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Effects of Isotretinoin treatment on human body - review

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ABSTRACT:

Introduction: Isotretinoin (13-cis-Retinoic Acid) is a part of the retinoid group, and is used in dermatology for the treatment of acne, due to its demonstrated inhibitory effect on sebaceous gland activity and proliferation. Isotretinoin is a highly lipophilic drug, for this reason taking it with food, doubles the bioavailability of the substance, during systemic treatment. Isotretinoin as a drug has been used effectively for more than 40 years in the treatment of acne, although its exact mechanism of action is not known.

Objective: The objective of this study is to gather and analyze literature regarding the adverse effects of isotretinoin therapy on mental health and the digestive, cardiovascular, immune, urinary, and reproductive systems.

Materials and Methods: A literature review was conducted using the PubMed database with the following search terms : retinoids, isotretinoin, acne, 13-cis-retinoic acid.

Current Knowledge: Isotretinoin therapy has a vast spectrum of side effects affecting various systems of the human body. During the use of isotretinoin, special caution should be taken in patients with depression, lipid disorders, and abnormal liver function. In addition, in

patients of childbearing age, make sure to use contraception one month before, during and one month after the end of isotretinoin therapy due to its teratogenicity.

Conclusion: Isotretinoin is still the most effective drug in the systemic treatment of severe forms of acne, nevertheless its potential side effects should be kept in mind. Regular monitoring of patients should be a mainstay during isotretinoin therapy, especially with regard to lipid profile and liver parameters.

Keywords: retinoids, isotretinoin, acne, 13-cis-retinoic acid.

Introduction

Isotretinoin is a synthetic derivative of Vitamin A, classified as a first-generation I drug of the Retinoids group, and is mainly used by dermatologists to treat severe forms of acne vulgaris. The action of isotretinoin focuses in particular on inhibiting the activity and proliferation of sebaceous glands and also leads to their involution. The exact mechanism of action is not known.

During systemic therapy with isotretinoin, the most common side effects are dry skin, dryness of the mucous membranes of the nose and throat, and dry eyes. The most important contraindications to the use of isotretinoin in the treatment of acne are pregnancy and lactation, liver failure, hypervitaminosis A and allergic reactions to isotretinoin. The use of isotretinoin is also contraindicated during concomitant use of antibiotics from the tetracycline group, due to the increased risk of a serious complication which is pseudotumor cerebri.

Currently, 42 years after isotretinoin was approved by the American Food and Drug Administration (FDA) for the treatment of acne, many publications are still being published expanding our knowledge of the adverse effects of isotretinoin therapy on mental health and the digestive, cardiovascular, immune, urinary, and reproductive systems. The purpose of our

paper is to collect and publish current knowledge regarding the effects of isotretinoin on various systems of the human body.

1. Mental health

Numerous publications have shown an association between isotretinoin therapy and the occurrence of psychiatric disorders, such as depression, anxiety, suicidal thoughts and even psychosis [1]. It was shown that psychiatric disorders were 50% more common in patients using isotretinoin, compared to the control group. Disorders most often manifested as fatigue [2].

2. Digestive system

During oral retinoid therapy, presenting symptoms mainly include nausea, abdominal pain and diarrhea, but such symptoms are not common [3]. In a study by Brzezinski et. al, involving 3525 patients, abdominal pain during received therapy occurred in 3.71%, while gastrointestinal distress occurred in only 0.19% of participants [4].

Attention is also drawn to information that isotretinoin therapy can induce inflammatory bowel disease including Crohn's disease and Ulcerative Colitis. However, Mohammed A Migdad et. al [5], suggested that there is no significant association between isotretinoin therapy and IBD development, nonetheless isotretinoin could be a trigger inducing Colitis Ulcerosa for patients with high risk factors to UC[5,6].

3. Cardiovascular system

The use of isotretinoin may indirectly increase the risk of a cardiovascular incident, due to the possible occurrence of lipid disorders accompanying isotretinoin therapy[7,15]. In particular, the occurrence of hypercholesterolemia and hypertriglyceridemia in patients taking isotretinoin is a risk factor for the development of atherosclerosis, which can lead to myocardial infarction or stroke[7-10].

Furthermore, a case of arrhythmia was reported from a patient who had been using isotretinoin for acne therapy for 3 months, with no other risk factors for heart disease previously identified. After discontinuation of isotretinoin, all complaints (palpitations) disappeared within a week; additionally, in control ECG Holter recordings performed in 4 and 6 week after discontinuation of isotretinoin intake, the occurrence of pathological changes

was no longer described, suggesting a significant association between isotretinoin intake and the occurrence of arrhythmias [7,11].

Isotretinoin therapy can also potentially affect the myocardium directly, causing cardiac hypertrophy and hypovolemia among patients [12]. A case of significant left ventricular dilatation, along with a significant decrease in ejection fraction, during treatment of acne with isotretinoin has also been described, while other causes of dilated cardiomyopathy have been ruled out [13].

During treatment with isotretinoin for acne, the 30-year-old patient was reported to have had two episodes of stroke, over a period of 7 years. The patient's symptoms in both cases occurred after 3 months of isotretinoin therapy. The patient's drug dosage was 50 mg of isotretinoin daily during the first stroke episode, and 45 mg of isotretinoin daily during the second episode. The patient had no other risk factors[14].

It is worth mentioning that so far, no statistical association has been found between the use of isotretinoin and the incidence of cardiovascular incidents and strokes[7,11]. However, furthermore investigation is needed.

