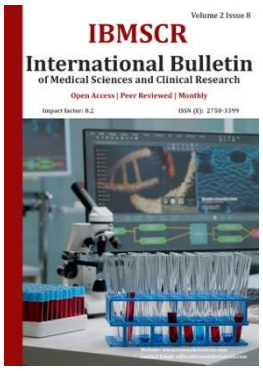

ISOTRETINOIN: FACTS AND CONTRADICTIONS

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Summary Acne is one of the most common skin diseases that leads to persistent stigmatization and negatively affects the quality of life of patients. Currently, there are many treatments for this disease, but isotretinoin is the most effective against severe forms of acne and those cases where other forms of therapy have failed. Isotretinoin is an oral retinoid that has been used in clinical practice for about 40 years. This drug affects all the key links in the pathogenesis of acne, which determines its high effectiveness. Many clinical studies have been devoted to the study of the mechanisms of action of this drug, the specifics of its purpose, and undesirable side effects. Nevertheless, today, both patients and doctors have a number of misconceptions about the use of isotretinoin, which raises concerns about its administration, errors in treatment tactics, and low adherence to treatment. This article discusses the main issues about the mechanisms of action of isotretinoin, the specifics of its administration, indications and contraindications for use, undesirable side effects and ways to correct them, as well as the contradictions in the tactics of prescribing this drug that prevent its effective use. Special attention is paid to choosing the optimal therapeutic dose of isotretinoin and the duration of the course of treatment. In addition, the article discusses the main factors leading to failures in systemic retinoid therapy: slowing the onset of clinical response, the development of relapses after treatment, among which are the features of the course of the disease, the patient's age, his hormonal background, as well as the specifics of the dosage of the drug and the duration of its administration.

Keywords: acne, isotretinoin, treatment, dosage, side effects
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The oral retinoid isotretinoin (13-cis-retinoic acid), approved for the treatment of acne in 1982, remains the most effective treatment for this disease [1]. In addition, isotretinoin has the best effect on the quality of life of patients among all acne treatment methods [2]. However, despite the fact that isotretinoin has been successfully used for more than four decades, there are still a number of contradictions among specialists regarding its use schemes. This is partly the result of the low quality of the available clinical trial results, which, as shown by one of the Cochrane reviews, make it difficult to accurately determine the role of this drug in clinical practice, as well as the schemes of its use to achieve the highest efficacy and safety profile [3]. In addition, there are quite a large number of misconceptions among patients and even doctors about the specifics of isotretinoin therapy, the selection of an adequate dose of the drug, and undesirable side effects, which in some cases somewhat limits the prescription of this drug, leading to the unjustifiability of myths and misconceptions about acne therapy with systemic retinoids. In this article, we will review relevant information about the pharmacokinetics, mechanism of action, contraindications, interactions, and appropriate dosage regimen of isotretinoin in the treatment of acne.

Pharmacokinetics Isotretinoin (13-cis-retinoic acid) is a natural retinoid found in human blood serum, which is produced after oral administration of vitamin A. After oral administration, the bioavailability of isotretinoin is approximately 25% [4]. Due to the fact that isotretinoin has high lipophilicity, its relative bioavailability increases 1.5 - 2 times when taken with food [5]. This was the reason for the recommendations to take this medicine exclusively during or immediately after a meal, preferably fatty. However, modern preparations of isotretinoin contain lipid agents that make it possible to take it regardless of food intake [6]. Upon entering the body, a significant portion of isotretinoin binds to plasma proteins, especially albumin. It is rapidly distributed in both the epidermis and dermis, but in lower concentrations compared to blood plasma [7]. The metabolism of isotretinoin is associated with the metabolism of its isomer. The main metabolite of isotretinoin is 13-cis-4-oxo-retinoic acid. However, there are a number of other metabolites: trans -retinoic acid, glucuronide metabolites 13-cis, 13-cis-4-oxo- and completely trans-retinoic acid. Isotretinoin and 4-oxo-isotretinoin have been shown to reach steady-state serum concentrations within 10 days when taken at a dose of 40 mg 2 times a day [b). The main metabolite, 13-cis-4-oxo-retinoic acid, reaches stable concentrations that are 2-5 times higher than the dose of the unchanged drug. In this case, enterohepatic recirculation of the drug may play an important role in the pharmacokinetics of isotretinoin. Isotretinoin and its metabolites are excreted in the same amounts in the faeces and urine. In patients receiving this drug in doses of 0.5- 1 mg/kg/day, the concentration of both the initial drug and the metabolites returns to endogenous concentrations within 2 weeks after discontinuation [6].

