Dermatology Practical & Conceptual

Skeletal Side Effects of Systemic Isotretinoin Treatment: Do They Depend on Age, Gender, Treatment Duration, Daily Dose and Isotretinoin-Naiveness?

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ABSTRACT

Introduction: Systemic isotretinoin is the most effective treatment modality in acne vulgaris; however, both patients and physicians hesitate to use it due its side effects.

Objectives: The aim of this study is to determine the prevalence of fatigue, myalgia and low back pain during systemic isotretinoin treatment; and to determine their relationship with age, gender, treatment duration, daily isotretinoin dose and isotretinoin-naiveness of the patient.

Methods: This is a cross sectional study including the acne vulgaris patients, aged between 13 to 40 years, who have at least received one month of oral isotretinoin treatment. Patients were questioned for side effects during their follow-up visits; a physical therapy and rehabilitation specialist further evaluated patients complaining of low back pain.

Results: Fatigue was reported by 4.4% of the patients, myalgia by 2.8% and low back pain by 25% of the patients; 2.2% had inflammatory and 22.8% had mechanical low back pain. None of the patients

had sacroiliitis. All the side effects that were examined were found to be independent of age, gender, isotretinoin dosage (mg/kg/day), treatment duration and isotretinoin-naiveness.

Conclusions: The side effects are not as common as feared; thus, patients and physicians should not hesitate to use systemic isotretinoin in indicated cases.

Introduction

Systemic isotretinoin (13-cis retinoic acid) is the most effective treatment modality for acne vulgaris given that it is the only treatment method that targets all four of the major etiological factors of acne vulgaris. The US Food and Drug Administration have approved its use for the treatment of severe acne vulgaris in 1982 [1]. The common side effects of systemic isotretinoin treatment are cheilitis, xerosis, xerophthalmia, and myalgias. Its tendency for causing depression, and suicidal ideation still remains controversial [2]. Arthralgia may also be experienced by the patients during systemic isotretinoin therapy; 20% of the patients complain of either myalgia or arthralgia [3]. Inflammatory low back pain is a very common side effect of systemic isotretinoin therapy; sacroiliitis and tendinitis may also occur although much rare. The low back pain ceases with dose reduction [4,5].

Objectives

The aim of this study is to determine the incidence of fatigue, myalgia and low back pain (inflammatory or mechanical) in acne vulgaris patients receiving oral isotretinoin therapy; and to determine the relationship of these side-effects to the age and the gender of the patient, the isotretinoin dosing regimen, the duration of isotretinoin therapy and the isotretinoin-naiveness of the patient.

Methods

Patient Selection

Acne vulgaris patients, aged between 13 to 40 years, who have at least received one month of oral isotretinoin treatment in the dermatology outpatient clinic of Zonguldak Atatürk State Hospital and who were willing to participate in this study were included in this cross-sectional study. Patients with already diagnosed rheumatic diseases, musculoskeletal diseases, inflammatory bowel disease, hormonal disturbances, psychiatric comorbidities and who were using non-steroidal anti-inflammatory drugs regularly were excluded from this study.

Data Acquisition

The blood chemistry including lipids and beta-human chorionic globulin (for female patients only) of the patients receiving oral isotretinoin were evaluated during monthly consultations. The age, gender, isotretinoin dosage (mg/kg/day), treatment duration (weeks) and whether the patient is using isotretinoin the first or the second time for acne vulgaris were noted during the monthly consultations. The patients were questioned for the presence of fatigue, myalgia or low back pain; and the patients with low back pain were referred to the physical therapy and rehabilitation outpatient clinic for further evaluation.

The physical therapy and rehabilitation specialist has evaluated the patients to determine the character of low back pain (inflammatory or mechanical) along with performing physical examination of the range of motion, muscle power and lordosis. Magnetic resonance imaging of the lumber vertebrae was performed on the patients who had inflammatory low back pain in order to evaluate sacroiliitis.

Statistical Analysis

SPSS version 21 was used for the statistical analyses. Mann-Whitney U test was used to determine the relationship of age, isotretinoin dosage and treatment duration to all of the side effects studied (fatigue, myalgia and low back pain). Pearson chi-square test was used to determine the relationship of gender to fatigue and low back pain; and of isotretinoin-naiveness to low back pain. Fisher exact test was used to determine the relationship of gender to myalgia; and of isotretinoin-naiveness to fatigue and myalgia.

Ethics

The approval of İstanbul Kent University Ethics Committee was obtained before the initiation of the study (27.05.2022). Informed consent was taken from all of the patients who were willing to participate in this study; and the study was conducted in accordance with the Helsinki Declaration.

