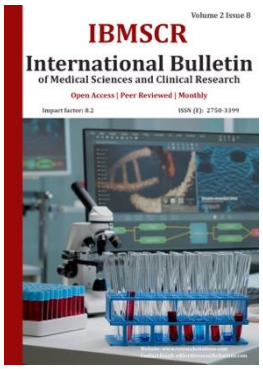

THE USE OF ISOTRETINOIN FOR TREATING MODERATE-TO-SEVERE AND NODULOCYSTIC ACNE

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Abstract

This article presents data on the pathogenesis of acne, therapeutic decision-making mechanisms, the strategy for prescribing isotretinoin, and further patient management. It addresses key questions regarding the appropriate daily dosage and the importance of achieving the cumulative dose, as well as the safety profile of isotretinoin-containing medications. The article also discusses the use of high-dose vitamin A (retinol palmitate) in acne patients and the associated adverse effects. Three clinical cases of patients diagnosed with acne are presented to illustrate treatment strategies.

Keywords: acne, isotretinoin, adapalene, vitamin A, efficacy, safety profile.

Relevance of the Study

Scientific advancements continually expand our understanding of the pathogenesis of acne and contribute to the improvement of treatment methods, which in turn impacts clinical practice by shaping patient management strategies in accordance with current standards.

Acne is considered a chronic inflammatory skin disease that affects 85% of adolescents and about 20% of adults under the age of 40. The clinical presentation of acne includes typical lesions such as open and closed comedones, papules, pustules, nodules, and cysts. The condition most commonly affects the face, although in severe cases, lesions may also appear on the torso. The progression of inflammatory lesions can lead to post-acne symptoms such as post-inflammatory hyperpigmentation and scarring.

The pathogenesis of acne is multifactorial, involving hormonal influence from androgens along with excessive sebum production, abnormal keratinization, inflammation, and stimulation of the innate immune system through various pathways, including the hypercolonization of *Cutibacterium acnes* (formerly *Propionibacterium acnes*)

The choice of treatment method depends on the severity of the condition, the effectiveness of prior treatments, and the patient's quality of life. Severe and moderate-to-severe acne that does not respond to topical therapy generally requires systemic treatment. In recent years, the rationale for prescribing systemic antibiotics for acne—particularly for prolonged courses—has been re-evaluated. Current clinical guidelines emphasize that neither topical nor systemic antibiotics should be used as monotherapy in the treatment of acne. Moreover, the growing issue of antibiotic resistance limits their use in acne management.

Today, there are many effective acne treatments that do not involve antibiotics, and clinicians are encouraged to select therapeutic strategies that minimize antibiotic use. A sub-antimicrobial dose of doxycycline (40 mg) is used in acne treatment due to its anti-inflammatory properties. However, this approach has not been thoroughly studied in terms of potential antibiotic resistance development, and this dosage is not currently registered in the Russian Federation.

Thus, oral isotretinoin should be considered the first-line therapy for severe forms of acne (nodular, cystic, and conglobate), as well as in clinical scenarios involving relapses or a lack of response to topical treatment.

Isotretinoin as an Effective Treatment for Severe Acne

Isotretinoin is a highly effective treatment for severe forms of acne. To achieve a cumulative dose of 120–150 mg/kg, the drug is administered at a daily dose of 0.5–1.0 mg/kg for a duration of no less than six months. Oral isotretinoin therapy should be continued until complete skin clearance is achieved. It is important to remember that delaying the initiation of appropriate treatment for severe acne may lead to scarring, which can negatively impact a patient's quality of life. Therefore, timely initiation of appropriate therapy—namely isotretinoin in cases of severe acne—is a key factor in patient treatment satisfaction.

J. Tan conducted a systematic literature review to assess the evidence supporting the efficacy of cumulative dosing of isotretinoin. The authors noted that the cumulative dose recommendations are based on studies that were not specifically designed to assess the correlation between cumulative dosing and relapse rates, as these studies often addressed isotretinoin use across varying severities and subtypes of acne (e.g., excoriated acne). However, a correlation was observed between lower dosing and higher relapse rates in severe forms. A large-scale study comparing the clinical efficacy and relapse-prevention potential of low (0.1 mg/kg), moderate (0.5 mg/kg), and high (1.0 mg/kg) daily doses of systemic isotretinoin found that most patients experienced significant clinical improvement within 12–20 weeks of treatment, regardless of dose. Patients were monitored for 18 months post-treatment, revealing a direct correlation between daily dose and the need for retreatment. The lowest rate of relapse was observed in patients who received 1.0 mg/kg per day.

According to C.C. Zouboulis, risk factors for acne relapse after systemic isotretinoin therapy include: low daily dosage (0.1–0.2 mg/kg), failure to reach a cumulative dose of at least 120 mg/kg, presence of polycystic ovary syndrome, and a low-calorie diet. A comprehensive literature review helped identify a range of relapse risk factors following treatment for severe acne.

