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Impact of oral isotretinoin therapy on musculoskeletal system and physical activity in patients with acne

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Abstract

Introduction and purpose: Isotretinoin, the vitamin A derivative, has been commonly used in treatment of acne vulgaris for years. Despite its unquestionable efficacy, chronic oral isotretinoin treatment leads to multiple side effects. The aim of study is analysis of musculoskeletal symptoms prevalence during oral isotretinoin treatment and their impact on physical activity.

Material and methods: The study was conducted using the original survey questionnaire shared online among members of Polish group of patients treated for acne. Total of 196 responses were analyzed and compared with up-to-date literature related to the topic.

Results: 86,7% of respondents reported at least one of the musculoskeletal symptoms. The most common were back pain (82,7%), fatigue and lethargy (70,4%), myalgia (55,1%) and arthralgia (32,1%). In 97,6% cases adverse effects were developed within the first 6 months of treatment. In 64,2% they persisted during the whole therapy, sometimes even beyond. Due to musculoskeletal side effects, in 2,4% cases dose reduction was necessary, 1,8% of respondents had to stop treatment and 48% had to limit or stop physical activity. 71,4% of respondents reported that lower back pain occurred or escalated during isotretinoin treatment.

Conclusions: Prevalence of reported musculoskeletal symptoms is very high and totals 86,7%. They result in prolonged limiting or stopping of physical activity in almost 50% of people. Although musculoskeletal symptoms are typically benign, possibility of severe disorders and potential permanent effects must be taken into consideration.

Key words: acne, isotretinoin, adverse effects, physical activity, musculoskeletal disorders

Introduction:

Acne vulgaris is the most common skin disease. In the European countries the overall adjusted prevalence of self-reported acne amounts up to 57.8%, the highest rate occurs in youth 15 to 17 years old and decreases with age [1]. This disease may affect more than 80% of teenagers. Acne, as non-inflammatory lesions (open and closed comedones) or inflammatory lesions (papules, pustules or nodules) mostly appears on the face, sometimes on the torso [2,3]. Acne vulgaris is a chronic condition that has strong impact on the quality of life. It causes low self-esteem associated with psychosocial burden and anxiety. Nevertheless, quality of life usually improves after successful treatment [4].

Isotretinoin is the vitamin A-derivative the cis-isomer of retinoic acid. It is converted in vivo to all-trans retinoic acid, which induces cellular effects via binding to nuclear acid receptors, retinoid X receptors (RXRs), and retinoid acid receptors (RARs) [5]. Recent studies report that retinoids have influence on cellular growth, differentiation, morphogenesis and apoptosis, they inhibit tumour promotion and malignant cell growth, exert immunomodulatory actions and alter cellular cohesiveness. Therefore, not only acne and rosacea can be treated with isotretinoin, but also some of inflammatory and malignant disorders [6].

Isotretinoin has remained the single most effective anti-acne therapy, since when it was introduced to the market by Hoffman-La Roche in 1982 [7]. It provides significant improvement in many patients and long-term remission [8–10]. It is the only therapy that affects all major etiological factors of acne.

Oral isotretinoin treatment results in a significant reduction in sebum production, comedogenesis, ceratinisation, has anti-inflammatory properties and indirectly lowers colonization with *Propionibacterium acnes* [9]. The indication for oral isotretinoin treatment is acne that does not respond to other treatment or acne that causes psychological problem as separate indication [11].

Despite isotretinoin's unquestionable efficacy, chronic oral isotretinoin treatment leads to multiple adverse effects. The highest prevalence of adverse effects were observed in patients that were treated with the highest doses [8]. The most common and well known problems are mucocutaneous, ocular, psychiatric, gastrointestinal side effects, as well as teratogenicity. Surprisingly, little attention has been paid to the potential musculoskeletal side effects of retinoids [5,12]. Myalgia, tiredness and arthralgia are one of the most frequently reported symptoms during isotretinoin therapy [11].

Aim:

The aim of this study is analysis of musculoskeletal symptoms among patients treated with isotretinoin for dermatological disorders, especially acne vulgaris and their impact on physical activity.

Materials and method:

The study was conducted in July 2020 using the original survey questionnaire, addressed to members of Polish group of patients treated for acne. Participation in the study was anonymous and voluntary. Participating members completed an online questionnaire that included questions about symptoms, especially musculoskeletal, which they observed during their anti-acne isotretinoin treatment and 1 month after its termination. They were also questioned about features of pain and its influence on their physical activity. Data was analysed and compared with current PubMed publications.

