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ANALYSIS OF THE EFFECTIVENESS AND SAFETY OF ACNE TREATMENT DEPENDING ON THE DOSE OF SYSTEMIC RETINOID

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Acne is a common dermatological disease that significantly affects the quality of life of young people during their period of greatest social activity. The purpose of the study was to evaluate the efficacy and safety of systemic retinoid therapy with different doses of isotretinoin in patients with moderate-to-severe acne, and to determine the frequency of relapse after treatment completion. 75 patients aged 16–35 years were examined and divided into three groups, each receiving isotretinoin at a dose of 0.3, 0.5, or 0.8 mg/kg. Increasing the daily dose accelerated the onset of the clinical effect and reduced the frequency of relapses, but was associated with an increase in adverse reactions, including retinoid xerosis, cheilitis, keratitis, dermatitis, and diffuse hair thinning. The optimal balance between efficacy and safety was observed with medium doses of isotretinoin. Extending the course of therapy until the target cumulative dose was achieved ensured sustained remission with minimal complications. The results emphasize the feasibility of individualized isotretinoin dose selection for acne treatment to optimize clinical outcomes and improve patients' quality of life.

Key words: acne, isotretinoin, systemic retinoids, side effects, acne recurrence, dose dependence, cumulative dose.

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АНАЛІЗ ЕФЕКТИВНОСТІ ТА БЕЗПЕКИ ЛІКУВАННЯ ВУГРОВОЇ ХВОРОБИ ЗАЛЕЖНО ВІД ДОЗИ СИСТЕМНОГО РЕТИНОЇДУ

Вугрова хвороба є поширеним дерматологічним захворюванням, що суттєво впливає на якість життя молодих людей у період їхньої найбільшої соціальної активності. Метою дослідження було оцінити ефективність і безпечність системної ретиноїдної терапії із застосуванням різних доз ізотретиноїну у пацієнтів із середньотяжкими та тяжкими формами акне, а також визначити частоту рецидивів після завершення лікування. Обстежено 75 пацієнтів віком 16–35 років, розподілених на три групи, які отримували ізотретиноїн у дозах 0,3; 0,5 та 0,8 мг/кг. Підвищення добової дози прискорювало досягнення клінічного ефекту та зменшувало частоту рецидивів, проте супроводжувалося збільшенням кількості побічних реакцій, таких як ретиноїдний ксероз, хейліт, кератит, дерматит, дифузне порідіння волосся. Оптимальне співвідношення ефективності та безпечності відзначено при застосуванні середніх доз ізотретиноїну. Подовження курсу терапії до досягнення цільової кумулятивної дози забезпечувало стійку ремісію з мінімальними ускладненнями. Отримані результати підкреслюють доцільність індивідуального підбору дози ізотретиноїну при лікуванні акне для оптимізації клінічних результатів і покращення якості життя пацієнтів.

Ключові слова: вугрова хвороба, ізотретиноїн, системні ретиноїди, побічні ефекти, рецидив акне, дозозалежність, кумулятивна доза.

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Acne is a fairly common condition that affects young people during their most socially active years. Patients with moderate and severe forms of acne often consult related specialists (family doctor, internist, allergist). Insufficient interaction between a dermatovenereologist and doctors of other specialties leads to a delay in the appointment of rational therapy and an increase in the number of complications. The increase in the frequency of severe forms of acne is associated with insufficient attention to acne prevention, improper use of topical agents, and untimely appointment of etiopathogenetic therapy [3, 6, 14].

The effectiveness of acne therapy largely depends on the effective interaction between the doctor and the patient, since, in most cases, treatment is a long, multi-month process. During this period, the dermatovenereologist must not only provide effective treatment but also dispel several common myths that patients bring to the appointment (the infectious etiology of acne, hopelessness about the disease, the need for aggressive care, retinoid phobia, etc.). It is important to encourage patients to change their lifestyle: increase physical activity, eat a balanced diet, properly cleanse the skin of makeup residue, and regularly use photoprotective agents in the form of fluids or light creams. The doctor should convince the patient of the importance of proactive therapy after completing the main course of treatment [8, 12].

Increased inflammation in the sebaceous glands in acne is associated with excessive colonization by facultative anaerobes, including Cutibacterium acnes (formerly Propionibacterium acnes and Propionibacterium granulosum). The degree of C. acnes colonization varies and peaks during puberty. It has been established that these microorganisms directly affect the development of both inflammatory and non-inflammatory components of acne. Extracellular lipases of microorganisms can

hydrolyze sebum triglycerides to glycerol, thereby significantly increasing their comedogenic properties [7, 9, 11].