Results

Patient Characteristics and Side Effects

A total of 180 patients were included in this study. The mean age of the patients was 20.3 years with a standard deviation of 5 years. Of all the patients, 57 (31.7%) were male and 123 (68.3%) were female. Fatigue was reported by 8 (4.4%) of the patients, myalgia by 5 (2.8%) and low back pain by 45 (25%) of the patients. Four (2.2%) of the patients were diagnosed with inflammatory low back pain by the physical therapy and rehabilitation specialist; and 41 (22.8%) were

diagnosed with mechanical low back pain. The mean isotretinoin treatment duration was 9.6 weeks with a standard deviation of 6.7 weeks; the mean isotretinoin dosage was 0.582 mg/kg/day with a standard deviation of 0.18 mg/kg/day; and 144 (80%) of the patients were isotretinoin-naïve, whereas 36 (20%) were using isotretinoin for the second time. Patient characteristics and side effects are summarized in Table 1.

Relationship of Side Effects to Patient Characteristics

Fatigue, myalgia and low back pain were the side effects that were examined in this study. All of the side effects that were examined were found to be independent of age, gender, isotretinoin dosage (mg/kg/day), treatment duration and isotretinoin-naiveness. The relationships of side effects to the patient characteristics are summarized in Table 2.

Character of the Low Back Pain

The patients with low back pain were further examined for the character of low back pain by the physical therapy and rehabilitation specialist. Within the patients with low back pain, only 4 (8.9%) had inflammatory low back pain. There was no statistically significant relationship between the age of the patient, gender of the patient, isotretinoin dosage (mg/kg/day), treatment duration (weeks) and isotretinoin-naiveness of the patient; and the character of low back pain. Table 3 summarizes the relationship of the character of low back pain to the patient characteristics.

Conclusions

Systemic isotretinoin therapy is known to have side effects in many organ systems, including the musculoskeletal system

Table 1. Patient characteristics and side effects.

Patient characteristics	N=180
Age	
Mean ± SD Median (IQR)	20.3 ± 5 20 (17 – 22)
Gender, N (%)	
Male Female	57 (31.7) 123 (68.3)
Side Effects, N (%)	
Fatigue Myalgia Low Back Pain	8 (4.4) 5 (2.8) 45 (25)
Character of Low Back Pain, N (%)	
Inflammatory Mechanical	4 (2.2) 41 (22.8)
Treatment Duration (Weeks)	
Mean ± SD Median (IQR)	9.6 ± 6,7 8 (4 – 12)
Isotretinoin Naiveness, n (%)	
Naive Not Naive	144 (80) 36 (20)
Isotretinoin dosage (mg/kg/day)	
Mean ± SD Median (IQR)	0.582 ± 0.18 0.565 (0.5 – 0.695)

IQR = interquartile range; SD = standard deviation.

Table 2. Relationship of side effects to patient characteristics.

	FATIGUE		MYALGIA		LOW BACK PAIN	
	Present	Absent	Present	Absent	Present	Absent
Mean Age ±,SD Median (Range) in years	19.8 ± 2 20 (18 -21)	20.3 ± 5.1 20 (17 – 22)	21.6 ± 2 21 (20 – 23,5)	20.3 ± 5.1 20 (17 – 22)	19.3 ± 4.2 19 (16 – 21)	20.6 ± 5.3 20 (17 – 22)
P	0.906[a]		0.162 [a]		0.1 [a]	
Gender						
Male Female	2 (25) 6 (75)	55 (32) 117 (68)	0 (0) 5 (100)	57 (32.6) 118 (67.4)	14 (31.1) 31 (68.9)	43 (31.9) 92 (68.1)
P	0.678 [b]		0.181 [c]		0.926 [b]	
Isotretinoin dosage (mg/kg/day)	0.625 ± 0.2 0.58 (0.46 – 0.73)	0.58 ± 0.2 0.57 (0.5 – 0.68)	0.582 ± 0.2 0.6 (0.4 – 0.76)	0.582 ± 0.2 0.56 (0.5 – 0.68)	0.599 ± 0.2 0.6 (0.5 – 0.69)	0.576 ± 0.2 0.5 (0.44 – 0.7)
P	0.608 [a]		0.951 [a]		0.23 [a]	
Treatment duration (weeks)	9.9 ±8.7 4 (4 – 19)	9.6 ± 6.7 8 (4 – 12)	13.6 ± 9.2 16 (4 – 22)	9.5 ± 6.7 8 (4 – 12)	8.9 ± 6.7 8 (4 – 12)	9.8 ± 6.8 8 (4 – 12)
P	0.583 [a]		0.324 [a]		0.391 [a]	
Isotretinoin-naiveness Naive Not Naive	 7 (87.5) 1 (12.5)	 137 (79.7) 35 (20.3)	 5 (100) 0 (0)	 139 (79.4) 36 (20.6)	 38 (84.4) 7 (15.6)	 106 (78.5) 29 (21.5)
P	1 [c]		0,585 [c]		0,389 [b]	

[a] Mann Whitney U test; [2]Pearson chi-squared test; [c] Fisher exact test.

