

Evaluation of musculoskeletal adverse effects in patients on systemic isotretinoin treatment: A cross-sectional study

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ABSTRACT

Objectives: This study aims to investigate the frequency of musculoskeletal adverse effects in acne vulgaris patients receiving systemic isotretinoin treatment.

Patients and methods: Between January 2016 and December 2017, a total of 200 severe acne patients (22 males, 178 females; mean age: 21.8±0.4 years; range, 15 to 53 years) who were on isotretinoin treatment were retrospectively analyzed. Data including age, sex, body mass index (BMI), duration of disease, diagnosis, and comorbidities were recorded. Back pain severity was evaluated with the Visual Analog Scale (VAS).

Results: The treatment period was mean 8.5±0.1 (range, 6 to 12) months. The dose of isotretinoin was mean 0.6±0.1 (range, 0.5 and 1) mg/kg. Musculoskeletal side effects were seen in 99 (49.5%) patients. Back pain was reported during the treatment period in 78 (78.7%) patients. The diagnosis was mechanical back pain in 31 (39.7%) and inflammatory back pain in 47 (60.3%) patients. The moderate-severe back pain group received higher cumulative isotretinoin doses than the mild back pain group (p=0.003). The BMI values did not show a significant difference between the patients with and without back pain (p=0.55). There was no significant correlation between the BMI and VAS scores (p=0.06). The VAS scores were found to be correlated with age (p=0.04). Sacroiliitis was diagnosed in four (4%) patients. One (1%) patient was diagnosed with enthesitis. Creatine kinase elevation was reported in 18 (18.1%) patients, while three (3%) patients described myalgia of mild severity.

Conclusion: Low back pain is one of the most common musculoskeletal side effects of isotretinoin treatment that usually resolves with dose reduction. The cumulative dose of isotretinoin does not seem to play a role in the development of back pain, but can determine pain severity. Pain severity is directly correlated with the increasing age. Evaluation of the patients for musculoskeletal side effects during isotretinoin use is important in clinical practice, as it is a common occurrence.

Keywords: Acne, hyperostosis, inflammatory back pain, sacroiliitis, spondyloarthropathy, systemic isotretinoin.

Acne vulgaris is a chronic inflammatory skin disease, particularly affecting the young population. Topical and systemic treatment regimens are used to treat the condition. Isotretinoin is a synthetic vitamin A derivative that is effective on four of the factors that play a role in acne pathogenesis: sebum hypersecretion, follicular hyperkeratinization, Propionibacterium

acnes proliferation, and inflammation.¹ It affects acne pathogenesis by binding to cellular retinol binding protein or retinoic acid nuclear receptors.²

Isotretinoin use is associated with mucocutaneous, ocular, neurological, musculoskeletal, and hepatic side effects. Musculoskeletal side effects are common during systemic isotretinoin treatment and include

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enthesopathy, arthritis, sacroiliitis, costochondritis, osteoporosis, hyperostosis, extraspinal calcifications, and premature epiphyseal closure in children.³⁻¹⁰

Isotretinoin has detergent-like properties and can affect immunomodulation by causing alterations in the cytokine levels.^{11,12} The activation of matrix metalloproteinases (MMPs) which is stimulated by proinflammatory cytokines is known to play a role in the pathogenesis of osteoarthritis and rheumatoid arthritis.¹³ Retinol and retinoic acid have been shown to induce MMP-2 activity.¹⁴ The same mechanism may also play a role in the development of side effects such as sacroiliitis and tendinitis during isotretinoin treatment. Catabolic events such as the upregulation of ubiquitin ligases including atrogin-1 and muscle-specific ring finger protein-1 have been also noted in the etiology of muscle pain related to isotretinoin.^{15,16}

The results of the limited number of studies investigating the frequency of isotretinoin-related musculoskeletal effects in the literature have been variable.^{3,4,17-19} Myalgia, arthralgia, and low back pain have been reported as the most common musculoskeletal side effects.^{3,17,19} Sacroiliitis has been reported in 8.2% and 11.7% of the patients, respectively, in two different studies.^{3,19} Tendinopathy is another side effect, but it is less common. Tendinopathy has been reported in 4.3% of the patients in the study of Karaosmanoğlu and Mülkoğlu.¹⁹

The management of the musculoskeletal side effects related to isotretinoin use is important, as these side effects are frequently encountered in clinical practice. In the present study, we aimed to evaluate the frequency and sex distribution of these musculoskeletal side effects and to examine the effect of age, drug dose, and body mass index (BMI) on isotretinoin treatment.