The reasons for the low effectiveness of the treatment of severe forms of acne and the increase in the number of their complications may be the untimely appointment of systemic retinoid therapy (SRT) and the irrational reduction of their starting or course dose (less than 0.3 mg/kg), especially in patients with a body weight of more than 90 kg. It is important to take into account the individual characteristics of the body, the presence of concomitant pathology (e.g., impaired kidney, liver, or pancreas), and to monitor blood biochemical parameters and correct any detected abnormalities [4, 5, 10].

The purpose of the study was to investigate the effectiveness of treatment and the frequency of clinical complications in moderate and severe forms of acne depending on the use of different doses of systemic retinoids (low, medium and high), as well as to assess the risk of acne recurrence after completion of therapy, taking into account the achievement of the clinical effect and the target cumulative dose of the drug.

Materials and methods. During 2022–2024, we observed 75 people (38 men and 37 women) aged 16 to 35 years (mean age: 21.8 years; mean body weight: 59.5 kg) with moderate or severe acne. Patients underwent acne treatment with systemic retinoids at the Department of Infectious Diseases, with a course in Dermatovenerology at ONMedU and the Renaissance-Medical Multidisciplinary Medical Center (Odesa).

Regardless of disease duration, and taking into account the even gender distribution (1:1) and average age, patients were divided into three groups of 25 each. Considering the current guidelines of the American Academy of Dermatology, a significant number of scientific studies on the possibility of using medium-low and low doses of systemic retinoids (to reduce adverse effects in the treatment of acne) [15], patients under our observation were offered different dosing regimens of isotretinoin (we used the drug Aknetin, manufactured by the Belgian company Labaratories SMB Technology SA). Patients in the first group received isotretinoin at 0.3 mg/kg, the second at 0.5 mg/kg, and the third at 0.8 mg/kg.

The dose-dependent effects of systemic retinoid therapy in various forms of acne were evaluated during treatment. The evaluation criteria included: the speed of blocking excessive sebum secretion, the dynamics of rash regression, the time to disappearance of post-inflammatory pigmentation, and the frequency of relapses within 6 months, depending on the drug dose. Additionally, the frequency and duration of retinoid reactions (xerosis, cheilitis, keratitis, conjunctivitis, retinoid dermatitis, diffuse hair thinning, etc.) in each patient subgroup were assessed directly during the dermatologist's appointment. Patients with severe keratitis and conjunctivitis were referred for ophthalmologic consultation.

All stages of the study were conducted in accordance with the principles of the World Medical Association's Code of Ethics (Declaration of Helsinki, 2013). All participants provided written informed consent to participate in the study and to the processing of personal data. Permission was obtained from the Bioethics Commission of the Odessa National Medical University (protocol dated January 13, 2024, No. 19).

Statistical analysis of the results was performed using the Pearson χ^2 test to compare the frequency of adverse reactions and relapses between groups. For small expected values, Fisher's exact test was used. The level of statistical significance was accepted at $p<0.05$.

Results of the study and their discussion. Regardless of the isotretinoin dose, no patients in the observation groups discontinued treatment due to critical deterioration in health. There were also no complications that would significantly affect the patients' ability to work or require changes to their usual lifestyle. However, increasing the daily dose of systemic retinoid increased the frequency of adverse reactions characteristic of isotretinoin, with a peak observed in the 2nd–3rd month of treatment.

The use of low-dose isotretinoin (0.3 mg/kg) during the first 3 months of therapy contributed to the complete regression of inflammatory elements in 5 (6.6 %) patients; within 6 months, this number increased to 18 (24 %) cases. Increasing the daily dose to 0.5 mg/kg eliminated facial inflammation in the first 3 months in 7 (9.3 %) patients and after 6 months in 19 (25.3 %) patients. The maximum clinical effect was achieved in the group of patients receiving 0.8 mg/kg of systemic retinoid: at the 3rd month of treatment, regression of inflammatory elements was noted in 9 (12 %) patients, and after 6 months, the number of positive responses to therapy increased to 20 (26.7 %) (Table 1).

Table 1

Dynamics of clinical efficacy of treatment with different doses of systemic retinoids (SR) during 3 and 6 months of therapy

Duration of treatment	0.3 mg/kg (n=25)	0.5 mg/kg (n=25)	0.8 mg/kg (n=25)
3 months	5 (6.6 %)	7 (9.3 %)	9 (12 %)
6 months	18 (24 %)	19 (25.3 %)	20 (26.7 %)

One of the first clinical manifestations of systemic retinoid action was decreased sebum secretion, accompanied by the development of retinoid xerosis. Patients in all observation groups noted dry skin on the face and hands at 10–14 days after starting systemic retinoids. However, patients receiving high doses of isotretinoin (0.8 mg/kg) complained of progression of retinoid xerosis by the 3rd month of treatment, with the process becoming stable, unresponsive to moisturizing topical agents, and regressing after a reduction in the systemic retinoid dose.