Results:

A total of 196 answers were collected. The study involved 185 females (94,4%) and 11 males (5,6%) in age 13-41. The average age was 21,43, with a median of 21 and the standard deviation was 4,74. The causes of isotretinoin treatment were acne vulgaris (92%), acne fulminans (3%), acne keloidea (1,6%) and other types (3%): acne inversa/hydradenitis suppurativa -2, seborrheic dermatitis – 2, hormonal acne – 2, acne rosacea – 1. Reported daily isotretinoin dose range varied between 0,13 – 1,11 mg/kg/day (mean 0,54 mg/kg/day).

86,7% (170 out of 196 patients) provided an affirmative answer to the question if they experienced fatigue, lethargy, muscle pain, joint pain or stiffness. Lower back pain was reported by – 82,7% (162), fatigue and lethargy 70,4% (138), nonspecific back pain – 66,3% (130), myalgias – 55,1% (108), arthralgias – 32,1% (63), stiffness of muscle and joints – 26,0% (51), spine pain in the cervical and thoracic region – 25% (49), limb pain – 25% (49), heel pain - 16,3% (32) – table 1. Other, less frequently reported musculoskeletal symptoms were knee pain – 1% (2) and sternum and shoulders pain -1% (2).

| Symptom | Patient group (no. %) total no. 196 |
|--|-------------------------------------|
| Lower back pain | 162 (82,7%) |
| Fatigue and lethargy | 138 (70,4%) |
| Back pain | 130 (66,3%) |
| Myalgia | 108 (55,1%) |
| Arthralgia | 63 (32,1%) |
| Stiffness of muscle and joints | 51 (26,0%) |
| Spine pain in the cervical and thoracic region | 49 (25,0%) |
| Limb pain | 49 (25,0%) |
| Heel pain | 32 (16,3%) |

Table 1. The most common musculoskeletal findings and proportions.

These symptoms mostly developed in the first 6 months of therapy. 32,9% of respondents claim that they occurred in less than 1 month after starting the isotretinoin treatment, 64,7% - between 2nd and 6th month, 1,2 % - between 7th and 12th month, 0,6% - over 12 months after and 0,6% - within 1 month after the end of therapy (Figure 1). 48,8% of those who had musculoskeletal symptoms say that they persisted with variable intensity throughout the whole therapy. 15,4% experienced them during and over one month after termination of treatment. 13,6% had side effects, mentioned above, for more than one month, but less than time of entire therapy. In 11% of people they lasted short time, less than 7 days and in 11% - between 7 days and 1 month (Figure 2).