PATIENTS AND METHODS

This single center, cross-sectional, retrospective study was conducted at Kırşehir Training and Research Hospital, Department of Dermatology between January 1st, 2016 and December 31st, 2017. A total of 200 severe acne patients (22 males, 178 females; mean age: 21.8±0.4 years; range,

15 to 53 years) who were initiated on isotretinoin treatment were included (Table 1). Patients with a history of neuromuscular, rheumatoid, or systemic inflammatory disease were excluded. The patients on isotretinoin were referred to the Physical Medicine and Rehabilitation specialist during their monthly follow-up and the development of any musculoskeletal side effects was evaluated. The data of these patients were retrospectively analyzed together with the radiology findings. A written informed consent was obtained from each patient. The study protocol was approved by the Ahi Evran University Faculty of Medicine Ethics Committee (Date 31.10.2017, no: 2017-16/191). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data including age, sex, height, weight, BMI, duration of disease, diagnosis, and comorbidities of the patients were recorded. The BMI (kg/m²) was calculated. Pain was evaluated with the Visual Analog Scale (VAS) as 0 to 10. The VAS scores of 1-4 were classified as mild pain, 5-6 as moderate pain, and 7-10 as severe pain.²⁰

Inflammatory low back pain was evaluated using the Assessment of Spondyloarthritis international Society (ASAS) criteria. The ASAS criteria consist of disease onset under the age of 40 years, insidious onset, relief with exercise, no relief with rest, and nocturnal pain improving with rising.²¹

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The statistical difference between the groups was analyzed using the Student t-test for mean values. The correlation between the variables was evaluated using the Spearman correlation test. A *p* value of <0.05 was considered statistically significant.

RESULTS

The treatment period was mean 8.5±0.1 (range, 6 to 12) months. The dose of isotretinoin was mean 0.6±0.1 (range, 0.5 and 1) mg/kg. Musculoskeletal side effects were seen in 99

Table 1. Age, treatment duration, cumulative isotretinoin dosage and BMI of the patients

	Male	Female	Total
	Mean±SD	Mean±SD	Mean±SD
Age	20.5±0.6	22.0±0.4	21.8±0.4
Treatment duration (month)	4.7±1.2	5.1±0.1	5.1±0.107
Isotretinoin dosage (mg)	4745±310	4610±120	4630±110
BMI	21.4±1.7	21.7±1.6	21.6±0.1

BMI: Body mass index; SD: Standard deviation.

(49.5%) patients. Seventy-eight (78.7%) patients, including 12 males (15.4%) and 66 females (84.6%), described back pain during the treatment period. The number of female patients with back pain was significantly higher than the male patients ($p=0.001$). The rate of developing back pain was higher in the male patients than in the female patients, although the difference was not statistically significant ($p=0.089$). Thirty-one patients (39.7%), including eight males and 23 females, were diagnosed with mechanical back pain and 47 (60.3%) patients, including four males and 43 females, with inflammatory back pain. The ratio of the female patients developing inflammatory back pain was significantly higher than the male patients ($p=0.041$) (Table 2).

Considering the severity of back pain, 49 (62.8%) patients had mild, 23 (29.5%) patients had moderate, and six (7.7%) patients had severe pain. There was no significant correlation between the treatment duration, cumulative isotretinoin dosage, and the VAS score ($p=0.47$, $p=0.09$, $p=0.45$, respectively). However, the mean cumulative isotretinoin dose in the moderate and severe back pain groups was significantly higher than in the mild back pain group ($p=0.003$). There was a significant correlation between the VAS score and age ($p=0.04$). However, the mean VAS score was not statistically significantly different between the sexes ($p=0.088$). The mean BMI value of the patients with back pain was not statistically significantly different than those

Table 2. Isotretinoin related side effects according to genders

	Male		Female		Total		<i>p</i>
	n	%	n	%	n	%	
Back pain	12	15.4	66	84.6	78	77.2	0.00*
Inflammatory	4	8.5	43	91.5	47	39.7	0.00*
Mechanical	8	25.8	23	74.2	31	60.3	0.00*
Back pain severity							0.00*
Mild	9	18.4	40	81.6	49	62.8	
Moderate	3	13.0	20	87	23	29.5	
Severe	-	-	6	100	6	7.7	
Sacroiliitis	1	25	3	75	4	4	0.25
Enthesitis	-	-	1	100	1	1	-
Myalgia	1	33.3	2	66.7	3	3	0.33
CK elevation	13	86.7	2	13.3	15	14.8	0.1

CK: Creatine kinase; * Pearson chi square test; $p<0.05$ was considered statistically significant.