Mechanism of action Isotretinoin is believed to be highly effective in the treatment of acne by reducing the size of sebaceous glands and their production of sebum, normalizing keratinization of sebaceous follicle ducts, suppressing the growth of Cutibacterium acnes bacteria, by changing the follicular environment and reducing sebocytes. Isotretinoin acts as a prodrug that is exposed to intracellular isomerization and then binds to specific receptors. In addition, isotretinoin has been shown to exert a sebosuppressive effect through a mechanism independent of retinoic acid receptors, causing cell cycle arrest and inducing apoptosis in sebocytes [8]. In this case, sebocyte apoptosis can be mediated by increased induction of key genes, including genes encoding this process.

Thus, cell cycle arrest can be mediated by the induction of FOX01, which also suppresses keratinocyte proliferation, enhancing both their differentiation and programmed death [9]. It was found that the dosage of isotretinoin taken affects the severity of apoptosis of sebocytes and their precursor cells, which explains the longer sebosuppressive effect of relatively high doses of the drug (for 40 weeks after the course of 0.1 mg /kg / day against 80 weeks after the course of 1.0 mg/kg/day) [10]. The anti-inflammatory effect of isotretinoin is achieved by reducing the amount of C. acnes against the background of suppressing sebum secretion and, possibly, reducing the size of the sebaceous hair follicle, i.e. as a result of reducing the amount of substrate for the vital activity of these microorganisms. Isotretinoin also has an anti-inflammatory effect by reducing the level of Toll-like receptor-2 in monocytes and attenuating the subsequent inflammatory cytokine response to C. acnes.

The content of matrix metalloproteinase-y and matrix metalloproteinase-_3 in sebum -2 is an important representative of the combined systemic retinoids is Acnecutane, the active ingredient of which is isotretinoin, a stereoisomer of trans-retinoic acid (tretinoin). acnecutan

has all the above-mentioned pharmacological properties of systemic retinoids and is effectively used for the treatment of severe forms of acne (nodular, conglootic) or acne with a risk of scarring, as well as those forms of the disease that are not suitable for other types of therapy. Our own clinical experience shows that acnecutane is effective in the treatment of acne, is well tolerated, and is also suitable for dose adjustment due to the fact that it is available in two dosages - 16 and 8 mg.

Indications and contraindications

Indications for the use of isotretinoin vary depending on the country and local clinical recommendations, but include the treatment of severe forms of acne, moderate acne that cannot be treated, as well as acne that leads to scarring on the skin or severe psychoemotional disorders [13]. Thus, Acnecutan is indicated for the treatment of severe forms of acne (nodular cystic, globular acne or acne with a risk of scarring). as well as acne, which is not amenable to other types of therapy.

For example, a pregnancy test is performed on the day of the appointment of Acnecutane or 5 days before the patient's visit to the doctor. During therapy, the patient should visit a doctor every 28 days. And 5 weeks after the end of treatment, a test is performed to exclude pregnancy. As for men, the data available today indicate that the concentration of isotretinoin, which entered a woman's body from the semen and seminal fluid of a man taking this drug, is insufficient for the development of teratogenic effects upon the onset of a possible pregnancy [14].

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Hypersensitivity to isotretinoin or the components of the drug, hypervitaminosis a are also absolute contraindications to the appointment of the drug. The relative limitations to the use of isotretinoin are pronounced leukopenia. hyperlipidemia, liver failure, concomitant intolerance to the active ingredient or excipients of the drug, children under 12 years of age. As a rule, the relative contraindications depend on the dose of the prescribed drug

Nevertheless, there are several reports in the scientific literature about the unsafe use of isotretinoin in patients with established allergies to peanuts and soy. This is probably due to the fact that the proteins contained in soybean oil have low antigenicity in people with soy intolerance 15-1/. thus, allergy to peanuts and soy is a relative contraindication to taking isotretinoin, however, before prescribing this drug, it is advisable to find out from a patient with an allergy to these products in what form the allergic reaction manifested itself, and whether he developed symptoms of anachylaxis, Currently there is no There is no consensus on the optimal approach to the treatment of acne patients in need of isotretinoin who have a known allergy to peanuts or soy. If you have a burdened allergic history to these products, it seems reasonable to administer the first dose of isotretinoin under the supervision of a doctor who can provide the necessary medical care.