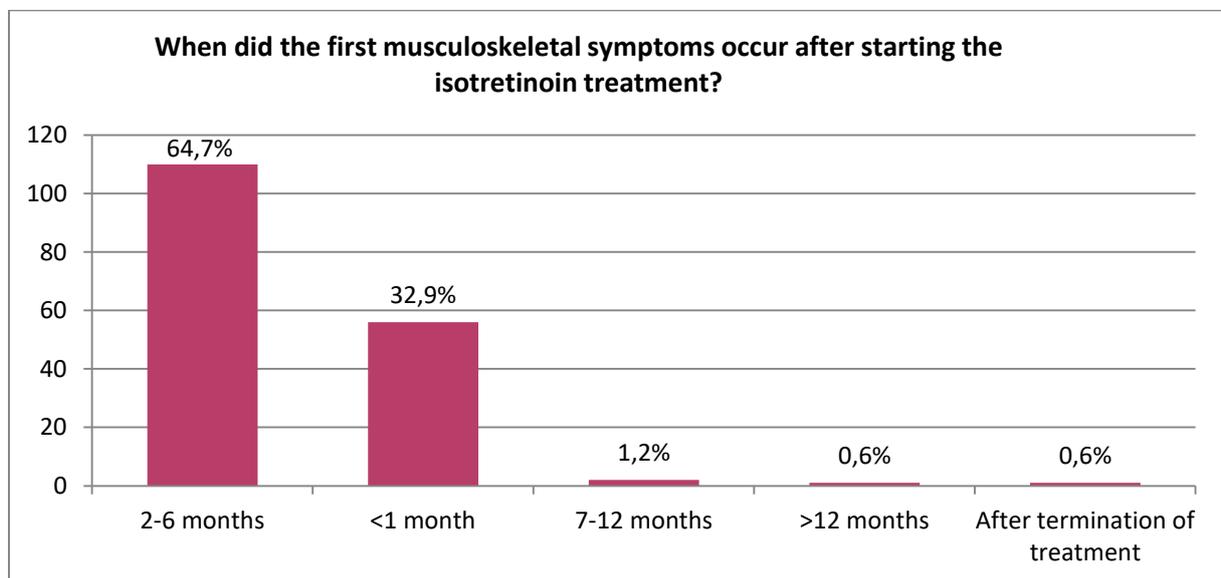


Figure 1. Time to onset of musculoskeletal symptoms in respondents.

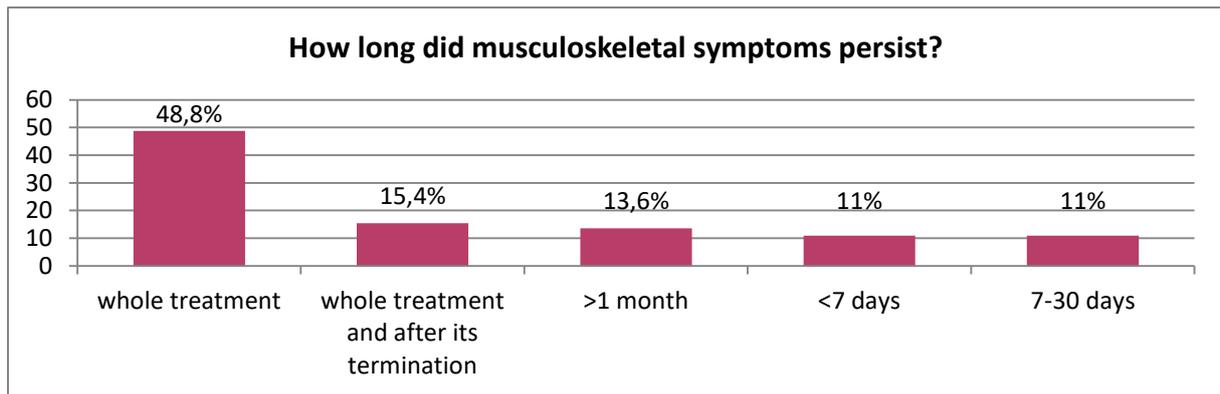


Figure 2. Duration of musculoskeletal symptoms reported by respondents.

In 95,3% (161) of people who experienced muscle symptoms (170) there was no need to stop treatment. In 2,4% (4) dose reduction was necessary and 1,8% (3) had to stop treatment due to musculoskeletal side effects of isotretinoin.

48% (94) of all respondents (196) had to limit or stop physical activity due to musculoskeletal symptoms during treatment. In the questionnaire physical activity was defined as 150 minutes of physical activity per week or doing manual work for 8 hours daily. 61,7% (121) considered themselves as physically active people, and 38,3% (75) as not. Among people physically active 47% (57/121) had to limit or stop physical activity because of musculoskeletal symptoms during treatment. Among people not physically active 49% (37/75) had to limit or stop physical activity.

CK levels were elevated in 6,1% of patients (12), remained within normal range in 39,8% (78) and were unknown in 54,1% (106). Among people physically active CK levels were elevated in 5,8% (7), normal in 43,0% (52) and unknown in 51,2% (62). Among people who are not physically active CK levels were elevated in 6,7% (5), normal in 34,7% (26) and unknown in 58,7% (44). Among people with musculoskeletal symptoms active CK levels were elevated in 5,9% (10), normal in 38,2% (65) and unknown in 55,9% (95). Among people without any musculoskeletal symptoms active CK levels were elevated in 7,7% (2), normal in 50% (13) and unknown in 42,3 (11).

Respondents were asked about lower back pain in detail. 82,7% (162) claimed that they experienced lower back pain during treatment. 44,9% (88) claimed that it occurred for the first time after starting isotretinoin treatment. 26,5% (52) said that pain had occurred before starting treatment and escalated during it. 11,2% (22) suffered from lower back pain which remained the same during therapy. 14,8% (29) did not have lower back pain and 2,6% (5) did not remember if they had (Figure 3).