Table 3. Correlation coefficients and significance values of VAS and age, cumulative isotretinoin dosage, treatment duration and BMI

Variables	VAS
Age	
Correlation coefficient	0.26
<i>p</i>	0.04*
Cumulative isotretinoin dosage	
Correlation coefficient	0.09
<i>p</i>	0.45
Treatment duration	
Correlation coefficient	0.02
<i>p</i>	0.47
Body mass index	
Correlation coefficient	0.20
<i>p</i>	0.06

VAS: Visual Analog Scale; BMI: Body mass index; * $p < 0.05$ was considered statistically significant.



Figure 1. Bilateral sacroiliitis in pelvic X-ray.



Figure 2. Enthesitis in right side of lateral foot X-ray.

without back pain ($p=0.55$), and there was no significant correlation between the VAS score and the BMI ($p=0.06$) (Table 3).

Dose reduction was used in patients with moderate and severe back pain, constituting 37.2% of the patients describing the complaint. The vast majority of these patients responded to dose reduction, while eight (10.2%) patients needed to use non-steroidal anti-inflammatory drugs for pain relief. Sacroiliitis was present in four (4%) patients, including three females and one male. There was no statistically significant difference between the sexes for sacroiliitis development ($p=0.25$). Bilateral sacroiliitis was detected in one patient (Figure 1). Sacroiliitis regressed 1.5 to 2.5 months after isotretinoin treatment cessation in all patients. The patients diagnosed with sacroiliitis were followed for six months. Three (3%) patients described myalgia, which was of mild severity and did not require additional treatment. Among these patients, two female patients also described low back pain. Creatine kinase (CK) elevation was observed in 18 (18.1%) patients, including 13 males and two females, one to three months after the beginning of treatment ($p=0.1$). The elevated CK values ranged between 233 and 940 IU and returned to normal levels after dose reduction. One (1%) female patients who was on low-dose isotretinoin treatment (0.5 mg/kg) was diagnosed with enthesitis at three months of treatment (Figure 2).

DISCUSSION

Isotretinoin use is associated with neuromuscular side effects, the most common of which are musculoskeletal pains and arthralgia. These side effects are seen in 20% of patients. They are usually mild and improve with discontinuation of treatment.^{3,7}

In the current study, the most common musculoskeletal side effect was back pain. Our results are in line with previous studies, suggesting a high rate of mechanical and inflammatory back pain in patients using isotretinoin.^{3,17,19} Türkmen²² reported that back pain in patients using isotretinoin was more common in females. However, there was a higher percentage of male patients developing back pain in the current study.

Karaosmanoğlu and Mülkollu¹⁹ reported low back pain in 70.2% of isotretinoin users (inflammatory in 37.8% and mechanical in 62.2%). Similarly, Baykal Selçuk et al.³ reported a higher percentage of mechanical back pain (27.3%) than inflammatory back pain (21.9%). In contrast, the current study revealed a higher frequency of inflammatory back pain, similar to the study by Taheri et al.¹⁷ where 54.7% and 45.3% of the patients experienced inflammatory low back pain and mechanical low back pain, respectively. Inflammatory low back pain was more common in the female population in our study. Similarly, Elnady et al.²³ reported that 70.7% of the patients developing inflammatory back pain were female.

In the literature, only a few studies have investigated the predisposing factors for the development of back pain related to isotretinoin use. Karaosmanollu and Mülkollu¹⁹ reported that patients with back pain received higher doses of isotretinoin than the group without back pain. In our study, we found no significant difference in terms of the cumulative isotretinoin dose between the patient groups with and without back pain. This finding indicates that the development of back pain may not be dependent on the isotretinoin dose. There was also no significant correlation between VAS score and the cumulative dose. However, the moderate and severe pain group received a higher cumulative isotretinoin dose than the mild pain group, suggesting that the severity of the back pain could be affected by the cumulative dose. This is also supported by the fact that the pain severity decreases with isotretinoin dose reduction in most patients.

Obesity has been associated with an increased risk of low back pain in some studies.^{24,25} Increased BMI values were not an additional risk factor for the development or increased pain severity in the current study. However, since patients with high BMI values (>25 kg/m²) constituted a small proportion of our cohort, further large-scale studies including patients with and without obesity and using isotretinoin are warranted.