Dose selection

To date, discussions regarding the choice of the optimal dose of isotretinoin and the duration of treatment with this drug for acne patients have not subsided. The choice of the dose of this drug depends on the severity of the disease, the patient's weight and ranges from 0.1 - 1.0 mg/kg/day [17]. The duration of isotoetinoin treatment depends on the rate at which the desired therapeutic effect is achieved. At the same time, the cumulative dose ranges from 120 to 150 mg/kg, which is currently not supported by convincing evidence

This recommendation is often supported by research data that have not been developed to assess the effect of cumulative dose on relapse rates [18]. In many cases, these studies used a fixed duration of treatment, which is not often found in routine clinical practice. In addition, such studies mainly estimated the recurrence rate only 6-12 months after discontinuation of treatment, rather than in the longer term, for example, after 3-5 years, which would be more consistent with the natural course of acne. The results of studies that did not use a fixed duration of treatment usually did not demonstrate a relationship between the risk of relapse and a cumulative dose of more than 120 mg/kg compared with an analogous value of less than 120 mg/kg [3, 19]. It should also be remembered that when describing the design of clinical trials or clinical cases, the authors often indicate the starting and total cumulative dose received by patients, however, in routine clinical practice it is advisable to focus not on these indicators, but on the clinical effect of the therapy. Therefore, in recent years, there has been a tendency to use lower but optimal therapeutic daily doses of isotretinoin without taking into account the cumulative dose. As for the choice of the daily dose of isotretinoin, there are currently several comparative and nonparametric studies that have investigated the effectiveness of this drug in various precise dosages [20-22]. It was shown that longer-term acne treatment with relatively low doses of isotretinoin was not only better tolerated by patients, but also had high efficacy and a low rate of recurrence after the end of therapy. The optimal duration of such therapy, according to clinical studies, is from 16 to 32 weeks. [23]. However, even in this case, one should focus on the clinical effect of therapy, rather than on its duration. The main causes of the development of acne recurrence after isotretinoin therapy, as a rule, were the presence of gynecological pathology in women, accompanied by changes in the hormonal background, as well as the transmission of severe somatic diseases by patients of both sexes, and surgical treatment. In a number of clinical recommendations for the treatment of acne, there are indications to start taking isotretinoin in patients with severe forms of acne at a dose of 0.5 mg/kg/ day, followed by an increase to 1 mg/kg/day, and to continue treatment until a cumulative dose of 120-150 mg/kg is reached [13]. However, in the international consensus published by the Global Alliance to Improve Acne Outcomes (Global Alliance to Improve Outcomes in Acne), on the contrary, there are no specific recommendations regarding isotretinoin dosages, but it is recommended to continue taking the drug until complete cure plus an additional month, regardless of the accumulated dose [19]. For example,

Acnecutane is prescribed for most patients at a dose of 0.4 to 0.8 mg/kg/day. One should not expect significant additional benefits from taking the drug at a total dose of more than 100-120 mg / kg, which is optimal. At the same time, the duration of treatment depends on the individual daily dose, the clinical picture of the disease, and a course of therapy lasting 16-24 weeks is usually sufficient to achieve remission. In patients who do not tolerate the recommended dose of the drug very well, treatment can be carried out at a lower dose, but

for a longer time. Thus, based on modern published scientific data, as well as our own clinical experience, we consider it advisable to choose an isotretinoin dose that is adequate for the severity of the disease and the patient's body weight, followed by a slow decrease [24].

Factors that may lead to a slowdown in the clinical response

Despite the fact that isotretinoin is rightfully considered a highly effective drug for the treatment of acne, in some cases there may be a delay in the onset of the therapeutic effect, which undoubtedly reduces patient adherence to therapy and raises doubts about the

expediency of prescribing this drug from doctors. Factors contributing to slowing the onset of improvement in acne patients treated with isotretinoin include the presence of multiple closed comedones and macrocomedones [25].

Changes in the background of sex hormones in women, in particular polycystic ovarian syndrome, the development of hyperandrogenism caused by taking anabolic steroids or supplements containing androgens, may also predispose to a slower reaction to the drug. The smoking of patients has the same effect. If patients have persistent stool or nodular elements, it is advisable to take swabs from the lesions in order to exclude staphylococcal infection, which can also reduce the effectiveness of isotretinoin and requires the appointment of topical or systemic antibiotics [25]. It should be noted that most patients with slow development of the therapeutic effect eventually respond satisfactorily to isotretinoin therapy. At the same time, an increase in the daily dose of the drug is rarely beneficial. Therefore, if the effect of taking isotretinoin is delayed or insufficient, possible risk factors should be identified and excluded, patients should be advised to stop smoking and taking dietary supplements with anabolic hormones, cosmetic cleansing should be performed in the presence of multiple comedones, and women should be consulted by a gynecologist.