Table 3. Relationship of the character of low back pain to patient characteristics.

	Character of low back pain		P
	Inflammatory (N = 4)	Mechanical (N = 41)	
Age	22.8 ± 9.7 19 (16.3 – 33)	19 ± 3.4 19 (16 – 21)	0.631[a]
Gender			
Male Female	3 (21.4) 1 (3.2)	11 (78.6) 30 (96.8)	0.082[b]
Isotretinoin dose (mg/kg/day)	0.593 ± 0.1 0.585 (0.5 – 0.693)	0.599 ± 0.2 0.6 (0.5 – 0.695)	0.967[a]
Treatment Duration (weeks)	6.3 ± 6.7 4 (1.75 – 13)	9.2 ± 6.7 8 (4 – 12)	0.234[a]
Isotretinoin Naiveness			
Naive Not naive	3 (7.9) 1 (14.3)	35 (92.1) 6 (85.7)	0.505[b]

[a] Mann Whitney U test; [b] Fisher exact test.

[6,7]. Low back pain has been reported to be a common side effect of systemic isotretinoin therapy in the literature [5,8]. Low back pain can be categorized into two groups: inflammatory, and mechanical low back pain [9]. Approximately 16 percent of the patients receiving systemic isotretinoin therapy develop musculoskeletal side effects including myalgia, arthralgia and low back pain. Although rare, sacroiliitis can also be observed in patients receiving systemic isotretinoin therapy, which can be classified as a cause of inflammatory low back pain [10].

In this study, 45 patients (25%) have reported low back pain; of which 4 (2.2%) have been diagnosed with inflammatory low back pain and 41 (22.8%) have been diagnosed with mechanical low back pain by the physical therapy and rehabilitation specialist. None of the patients were diagnosed with sacroiliitis. Previous studies on this subject have reported a prevalence of low back pain, among patients receiving systemic isotretinoin treatment, of 78.7%, 46.9%, 49.3% and 10.4% [4,5,11,12]. Among the patients with low back pain, 60.3%, 54.7% and 44%[1] had inflammatory low back pain [4,11,12]. We report a lower prevalence of low back pain and inflammatory low back pain due to systemic isotretinoin use compared to most of the studies in the literature.

In our patient population, the prevalence of fatigue was 4.4% and of myalgia was 2.8%. In the literature, fatigue has been reported to have a prevalence of 54% and of 50.7% [11,12]; myalgia has been reported to have a prevalence of 46.9% and 42.5% [11,12] Again, we report a lower prevalence of fatigue and myalgia due to systemic isotretinoin therapy compared to the literature.

The average daily dose of systemic isotretinoin prescribed in our study (0.582 mg/kg/day) is similar to the average doses prescribed in the literature: 0.6 mg/kg/day, 0.55 mg/kg/day and 0.53 mg/kg/day[4,11,12]. There was no relationship between the daily dose of systemic isotretinoin treatment and the prevalence of the side effects. In alignment with this result, Karaosmanoğlu and Mülkoğlu also concluded that there is no correlation between the cumulative dosage of isotretinoin and the severity of low back pain [8].

Previously in the literature, Acar et al reported that low back pain was more common in male patients and pain severity increased with increasing age [4]. In contrast, this study revealed that the side effects of systemic isotretinoin treatment are independent of age and gender. Our study also revealed that side effects of systemic isotretinoin are independent of the treatment duration and isotretinoin naiveness of the patient.

Although systemic isotretinoin treatment is the most effective treatment modality for acne vulgaris, both patients and prescribing physicians express fear about the side effects [13]. Compared to the previous literature, we report a lower prevalence of fatigue and musculoskeletal side effects (namely myalgia and low back pain) and no case of sacroiliitis in our patient population, which supports the use of systemic isotretinoin in indicated cases of acne vulgaris. Furthermore, we also report that side effects of isotretinoin treatment are independent of age, gender, daily isotretinoin dose, treatment duration and isotretinoin naiveness of the patient.

Fatigue, myalgia and low back pain can be observed during systemic isotretinoin treatment. These side effects are independent of the patient age, gender, daily systemic isotretinoin dosage, treatment duration and isotretinoin-naiveness of the patient. The side effects are not that common; thus, patients and physicians should not hesitate to use systemic isotretinoin in indicated cases.

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