In our study, the correlation between the VAS scores and age suggests that the effect of isotretinoin on the musculoskeletal system increases with age. Musculoskeletal degeneration related to alterations in hormones, cytokines, growth factors, and altered connective tissue

biology occurs during the aging process.²⁶ Therefore, older patients may be more likely to develop more severe musculoskeletal side effects related to isotretinoin.

Sacroiliitis is the inflammation of the sacroiliac joint and can be seen as a component of various rheumatic diseases including psoriatic arthropathy, familial Mediterranean fever, and Behçet's disease.^{27,28} Acute sacroiliitis can also develop secondarily to hyperparathyroidism, gout, calcium pyrophosphate dihydrate deposition, infectious factors such as brucellosis, hematological malignancies, and intravenous drug use.²⁸ In this study, the patients having a history of such diseases associated with sacroiliitis were excluded. Isotretinoin-induced sacroiliitis develops days to weeks after starting the treatment.²⁹ The presence of human leukocyte antigen-B27 (HLA-B27) may also pose a tendency toward the development of sacroiliitis during isotretinoin treatment.³⁰ In a study by Baykal Selçuk et al.,³ the prevalence of sacroiliitis during isotretinoin use was found to be 8.2% and the symptoms developed within the first two to three months of isotretinoin treatment. In the current study, sacroiliitis developed within the first one to six months of isotretinoin treatment. Similar to the study by Baykal Selçuk et al.,³ there was no significant difference between both sexes in terms of sacroiliitis development. Another study reported that sacroiliitis related to isotretinoin treatment was more frequent in females than males.²³ Since the number of patients diagnosed with sacroiliitis is low in our study, future studies with larger series would be more helpful in determining the sex predominance for sacroiliitis development during isotretinoin treatment.

Previous studies provide insufficient data to assume that sacroiliitis development is dose-dependent. Karadağ et al.²⁹ reported sacroiliitis in four patients undergoing isotretinoin treatment at a dose of 0.5 mg/kg. The patients developing sacroiliitis in our study were also on a low dose of isotretinoin, supporting the notion that sacroiliitis development is not dose-dependent. The lower rate of sacroiliitis in the current study can be attributed to the careful selection of patients with no prior history of arthritis or arthralgia, as well as the heterogeneity of the genetic features of the study populations that can determine the susceptibility for the development of sacroiliitis. In our study, symptoms completely

regressed with treatment cessation in all patients with sacroiliitis.

Muscular side effects including myalgia and muscle stiffness have been reported in 15 to 50% of patients treated with isotretinoin.^{18,31,32} Myalgia associated with isotretinoin use is usually mild.³ Elevation of CK levels, which indicates serious muscular cell damage, has been reported in 5.6 to 41% of the patients with isotretinoin use.³³ The elevations in CK have been mostly reported to be detected incidentally on routine blood tests of the patients, with no concurrent clinical symptoms.³¹⁻³⁵ In a study by Kaymak¹⁸ including 89 patients on isotretinoin treatment, five patients had elevated CK levels and only one patient had myalgia. The main features of CK elevation include darker skin types, male sex, and a history of regular athletic activity.¹⁸ Male patients constituted the majority in our study, and all had a history of vigorous physical activity. Elevated CK levels (approaching or exceeding 1,000 to 2,500 IU) during isotretinoin treatment also raise a concern for rhabdomyolysis, which is characterized by generalized muscle damage, acute kidney injury, and myoglobinuria.³³ Severe acute myopathy has also been reported in two patients on isotretinoin treatment in the literature.³⁶ In the present study, we observed no rhabdomyolysis, renal failure, or myopathy in any of the patients.

Enthesopathy is a reported side effect of isotretinoin and usually develops after long-term isotretinoin use.^{37,38} However, cases associated with short-term isotretinoin treatment have also been reported in the literature. Tendinitis of the Achilles tendon is a known side effect of isotretinoin and has been reported in 9.5% of patients.⁴ A close relationship between Achilles tendinitis and isotretinoin dose has also been described.^{39,40} In our study, the patient who developed tendinitis was on low-dose isotretinoin treatment. Dose reduction and interruption can be considered in patients developing tendinitis.³⁹ The symptoms of the patient in the current study regressed with the cessation of treatment.

The main limitations of this study include its retrospective nature and the lack of HLA-B27 assessment.

In conclusion, low back pain is one of the most common musculoskeletal side effects of

isotretinoin treatment that usually resolves with dose reduction. The cumulative isotretinoin dose and increasing age are the main determinants of the severity of low back pain. Since musculoskeletal side effects are common during isotretinoin use, questioning the patients about such side effects during the treatment is essential.

Declaration of conflicting interests

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