FACTORS ASSOCIATED WITH INCREASED RISK

Recurrence After Taking Isotretinoin, the main factors that increase the risk of acne recurrence after the end of treatment with isotretinoin are considered to be the patient's young age at the time of initiation of therapy [20], prepubescent acne, the presence of rashes on both the face and body, family history of acne [26] and severe the course of the disease with a large number of nodular and cystic elements. In addition, failures during isotretinoin treatment are often observed in women with late acne (especially over the age of 25), polycystic ovarian syndrome and hyperandrogenism [27], as well as, as mentioned above, in people taking dietary supplements with androgens. It should be noted that an increase in the daily dose of isotretinoin rarely affects the recurrence rate, however, in order to achieve a lasting therapeutic effect, it is recommended to continue treatment until the acne completely disappears, and then for another 1-3 months. To achieve lasting remission, it makes sense to slowly reduce the starting dose of the drug over several months, which should begin after achieving a lasting

improvement in skin condition and against the background of the absence of new inflammatory ones. In the event of a recurrence of the disease, in some cases it makes sense not to repeat the course of isotretinoin treatment, but to prescribe topical retinoids. actions or adapalene. If a repeat course of isotretinoin is chosen, the drug is prescribed in lower doses, for a shorter time, 3 months after the previous one [28]. It should be noted that only a small number of patients (1-2%) need multiple or even long-term continuous courses of isotretinoin to achieve complete control over acne, which once again confirms the high effectiveness of this medicinal product [29]-

Undesirable side effects Currently, the effectiveness of isotretinoin against acne is beyond doubt. The use of this drug in most patients allows achieving a stable positive clinical effect. However, the use of this drug has a number of limitations and may be associated with the development of undesirable side effects, which sometimes leads to a decrease in adherence to therapy in patients or even to drug withdrawal, and also causes certain difficulties and concerns among doctors, especially those who did not have proper work experience. with this medicinal product. To eliminate and prevent the development of such difficulties, it is necessary

to follow the procedure for examining patients before prescribing isotretinoin, as well as during treatment, it is necessary to have a clear understanding of the symptoms of possible side effects and methods of their correction. In addition, an extremely important component of the effective and safe use of isotretinoin is an explanatory conversation with the patient about the nature of possible side effects, the duration of treatment, and the need to follow certain therapy protocols. One of the common undesirable side effects that develop during the intake of 12 medical advice of isotretinoin, is the so-called retinoid dermatitis, which is observed in 90% of patients. It is characterized by pronounced dryness of the skin and mucous membranes caused by a decrease in sebum production and stratum corneum thickness, as well as changes in the skin barrier. Retinoid dermatitis is manifested by cheilitis, xerosis, sometimes erythema of the skin, itching, peeling, hypersensitivity of the skin, dryness of the nasal mucosa, nosebleeds, dry eyes, blepharitis, and sometimes conjunctivitis. These symptoms are dose-dependent, predictable, controllable, and reversible [30]. For the prevention and correction of these phenomena, it is necessary to start using mild detergents, moisturizing products of specialized cosmetics (for example, Perfectoin®) from the first day of treatment. Intensive moisturizing), designed to care for dry, very dry and sensitive skin of the face and body, hygienic lipsticks and lip balms, moisturizing eye drops (for example, Optinol") and nose (for example, Aqua Maris® Plus). Other side effects of isotretinoin are headache, alopecia, arthralgia, muscle pain (mainly in athletes), insomnia, and hypertension (31). These symptoms develop relatively rarely. Just like retinoid dermatitis, they are dose-dependent, reversible, and are corrected by taking nonsteroidal anti-inflammatory drugs, as well as standard treatment methods in case of hair loss.