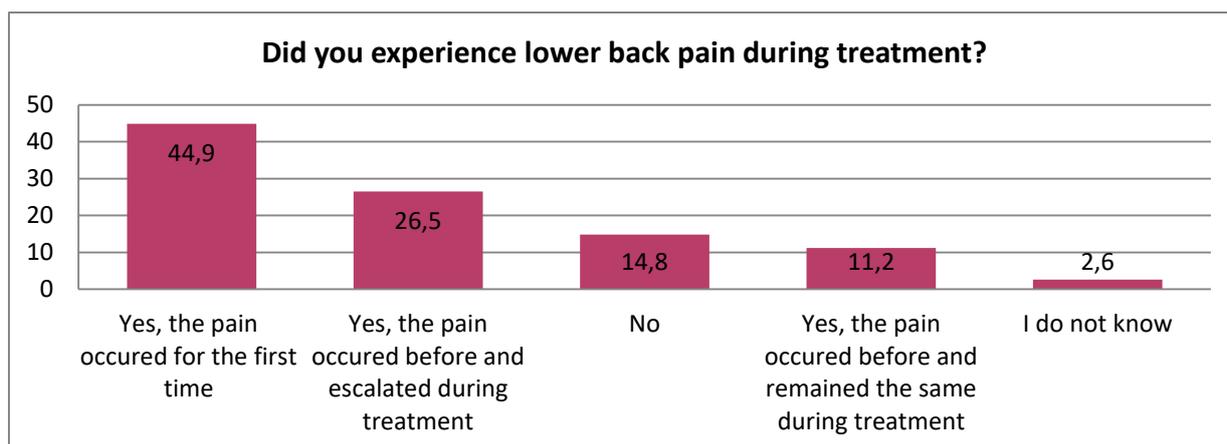


Figure 3. Prevalence of lower back pain during isotretinoin treatment among respondents.

Among those who answered the question about features of lower back pain affirmatively (162): In 56,8% of people (92) physical activity did not lessen the lower back pain, in 13,6% (22) physical exercises reduced pain and 29,6% (48) did not know. In 53,1% (86) rest brought pain relief, in 39,5% there was no relief with rest, 7,4% (12) did not know. Lower back pain appeared at night and improved with rising in 24,7% (40). There was no nocturnal pain in 65,4% (106) and 9,9% (16) did not know (Table 2).

67 (41,4%) respondents reported one of the features of inflammatory lower back pain, 26 (16,0%) - two features and 2 (1,25%) - all three features, pain relieved with exercise, did not relieve with rest and occurred at night.

| Feature of inflammatory lower back pain | Yes | No | I don't know |
|---|-------|-------|--------------|
| Relief with exercise | 13,6% | 56,8% | 29,6% |
| No relief with rest | 39,5% | 53,1% | 7,4% |
| Nocturnal pain (improving with rising) | 24,7% | 65,4% | 9,9% |

Table 2. Inflammatory features of pain among patients with lower back pain.

Discussion:

Musculoskeletal and mucocutaneous symptoms are the most common side effects of isotretinoin treatment. According to the one of the large retrospective reviews, myalgia occurs in 39% of patients, tiredness in 18% and arthralgia in 12% [11]. Results of our study point out even higher frequency of musculoskeletal side effects, despite the fact that all of the respondents were treated with low doses of isotretinoin. Lethargy was reported more often (70,4%) than in another clinical study, conducted on the group of 73 patients with acne vulgaris, where it was found in 50,7%. Similarly, lower back pain was reported in 82,7% vs. 49,3% and myalgia – 55,1% vs. 42,5% [13]. The other symptoms, listed with substantial frequency, were arthralgia, nonspecific back pain, spine pain in cervical and thoracic region, limb pain and heel pain.

Almost all of the respondents reported that musculoskeletal symptoms appeared within first 6 months of treatment, out of which 33% started on the first month of therapy and 65% between 2nd and 6th month. Still, in 2% of respondents, symptoms occurred later or even after termination of the treatment. They can result in limiting physical activity for the long time. Almost 50% of respondents say that adverse effects persisted with variable intensity throughout the whole therapy, which usually lasts for months [6]. Moreover, 15,4% experienced them even long time after termination of treatment. In 35,6% of responders, musculoskeletal symptoms lasted shorter, sometimes for less than one month or even less than 7 days.