Additionally, an analysis of the most typical complications of systemic retinoid therapy was conducted. Respondents in the first group (isotretinoin dose – 0.3 mg/kg) had the fewest complications: moderate signs of retinoid xerosis of the skin (mainly on the face and hands) were noted by 3 (4 %) patients in the second month of treatment; symptoms of retinoid cheilitis were mostly transient and quickly resolved with the use of moisturizers; no cases of diffuse hair loss or the formation of focal alopecia were recorded. Patients in the second group (isotretinoin dose – 0.5 mg/kg) noted moderate manifestations of dry skin with predominant localization in the perioral area and on the cheekbones; in 5 (6.7 %) patients, retinoid reactions also occurred on the hands in the second month of therapy, but responded well to topical moisturizers and regressed without reducing the dose of systemic retinoids. Diffuse thinning of the scalp was observed in 4 (5.3 %) patients receiving medium doses, and 1 (1.3 %) patient complained of persistent gastrointestinal dysfunction (Table 2).

Table 2

Analysis of complications of systemic retinoid therapy depending on isotretinoin dose (6th month of treatment)

Nature of the complication	0.3 mg/kg (n=25)	0.5 mg/kg (n=25)	0.8 mg/kg (n=25)	p-value	Stat. test
Retinoid-induced cheilitis	6 (8 %)	8 (10.7 %)	15 (20 %)	p=0.018*	$\chi2$ (Pearson)
Retinoid xerosis	3 (4 %)	6 (8 %)	11 (14.7 %)	p=0.031*	$\chi2$ (Pearson)
Retinoid dermatitis	2 (2.7 %)	5 (6.7 %)	10 (13.3 %)	p=0.047*	$\chi2$ (Pearson)
Retinoid keratitis	0 (0 %)	0 (0 %)	2 (2.7 %)	p=0.487 (NS)	Fisher’s exact
Diffuse thinning	0 (0 %)	4 (5.3 %)	11 (14.7 %)	p=0.004*	$\chi2$ (Pearson)
Impaired gastrointestinal function	0 (0 %)	1 (1.3 %)	3 (4 %)	p=0.298 (NS)	Fisher’s exact
Persistent headache	0 (0 %)	1 (1.3 %)	2 (2.7 %)	p=0.512 (NS)	Fisher’s exact
Muscle pain	0 (0 %)	0 (0 %)	1 (1.3 %)	p=1.000 (NS)	Fisher’s exact

* – statistically significant differences ($p<0.05$); NS – not significant.

The highest number of adverse reactions was observed in patients receiving high-dose systemic retinoids (0.8 mg/kg). Complaints of retinoid xerosis symptoms increased almost fourfold, to 11 cases (14.7 %), compared with the first group. The number of cases of retinoid cheilitis and retinoid dermatitis increased to 15 (20 %) and 10 (13.3 %), respectively. The undesirable effect of diffuse hair loss in patients receiving high doses of systemic therapy increased almost threefold, noted by 11 (14.7 %) respondents after 3–4 months of isotretinoin. Retinoid keratitis was observed in 2 (2.7 %) patients on high-dose isotretinoin; both cases rapidly regressed after hyaluronic acid eye drops. Persistent headache was noted as an undesirable effect of SRT by 2 (2.7 %) respondents in the third observation group.

Thus, the number of adverse reactions (retinoid xerosis, keratitis, cheilitis, dermatitis, diffuse hair thinning) increased significantly with increasing systemic retinoid dose, with the peak frequency observed in the group receiving 0.8 mg/kg body weight. Statistical analysis of the results (Pearson's χ^2 test, Fisher's exact test) revealed a statistically significant increase in the frequency of the main adverse reactions – retinoid cheilitis, xerosis, dermatitis, and diffuse hair thinning – with increasing isotretinoin dose ($p<0.05$).

At the same time, differences in the frequency of rare complications (retinoid keratitis, headache, muscle pain, gastrointestinal disorders) did not reach statistical significance ($p>0.05$).

It should be noted that some patients in the third group had combined complications, in particular retinoid cheilitis with keratitis or retinoid dermatitis with diffuse hair loss, which negatively affected quality of life and increased the need for additional therapeutic interventions.

Another important aspect of SRT is assessing the persistence of the clinical effect after discontinuing isotretinoin. It is known that about 30 % of respondents are at risk of acne recurrence even when the required cumulative dose is reached. In our observation, the frequency of acne exacerbations during the year following completion of SRT depended on both the retinoid dose and the treatment duration.

Relapses of the disease were most often observed when using low doses of isotretinoin (0.3 mg/kg): within a year, repeated exacerbation of acne was noted

in 10 (13.3 %) patients. In the medium-dose group (0.5 mg/kg), relapses were recorded in 8 (10.7 %) individuals, and in the high-dose group (0.8 mg/kg), in 6 (8 %) cases. Differences between groups did not reach statistical significance ($p>0.05$); however, there was a trend toward a decrease in recurrence rate with increasing systemic retinoid dose.