Patients with a severe inflammatory process on the skin, an abundance of macrocomedones, and a burdened family history may experience pseudo-exacerbation of the disease during the first 6-8 weeks. isotretinoin therapy. This undesirable side effect is associated with intense sebocyte apoptosis, subsequent release of antigens, and the development of local inflammation, which spontaneously resolves in 15-18% of patients even without additional therapeutic effects. In some cases, such manifestations on the skin prompt the attending physicians to reduce the dose of the drug they are taking, which, in our opinion, is not justified, since these symptoms can overwhelmingly be controlled using topical acne treatments (for example, drugs with the anti-bacterial component Zerkalin®, Zerkalin®

Intensive) and adequate skin care [1]. Another extremely important aspect that can affect the treatment of acne patients with isotretinosis is changes in laboratory blood parameters, which correspond to about 2% of adverse events: increased levels of triglycerides, total cholesterol and LDL cholesterol, transaminases. They are rare or discrete in patients without pronounced, decompensated somatic pathology and, as a rule, occur at the beginning of treatment [1, 31]. Various retrospective clinical studies confirm the recommendations to conduct preliminary biochemical blood tests, which should be repeated 1-2 months after the start of therapy. It should be noted that complete elimination of isotretinoin is indicated only with a threefold increase in the above-mentioned biochemical parameters of the blood compared with the initial value [32, 33]. Finally, clinicians have certain concerns about the possible development of psychiatric pathology against the background of the use of isotretinoin. The relationship of this drug with depression, suicidal thoughts and attempts is controversial, the exact pharmacological mechanism of how the drug leads to such mental

symptoms is unknown. Special care should be taken in patients with a history of depression and all patients should be monitored for signs of depression during treatment with the drug, referring them to an appropriate specialist if necessary

Acne is indeed a skin disease in which various psychoemotional disorders are often observed, primarily associated with patients experiencing their cosmetic defect against the background of changes in appearance. However, there is currently no reliable association between isotretinoin intake and the development of psychiatric disorders in acne patients [34-37]. In addition, many prospective controlled studies have demonstrated a significant improvement in the quality of life of patients taking isotretinoin. Thus, this medicinal product should not be contraindicated in patients with a history of mental disorders or at the time of curation, which is confirmed by our own clinical experience working with patients suffering from various mental illnesses. As for Acnecutane, this drug is well tolerated. Of course, the undesirable side effects inherent in systemic retinoids occur against the background of taking this drug, but they are less pronounced than their analogues. This is certainly an advantage of the drug and significantly increases the commitment to treatment in patients.

Conclusion The use of isotretinoin for the treatment of severe acne resistant to other drugs is a modern and effective method of treating this disease. In addition, the appointment of isotretinoin provides the best price-quality ratio for the treatment, since in most cases it is possible to achieve stable remission of the disease after only one course. Oral retinoid administration should be indicated to acne patients as early as possible, in cases where there is no positive response to other treatment options. The idea of using a low daily dose of isotretinoin for oral administration without taking into account the total cumulative dose and duration of treatment is not new. However, our own clinical experience, as well as data from a number of literature sources, show that prescribing low doses of this drug and gradually increasing them does not produce a stable clinical effect, and in some cases it is associated with relapses of the disease. Also, low doses of isotretinoin do not prevent the development of the most common non-fatal side effect, retinoid dermatitis, the course of which is effectively controlled by using special therapeutic cosmetics without changing the dosage of the drug taken. Concern about the teratogenicity of isotretinoin is also not an obstacle to prescribing this drug. But it is really important to establish a trusting relationship between the doctor and the patient and to discuss various effective methods of contraception, as well as to clarify the necessity of using such means. Another reason for concern related to the appointment of isotretinoin is its possible effect on blood biochemical parameters that demonstrate the state of the hepatobiliary system.

However, the valid indication for discontinuation of this drug is only a 2-3-fold increase in the content of transferases, alkaline phosphatase, bilirubin, lipoproteins in the patient's blood serum, and not one of these indicators, but several at once. Also, continuous monitoring of these laboratory parameters is not necessary, according to the literature data and based on our experience.

Laboratory screening is sufficient before the start of therapy, as well as a month later, and then after 2-3 months. The development of drug-related liver pathology, which is an indication for drug withdrawal, should be established by conducting a comprehensive examination of the patient and a conclusion made by an appropriate specialist. Acnecutan is a modern representative of the isotretinoin line, an effective acne treatment agent, which fully includes

all the above information about this group of drugs, at the same time, our own experience with the drug indicates a favorable level of its tolerability in comparison with other isotretinoin preparations. Thus, successful treatment with isotretinoin depends on whether the doctor can take the time, mainly at the first consultation, to explain in detail the mechanism of action of this drug, the duration of treatment, dispel the myths and contradictions associated with it, as well as provide comprehensive recommendations for the prevention and control of expected adverse events.

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