Because of these side effects almost half of the patients had to limit or even stop any physical exercises. That information in addition to high frequency of musculoskeletal side events and their long persisting emphasizes the importance of this issue. A large amount of people during isotretinoin therapy may lose all of the benefits of physical activity by its limiting or stopping. Despite the unarguable positive impact on cardiovascular system, physical activity has favorable effect on bone and joints, such as increasing bone mineral density in femoral neck, slowing down the damage in small joints, improving of endothelial function and slowing of atherosclerotic process. It may also increase self-esteem and decrease pain perception. Resistance training decreases systemic inflammation and may have positive influence on isotretinoin-induced spondyloarthropathies and other inflammatory side events [14]. In results of our study, there was slightly no difference between group physically active and inactive in frequency of limiting physical activity during isotretinoin therapy due to musculoskeletal symptoms.

Muscle symptoms may be associated with elevation of blood levels of creatine kinase(CK), a specific marker of muscle destruction. During isotretinoin treatment CK may be elevated occasionally up to 100 times the normal value, particularly in patients undergoing vigorous physical exercise, with or without any muscle symptoms. Hiper-CK-emia is a benign phenomenon, that may occur in 15-50% patients treated with isotretinoin. Nevertheless, measurement of CK levels as well as renal tests should be conducted in patients with musculoskeletal symptoms in order to detect possible rhabdomyolysis [15,16]. Acute rhabdomyolysis is the most severe muscle-related adverse effect, which left untreated can lead to acute renal failure [12]. In our study elevated level of creatine kinase occurred in total of 6,1% respondents, in 5,8% among people physically active and in 6,7% of those who are inactive. In patients with musculoskeletal symptoms elevated CK level occurred in 5,1%, without them – in 7,0%. However, in 54,1 % of respondents CK level remained unknown, seriously limiting the analysis.

Elevation of CK levels may occur due to cytokine-mediated muscle damage during physical activity or viral infections in patients treated with isotretinoin. The other mechanism seen in vitro is rapid decreasing of mitochondrial membrane potential by isotretinoin, then releasing cytochrome c to the cytosol, which initiates the apoptosis, in similar way as in mitochondrial myopathies. CK levels may be also in normal range, despite clinical symptoms of myopathy [12]. Isotretinoin-induced myalgia may be related to TRAIL-mediated muscle cell apoptosis, although direct evidence is missing [7].

In patients with myalgia, weakness or elevated CK levels isotretinoin dosage should be reduced or temporarily discontinued. Moreover, those patients should avoid strenuous physical activity [15]. Elevated CK is not a contraindication for isotretinoin therapy [16].

In our study arthralgia were reported by 32,1% of respondents and stiffness of muscles and joints by 26%. Arthralgia are typically mild and disappear when the treatment is stopped [17]. However, physicians should stay alert and look out for inflammatory features of pain. Arthralgias and stiffness of muscles and joints during isotretinoin treatment may be symptoms of rheumatologic side effects, such as bilateral and unilateral sacroiliitis, acute arthritis, enthesopathy, inflammatory lower back pain, polyneuropathy and myopathy [18]. They may be also symptoms of less frequent skeletal side effects - arthritis, skeletal and soft tissue calcification, premature epiphyseal closure, exostosis cartilaginea, periosteal proliferation, diffuse radiological bone hyperlucency [19].

In majority of our respondents musculoskeletal symptoms were localized in the back, especially in its lower regions, less frequently in cervical and thoracic region of the spine. They were also reported in the limbs, specifically in the heel, knee and sternum and shoulders. In lower back pain physicians should look out for sacroiliitis, an inflammation occurring in the sacroiliac joint [13]. Spine pain may be a symptom of spondyloarthropathy and hyperostosis. Hyperostosis may be responsible for limitation of movement and localizes in cervical and thoracic spine. Enthesopathies might occur in the foot, pelvis, hip, shoulder and elbow. They are usually mild and asymptomatic [19]. Heel pain reported by 16,3% of our respondents may be associated with Achilles enthesopathy if the pain has inflammatory features [18].