4. Immune system

Intake of isotretinoin also affects the immune system, reducing the number and disrupting the function of NK cells, and there was a decrease in the number of neutrophils and the ratio of neutrophils to lymphocytes[16,19]. In addition, isotretinoin therapy in patients treated for acne vulgaris has been shown to reduce levels of IFN-gamma, TNF-alpha, IL-4 and IL-17 [17]. Nevertheless, there is no strong evidence linking isotretinoin use to an increased risk of upper respiratory tract infections, among others. The effect of isotretinoin on the immune system is not fully understood and requires further research[18].

5. Kidneys

Armaly et. al [20], described a case of acute kidney injury in the second month of repeated isotretinoin therapy in a young, previously healthy patient. Other causes of acute kidney injury were ruled out. In addition to complaints of flank pain and nausea with vomiting, the patient had an increase in creatinine levels to 2 mg/dl[20]. Isotretinoin therapy was discontinued at the onset of symptoms. Additionally, Oers et al [21], documented a case of minimal change disease in the kidneys in a patient during isotretinoin therapy used for 4

months at a dose of 40 mg/d. The patient presented, with swelling of the face and ankle joint, additionally reporting a weight gain of 12 kg over 2 months. Laboratory tests confirmed the presence of nephrotic syndrome: decreased albumin and total plasma protein levels, and increased cholesterol. In a daily urine collection, 10.3 g of protein was determined. In addition, renal ultrasound and biopsy showed no abnormalities. Isotretinoin therapy was discontinued, and prednisolone treatment was implemented. Nephrotic syndrome resolved after 4 weeks of treatment[21].

Renal dysfunction due to the use of isotretinoin is very rare, and it seems to be inadequate, ordering laboratory tests to monitor renal function regularly in patients on therapy. However, it is important to be aware of the possibility of complications, in addition, further studies are needed to expand our knowledge of the effects of isotretinoin on renal function.

6. Liver

Isotretinoin therapy has a negative effect on liver function, resulting in an increase in serum liver enzymes - alanine aminotransferase (ALT) and aspartate aminotransferase (AST). In addition, the use of isotretinoin interferes with normal lipid metabolism, causing an increase in triglycerides (TG) , total cholesterol and low-density lipoprotein cholesterol (LDL-C). In addition, it also causes a decrease in high-density lipoprotein cholesterol (HDL-C) [22,23].

However, in a publication by Kızılyel et. al [23] on the effect of long-term isotretinoin therapy, the authors noted that the increase in parameters occurred mainly at the beginning of therapy, while in the later period, the parameters remained stable.

As for the levels of liver enzymes AST and ALT, their concentrations were elevated, compared to the beginning of therapy, nevertheless, they continued to remain within the accepted normal range throughout isotretinoin therapy (ALT and AST levels <40 U/L). The lipid profile including TG, LDL-C, HDL-C during isotretinoin therapy was as follows: during the initial period of therapy, LDL-C and TG levels were elevated above normal (TG <150 mg/dL, LDL-C <100 mg/dL), while HDL-C levels were reduced below normal (HDL 40-59 mg/dL). Later in the therapy period, there were no further significant changes in the levels of the above-mentioned lipids [23].

7. Pancreas

Isotretinoin therapy, due to its effect of increasing plasma triglycerides levels, may lead indirectly to acute pancreatitis [24]. Additionally, there have been reports regarding the induction of acute pancreatitis as a direct result of isotretinoin, however furthermore investigation is needed, due to a small number of case reports and analysis [25].

7.1 Effect on plasma glucose levels

During isotretinoin treatment, plasma glucose levels do not change significantly[26]. In addition, Eleni Paschalidou et al[27], in a meta-analysis using data from 9 studies, also found no statistically significant changes in plasma glucose levels before and after isotretinoin therapy.

8. Reproductive system

There are few studies on the effects of isotretinoin use on the male reproductive system, and they are mainly conducted on animal models[28]. One study was conducted on male mice, which showed, in particular, a reduction in the weight of the reproductive organs after administration of isotretinoin[29]. Çinar et. al[28]conducted a study involving men who were administered 0.5-1 mg/kg of isotretinoin, noted a positive effect on all measured parameters of semen analysis and thus, a possible positive effect on fertility in men. In the case of hormones such as testosterone, follicle-stimulating hormone (FSH) and luteinizing hormone LH, their values did not change with statistical significance. However, to conclusively state the effect of isotretinoin on fertility in men, more studies are required[28].

During isotretinoin therapy in women, attention is primarily turned to menstrual cycle disorders and teratogenicity to the fetus, which is one of the most dangerous side effects of isotretinoin use. Isotretinoin can cause both prolongation and shortening of the menstrual cycle and lead to irregular menstruation in women who were menstruating regularly before starting therapy. The risk of irregular menstruation increases when isotretinoin and birth control pills are used simultaneously[30]. The primary mechanism of action of isotretinoin is sebocyte apoptosis and cell cycle arrest which is directly related to the teratogenicity of the drug. Excessive apoptosis of neural crest cells is mainly responsible for the development of malformations in neonates exposed to isotretinoin during the fetal period. The risk of

congenital malformations due to fetal exposure to isotretinoin is 20%-35% and includes cardiovascular and neurological malformations, thymic disorders or craniofacial defects [29]. Therefore, it is imperative that women use effective pregnancy interventions a month before, during and one month after therapy, and it is additionally recommended to perform a pregnancy test before, during and after therapy[29].

Summary:

A review of the available literature highlights the monitoring of patients for lipid disorders and liver parameters during isotretinoin therapy. Hyperlipidemia induced during therapy may be a cause of excessive atherosclerosis, but a statistically significant association with the incidence of cardiovascular incidents has not been demonstrated.
The effect of isotretinoin on the digestive system, cardiovascular system, immune system and urinary system, is still not fully understood and requires further research and knowledge.

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