with synthetic tears, nose bleeding was mild and it regressed with topical moisturizers. Especially in male patients, I observed that when the treatment is given in summer, decreasing the drug dose to less than 0.5 mg/kg/day may increase patient tolerance.

A deterioration in acne severity may be observed in the first six-week period of isotretinoin treatment in about 6-8% of the patients, for which discharge of propionibacterium acnes is thought to be responsible[18]. In the present study, a deterioration in acne severity was found to be 44% of the patients, generally in the first 45 days of the treatment. However, most of these clinical entities were short-term and mild. We did not decrease the dose of the drug. In a few patients, it regressed by adding topical antibiotic creams to treatment.

In patients who use isotretinoin, photosensitivity may be seen if the treatment is in summer season and it generally occurs in the form of erythema on the face. Çıkım and Seyhan[14] reported that 35.1% of the patients had photosensitivity in their study. In our study, 44.7% of the patients, especially those who got treatment in summer had photosensitivity and these patients were recommended to use sunscreen regularly.

Arthralgia and myalgia are more common in patients who use isotretinoin and especially in those who have intense exercise. These symptoms may usually be controlled with analgesic drugs[19]. Especially arthralgia is very common and back pain has been reported the most one. Acute arthritis may also be seen and it is reversible, however, in rare cases, it has been reported to continue even years after the treatment is discontinued[20]. In previous studies, back pain has generally been assessed as part of arthralgia. In my study, back pain was assessed as a distinct symptom from arthralgia. Back pain was seen in 41.1%, and arthralgia in 19.1% of our patients. Myalgia frequency was seen in 29.1% of my patients and it was more common in females. When the patients compared with regard to lower (<0.5 mg/kg/day) and higher dose (≥0.5 mg/kg/day) treatment, myalgia was found to be higher in patients who received higher dose than those who received low dose treatment. Myalgia was also higher in patients who were 21 years old and older when compared with those who were younger than 21 years old. Drug dose should be kept low especially in patients who have intense exercise and in athletic patients.

Previous work has shown that mild or moderate increase in liver function tests may be seen in 15% of the patients[20]. Hyperlipidemia is the most common laboratory side effect in patients using isotretinoin and its frequency may be seen as high as 35%[21]. After completion of isotretinoin treatment, serum liver function tests and lipid levels return to their normal values in a few months. Blood tests are recommended before treatment and repeated in every 1-2 months. Decrease in drug dosing is recommended when liver function tests increase 2-3 times higher than their normal upper limits. If they do not return to normal despite lower dosing, drug treatment should be discontinued[9]. In our study, total cholesterol and/or triglyceride elevations were seen in 29 (20.6%) patients. In only one of these patients, total triglyceride levels increased more than two times and it returned to normal when the drug dose was decreased. We stopped treatment in one patient due to elevated liver enzymes more than two times that didn't returned to normal levels with decreasing of the dose. Mild increases were seen in liver enzyme levels in 11 (7.8%) of patients and these patients were followed more often. Eventually, liver enzyme levels returned to normal levels with temporary decreases in drug dose.

Study Limitation

In our study, the number of patients using low dose drugs was low. Therefore, we could not make a full comparison between low dose and high dose drug users. There was no follow-up after treatment in our study format. Therefore, the effectiveness of the treatment remains unclear.

Conclusion

Our study showed that myalgia and lumbar pain is higher especially in female patients. Increase in drug dose will also increase especially xerosis, myalgia and triggering acne complaints. Relatively older patients also experience more myalgia. Since isotretinoin treatment is a long-term treatment, patient tolerance is of paramount importance. Knowing well how frequent side effects occur in different group of patients and informing the patients beforehand will decrease patients' anxiety, increase their confidence in physician and minimize the compliance problems.

Ethics

Ethics Committee Approval: The study was conducted in line with the Declaration of Helsinki. Ethics board approval was taken from Malatya Clinical Researches Ethics Board (approval number: 2018/27, date: 27.03.2018).

Informed Consent: Written consent was taken from all participants in the study.

Peer-review: Externally peer-reviewed.

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