The results of the analysis showed that high doses of systemic retinoids significantly accelerated the achievement of the clinical effect: after three months, the number of positive responses reached 12 %, which was twice as high as with low-dose isotretinoin (0.3 mg/kg). Complete regression of inflammatory elements with low-dose therapy was observed on average 3.2 months later than with high-dose isotretinoin. This difference is due not only to the speed at which the target cumulative dose is achieved, but also to the organism's individual characteristics, the patient's body weight, the presence of concomitant pathology, and other factors.

However, the use of low doses of retinoids, although requiring longer treatment to achieve the course dose, was accompanied by a significant decrease in the frequency of adverse reactions characteristic of systemic retinoid therapy –retinoid xerosis, cheilitis, keratitis, retinoid dermatitis, and diffuse hair thinning, etc.

Thus, increasing the daily dose of systemic retinoid in the treatment of moderate and severe forms of acne (from 0.3 mg/kg to 0.8 mg/kg) contributes to a moderate decrease in the frequency of disease recurrences (on average by 5.3 %), but is accompanied by a significant increase in the frequency of adverse reactions characteristic of systemic retinoid therapy. Similar results were obtained by Boyar N. et al., who indicate the possibility of using low doses of isotretinoin, especially in compromised groups of patients, in particular in the presence of diseases of internal organs, phobias, or unsuccessful experience with the use of high doses of systemic retinoids in the past [2].

It should be noted that Afsaneh Sadeghzadeh-Bazargan et al. indicate the possibility of using isotretinoin at an ultra-low dose of 0.1 mg/kg of body weight. Their results coincided with our conclusions in many respects. The authors noted improved long-term disease control with minimal adverse reactions. At the same time, researchers suggest significantly extending treatment duration beyond standard terms – even after achieving stable remission [13]. In our study, the duration of low-dose isotretinoin therapy for severe acne also exceeded 12 months.

Given the relative safety of low-dose isotretinoin, Fatimah Al Muqarrab et al. propose expanding its use for milder forms of acne [1]. The results of these studies are consistent with our data showing a reduction in the acne remission period with low-dose isotretinoin (0.3 mg/kg). Our observations are also consistent with the work of Fatimah Al Muqarrab et al. on preventing acne recurrence with sub-low-dose isotretinoin, but the safety and efficacy of this approach require further study.

Taking into account the pronounced impact of systemic retinoid side effects on patients' quality of life, it is advisable to use medium doses; in some cases, in the presence of concomitant pathology or with unsatisfactory tolerability, low doses of isotretinoin. In this case, achieving the target cumulative dose is ensured by extending the total treatment duration, which allows for stable remission with a minimal incidence of complications.

Further study of the potential of low and sub-low doses of isotretinoin, as well as the development of therapeutic standards for treating different types of acne, is an important task for modern dermatology.

Limitations. It should be noted that the increased duration of acne treatment somewhat complicated patient monitoring: some patients were unable to undergo follow-up examinations in a timely manner (in particular, because they were abroad) and were therefore excluded from the study. In addition, in emotionally labile patients, long-term use of systemic retinoids contributed to the occurrence of phobic reactions, which was one of the reasons for discontinuation of therapy.

Conclusions

1. Complete regression of inflammatory elements when using low doses of systemic retinoids (0.3 mg/kg) is observed on average 3.2 months later than when using high doses of isotretinoin. This difference is due not only to the speed of achieving the target cumulative dose but also to the organism's individual characteristics, the presence of concomitant pathology, and other factors.

2. The frequency of adverse reactions in the treatment of acne (retinoid xerosis, keratitis, cheilitis, retinoid dermatitis, diffuse hair thinning) significantly increases with increasing dose of systemic retinoid ($p<0.05$, Pearson's χ^2-test), and the highest number of such complications is observed at a dose of 0.8 mg/kg.

3. The use of medium, and in some cases low doses of isotretinoin, contributes to better tolerability of systemic retinoid therapy and has a positive effect on the quality of life of patients. Achieving the target cumulative dose in such cases is ensured by extending the total treatment duration, thereby minimizing the risk of side effects without reducing efficacy.

4. The frequency of relapses after the completion of the course of therapy tends to decrease with increasing dose of systemic retinoid: at a dose of 0.3 mg/kg, relapses are recorded in 13.3 % of patients, at 0.5

mg/kg – in 10.7 %, and at 0.8 mg/kg – in only 8 %, however, these differences did not reach statistical significance ($p>0.05$).

5. The results obtained confirm the feasibility of individual selection of the dose of isotretinoin, taking into account body weight, clinical form of acne, and tolerability of the drug to achieve the optimal ratio of effectiveness and safety of treatment.

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