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Is the effect worth the risk? - The most common complaints during oral isotretinoin anti-acne therapy and controversies around its adverse effects

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Abstract

Introduction and purpose: Acne vulgaris, the most common skin disease, causes medical, esthetic and psychosocial problems. Isotretinoin, the vitamin A-derivative, has been the most effective treatment for acne vulgaris. It provides significant improvement and long-term remission. However, it leads to multiple side effects. The aim of our study was to evaluate the prevalence of adverse effects in patients treated with isotretinoin and analyze the most commonly reported symptoms.

Material and methods: The study was conducted using original survey questionnaire addressed to members of Polish group of patients treated with isotretinoin. 196 responds were collected and confronted with current PubMed publications.
Results: The most common mucocutaneous side effects, such as dry lip, dryness of the mucous membranes, xerodermia and dryness of the conjunctiva occurred in 92,6%, 73,5%, 66,8% and 66,3% of respondents, respectively. Both, tiredness and back pain were reported by 70,4% of respondents; myalgia - 55,1%, arthalgia - 32,1% and stiffness of joints - 26,0%. Mood change occurred in 54,6%, hair loss in 50,0%, gastrointestinal symptoms, such as abdominal pain and diarrhea – in 15,8% and 10,7%.
Conclusions: All of the most common isotretinoin side effects are usually mild and dose-dependent. However, their prevalence is very high. Isotretinoin's association to depression and suicidality remains unclear. In spite of the previous data, the risk of inflammatory bowel disease is probably not increased in patients isotretinoin exposed. However, more studies are necessary.

Key words: acne, isotretinoin, adverse effects, depression

Introduction:
Acne vulgaris is the most common skin disease that affects up to 80-90% of teenagers [1]. However, it may occur in every age group with the prevalence of 57,5% in general population [2]. Lesions, such as open and closed comedones, papules, pustules or nodules mostly appear on the face and the torso. In some cases scarring is present [3]. Acne vulgaris is not only the esthetic problem, but also a psychosocial burden. Low self-esteem and anxiety lessen the quality of life. Nevertheless, quality of life improves after successful treatment [4].
Isotretinoin is the vitamin A-derivative the cis-isomer of retinoic acid. It induces cellular effects via binding to nuclear acid receptors as all-trans retinoic acid [5]. Isotretinoin affects all major etiological factors of acne, by reducing in sebum production, comedogenesis, ceratinisation, inflammation and colonization with *Propionibacterium acnes* [6].
Over the last few decades, oral isotretinoin has been the most effective anti-acne therapy, that provides significant improvement and long-term remission [7]. The main indication for treatment is moderate to severe acne vulgaris that is resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy or causes psychological problem [4,5]. Unfortunately, therapeutic effects are usually accompanied by multiple side effects of isotretinoin. The most common are mucocutaneous, ocular, musculoskeletal, psychiatric and gastrointestinal side effects, out of which isotretinoin's association to depression and inflammatory bowel disease remain the most controversial [9].

Aim:
The aim of this research was to analyse the most commonly reported symptoms and their association to isotretinoin.

Materials and method:
The study was conducted in July 2020 using the original survey questionnaire, addressed to members of Polish group of patients with acne treated with isotretinoin. The participation in

our study was anonymous and voluntary. Questionnaires were asked about the symptoms they noticed during isotretinoin treatment and within less than one month after its termination. The total number of 196 answers were collected and their link to isotretretinoin were analyzed with current PubMed publications.

Results:

The study involved 196 members – 185 females (94,4%) and 11 males (5,6%) in age 13-41 (average – 21,43, median - 21, standard deviation – 4,74). Indications for isotretinoin treatment were acne vulgaris (in 92% of questionnaires), 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).

191 per 196 respondents reported one or more symptoms during isotretinoin treatment and less than one month after its termination (Table 1.). Only 5 per 196 respondents did not notice any of the disturbing symptoms.

Mucocutaneous side effects were the most commonly reported symptoms. 182 out of 196 (92,6%) respondents experienced dry lip and 144 (73,5%) - dryness of mucous membranes of the mouth or nose. Xerodermia or itching of the skin were noticed by 131 (66,8%) respondents and dryness of the conjunctiva were reported by 130 (66,3%) respondents.

138 (70,4%) research participants experienced tiredness or fatigue. Musculoskeletal symptoms were also reported with significant prevalence. Back pain, especially in lower regions of the spine, occurred in 138 (70,4%) respondents, myalgia – in 108 (55,1%), arthalgia – in 63 (32,1%) and stiffness of joints – in 51 (26,0%).

Mood changes, such as irritability or depression, were reported by more than a half of the respondents (98 – 54,6%). Increased hair loss was noticed by 98 questionnaires (50,0%).

Gastrointestinal symptoms were the last of the most commonly reported disorders during anti-acne treatment. Abdominal pain occurred in 31 (15,8%) and diarrhea in 21 (10,7%) respondents. Elevation of liver enzymes, AST (aspartate aminotransferase) and ALT (alanineaminotransferase) were reported by 33 respondents (17,2%).