Mono- or oligoarthritis are one of the less common isotretinoin's side effects. A few cases of true arthritis have been reported, the most frequently in the knee. Another significant side effect, sacroiliitis, is an inflammation occurring in the sacroiliac joint and its association with isotretinoin has been recently well described [17]. Sacroiliitis may also occur in patients with acne fulminans without isotretinoin treatment with 21% frequency and in SAPHO syndrome [20]. The mechanism by which isotretinoin leads to arthritis or sacroiliitis is poorly understood, because retinoids foster the outgrowth and suppressive properties of regulatory T cells, which are likely to be protective mechanisms against spondyloarthropathy [18]. Isotretinoin may alter the structure of the liposomal membrane and sensitize the joint to degeneration with mild trauma. It may also increase MMP-2 activity, which is present at high levels in arthritic joints [17]. Isotretinoin-induced arthritis and sacroiliitis are typically self-limiting and resolve within a few weeks or months after discontinuation of isotretinoin treatment and NSAIDs use [17,21]. However, they can lead to ankylosing and potentially permanent disability. For example, in one of the studies, indicating relation between sacroiliitis and isotretinoin usage, 1 per 5 patients presented chronic sacroiliitis in 1 year follow-up, despite discontinuation of isotretinoin treatment [21].

Lower back pain was reported with significant 82,7% frequency. 86,4% of those who reported lower back pain, claimed that the pain occurred for the first time during isotretinoin treatment or occurred also before, but escalated during treatment. Lower back pain may have inflammatory or mechanical features. In one prospective study inflammatory back pain occurred in 14,28% patients, while unilateral sacroiliitis appeared in 2,38% [18]. Inflammatory lower back pain is one of the features of spondyloarthropathy and the main symptom of sacroiliitis [22].

According to ASAS 2010 criteria, diagnosis of inflammatory back pain can be stated when minimum 4 out of 5 conditions are fulfilled: commencement under the age of 40, insidious onset, relief with exercise, no relief with rest, nocturnal pain (improving with rising). In our study we asked all of respondents under 40 years old with lower back pain (160) about features of pain as a screening for inflammatory pain. 95 out of 160 respondents (59,4%) had at least one of the inflammatory features of pain. Among that group only 2 respondents (1,25%) confirmed the occurrence of all three features - pain relieved with exercise, did not relieve with rest and occurred at night (three inflammatory features). As a result they fulfilled ASAS criteria for inflammatory back pain (4/5 conditions) and should be diagnosed towards isotretinoin-induced spondyloarthropathy with more objective methods, such as MRI in order to detect sacroiliitis [13,18]. This analysis had limitations, for example insidious onset was difficult to assess. As a result, the prevalence of inflammatory low back pain was lower than in the one of the clinical studies, where it represented 44% of all patients with low back pain, while mechanical back pain - 66% [13].

Rheumatologic disorders induced by isotretinoin, although commonly benign, can lead to permanent effects [23]. Destruction of cartilage and bone joints, as a consequence of ongoing inflammation in joints and hyperostosis may lead to disability [24]. Rheumatologic side effects can limit temporarily or even permanently patients' physical activity and as a result reduce its' positive influence on health.

There are number of limitations to this study. Respondents were members of the online group concentrating on isotretinoin treatment, so they may have joined it because of side effects and maybe they would have not searched for help online if they did not have any symptoms. As a result, the prevalence of side effects may be overstated. Moreover, there was no control group. Reported information were subjective and could not be verified with more objective methods. Nevertheless most of the side effects were reported in studies without such limitations. Musculoskeletal side effects of isotretinoin are widely discussed by patients online and considered to be a significant problem during therapy. This study may show the importance of the matter that remained ignored by clinicians.

Conclusions:

Prevalence of reported musculoskeletal symptoms is very high and totals 86,7%. Majority of isotretinoin-induced musculoskeletal symptoms occurs early, within first 6 months of therapy and in most cases lasts for the entire therapy, resulting in prolonged limiting or stopping of physical activity in almost 50% of the people, with no difference between physically active and inactive people. High prevalence of musculoskeletal symptoms, its long persisting and high frequency of limiting physical activity emphasize the importance of the issue. Elevated CK with or without musculoskeletal symptoms is an indication to avoid strenuous physical activity, but not a contraindication to isotretinoin therapy. Although musculoskeletal symptoms are typically benign, the possibility of severe disorders and potential permanent effects must be taken into consideration. The investigation of inflammatory pain, especially in lower back, and osteoarticular symptoms are necessary in order to avoid permanent disability due to rheumatologic diseases.

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