Reported symptom	Patient group (no. %) total no. 196
Dry lip	182 (92,6%)
Dryness of mucous membranes of the mouth or nose	144 (73,5%)
Tiredness, fatigue	138 (70,4%)
Back pain (mostly lower)	138 (70,4%)
Xerodermia or itching of the skin	131 (66,8%)
Dry eyes	130 (66,3%)
Myalgia	108 (55,1%)
Mood change	107 (54,6%)
Hair loss	98 (50,0%)
Arthralgia	63 (32,1%)
Stiffness of joints	51 (26,0%)
Abdominal pain	31 (15,8%)
Diarrhea	21 (10,7%)

Table 1. Prevalence of reported symptoms during isotretinoin treatment.

Discussion:

Mucocutaneous symptoms occur in almost every patient. In our study dry lip, dryness of mucous membranes of the mouth or nose, xerodermia or itching of the skin affected up to 92,6%. The most common mucocutaneous side effects are usually mild, dose dependent and can usually be reduced by moisturizers. Our data correspond with a large retrospective review, in which dry lips and xerosis affect almost 100% of users and symptoms, such as facial erythema, epistaxis, cheilitis, itching of the skin, exfoliation of the skin were observed in more than 30% patients [9].

Although not as common as mucocutaneous side effects, ophtalmological side effects may also occur with significant frequency. Dry eyes affected 66,3% of our respondents. Ophtalmological symptoms can manifest themselves as blurred vision, conjunctival infection, conjunctivitis, dry eyes, irritation, pain, photophobia, pterygium [10].

Tiredness and fatigue were reported by 70,4% of respondents and were as common as musculoskeletal symptoms. Back pain, especially in lower regions of the back, was the most frequently reported musculoskeletal symptom with the prevalence of 70,4%. The other symptoms, such as myalgia, arthralgia and stiffness of joints were reported by 55,1%, 32,1% and 26%, respectively. Isotretinoin-induced musuloskeletal symptoms, including less common disorders, such as arthritis and sacroilitis are typically self-limiting and resolve within a few weeks or months after discontinuation of isotretinoin treatment and NSAIDs use [11]. It is known that oral isotretinoin does not significantly alter muscle strength, fatique and endurance[12]. However, subjective musculoskeletal symptoms are unpleasant and almost half of the all patients treated with isotretinoin has to limit or stop physical activity due to musculoskeletal side effects [13].

Mood changes, such as irritability or depression, were reported by 54,6% of respondents of our survey. In the past decade isotretinoin has been surrounded by the controversy due to its inconsistent association to depression and suicidality. Mood changes, suicidal thoughts,

depression and psychoses has been the major concern. Nevertheless, the evidence has been still incomplete and unclear [14]. Theoretically, isotretinoin itself may cause depressive disorders by inducing neurogenic apoptosis in hippocampus and altering intracellular serotonin level and serotonin receptors [14,15]. However, beneficial psychological effects as a result of clearance of skin lesions may compensate potentially increased risk of depression [14,16].

Exactly the half of the respondents reported increased hair loss. Isotretinoin is linked to telogen effluvium and thinning hair. However, when the high doses are not used the drug does not alter hair growth parameters in the short term [17].

Oral isotretinoin may lead to gastrointestinal adverse events as well, such as abdominal pain and diarrhea reported by 15,8% and 10,7% of our respondents. Moreover, isotretinoin is responsible for altered appetite, indigestion, nausea and vomiting. Systemic isotretinoin may cause transient, dose-dependent elevation of liver enzymes. 17,2% of our respondents have been informed by physician about AST or ALT levels elevation. Hepatotoxity is rare, however it is relevant that alcoholics, diabetics and obese patients have a higer risk of hepatotoxity [10]. Isotretinoin-induced abnormal blood work reveals itself in elevated cholesterol, elevated triglycerides, reduced haemoglobin [18]. In the past decade isotretinoin has been surrounded by the controversy due to its inconsistent association to inflammatory bowel disease. Isotretinoin is suspected of possible increase in the risk of flaring inflammatory bowel disease (IBD) in patients already diagnosed with IBD. The latest retrospective cohort analysis reports that IBD incidence among isotretoin exposed patients with acne vulgaris is very low and the risk of IBD is similar to unexposed patients with acne vulgaris [19].

Headache was not reported by any of our respondents. Nevertheless, according to current literature, it is the most frequent neurological adverse effect associated with oral isotretinoin and may occur as an independent symptom or as a part of benign intracranial hypertension and rare pseudotumour cerebri, especially in addition to tetracycline [9,20]. Similarly, due to obligatory contraception, none of respondents experienced teratogenicity. However, it is crucial to still inform women in reproductive age, that 50% of pregnancies spontaneously abort and 50% of infants are born with cardiovascular or skeletal deformities [6]. Isotretinoin treatment must be always prescribed in full compliance with pregnancy prevention programme. However, according to 2011 data from Europe pregnancy incidence was seen in 0,2-1,0 per 1000 woman of childbearing age using isotretinoin and between 65% and 85% were terminated [21].

Conclusions:

Starting the treatment with oral isotretinoin should be a mutual decision of physician and patient, both aware of the prevalence of possible adverse events. Every patient has to know, that he will experience, with high probability, one or more isotretinoin adverse effect. The most common side effects of oral isotretinoin therapy are usually mild mucocutaneous, ophtalmological and musculoskeletal symptoms. More than half of patients experience mood change. Isotretinoin's link to depression and suicidality remains unclear. Gastrointestinal side effects are usually mild. In spite of the previous data, the risk of inflammatory bowel disease

is probably not increased in patients isotretinoin exposed. However, more studies are necessary.

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