Why Reaching the Cumulative Dose is Important

Literature data indicate that improper adherence to dosing schedules and insufficient total dosage may contribute to relapse in severe acne following a course of systemic isotretinoin. Earlier studies demonstrated that low-dose isotretinoin results in insufficient suppression of sebaceous gland activity, leading to a higher likelihood of recurrence after treatment completion. Observation of 1,411 patients across 15 studies over a ten-year period showed that achieving a cumulative dose of 120–150 mg/kg is optimal not only for achieving remission but also for preventing relapse [18]. This effect is attributed to significant reduction in sebaceous gland size at this dose level.

Clinical experience and literature reviews indicate isotretinoin efficacy ranges from 80–95%, with the goal of therapy being complete lesion regression. According to some authors, full remission is achieved in 70% of patients with severe acne treated with an average daily dose of 0.5 mg/kg. The risk of relapse in severe acne is 8.2 times higher in patients who received a cumulative dose below 100 mg/kg compared to those who exceeded that threshold. Moreover, 16–23% of such patients may require additional treatment.

Indications for Systemic Isotretinoin Therapy

- Severe nodulocystic acne
- Moderate to severe nodular acne
- Severe papulopustular acne
- Inadequate response to previous treatments
- Tendency for scarring
- Relapse after previous therapy
- Significant psychological distress

Table 2: Risk Factors for Acne Relapse After Treatment [13–16]

- Family history of severe seborrhea and acne
- Male sex
- Early disease onset
- Hyperseborrhea
- Lesions on the back and torso
- Predominance of macrocomedones
- Hormonal dysfunction in women
- Environmental influences, urban lifestyle
- Inadequate systemic isotretinoin dosage
- Incorrect dosing regimen

Safety Profile of Systemic Isotretinoin

Isotretinoin is a physiologically active metabolite of vitamin A (retinol). Its safety profile is well established through extensive clinical practice and numerous studies spanning several decades. A standard course of isotretinoin for moderate-to-severe acne is generally well tolerated and has a favorable safety profile. Common adverse effects include xerosis (dry skin) and cheilitis (lip inflammation), which are reversible and usually manageable with local moisturizers, without requiring treatment discontinuation. Xerosis, skin cracking, and eczema are frequently reported side effects, often related to compromised skin barrier function due to imbalances between moisture loss and retention, as well as decreased antioxidant protection.

There is a loss of contact between desmosomes and a reduction in the number of tonofibrils. Corneocytes detach easily from the outer layers of the stratum corneum, which explains the peeling commonly observed in patients.

During treatment, systemic side effects may occur, such as headache, fatigue, and visual disturbances—including night vision impairment, keratitis, and corneal opacity—which are dose-dependent. Laboratory abnormalities are rare and usually clinically insignificant, not requiring treatment discontinuation. However, baseline liver function and lipid profile parameters must be assessed prior to starting therapy, and repeated after 4–6 weeks, then every 3 months thereafter.

Two effective methods of contraception (barrier methods + combined oral contraceptives) must be used for at least one month prior to starting isotretinoin, throughout the entire course, and for one month after discontinuation. Recommendations for systemic isotretinoin administration are summarized in Table 3.

Some patients may experience a worsening of their skin condition during the first month of treatment.

Table 3

Recommendations for Systemic Isotretinoin Administration

- **Detailed medical history**

- Assessment of comorbidities
- Use of medications, vitamins, or supplements (especially those containing vitamin A)
- Previous isotretinoin use: dose and duration

- **Laboratory testing**
  - Lipid profile (triglycerides, cholesterol, HDL, LDL)
  - Liver enzymes (AST, ALT, alkaline phosphatase)
- **Patient education**
  - Expected side effects and how to manage them
  - Mandatory contraception (informed consent required)
  - Importance of adhering to the prescribed dose, schedule, and treatment duration
- **Improving treatment tolerance**
  - Splitting the daily isotretinoin dose into two administrations (morning and evening)
  - During the first month (average 2–4 weeks), low-dose systemic corticosteroids (10–20 mg in prednisone equivalents) may be prescribed
  - Initial dosing of 0.2–0.3 mg/kg for the first month with subsequent escalation to 0.5–1.0 mg/kg
- **Treatment duration and expected outcomes**
  - Minimum treatment duration: 24 weeks
- **Supportive care**
  - Use of specialized dermocosmetics (gentle cleansing, moisturizing, sun protection)
  - Eye drops and gels are particularly helpful for contact lens users or patients in areas with high air pollution
  - Wearing sunglasses is also recommended
- **Dietary guidance**
  - Avoid oily fish and vitamin A-rich foods
  - Follow an acne-associated diet (eliminate high-glycemic index carbohydrates)
- **Cosmetic procedures**
  - Mechanical dermabrasion and ablative laser treatments are contraindicated for 6 months post-treatment
  - Non-ablative and injectable procedures may be performed during treatment
- **Hair removal**
  - Cold waxing or shaving is preferable
  - Use of intense pulsed light (IPL) or Nd:YAG lasers should be approached with caution
- **Relapse prevention**
  - After completing isotretinoin therapy, maintenance treatment (e.g., adapalene, azelaic acid) is advisable
- **Post-acne prevention**
  - Acne therapy should be adequate and tailored to disease severity to minimize
  - post-acne complications

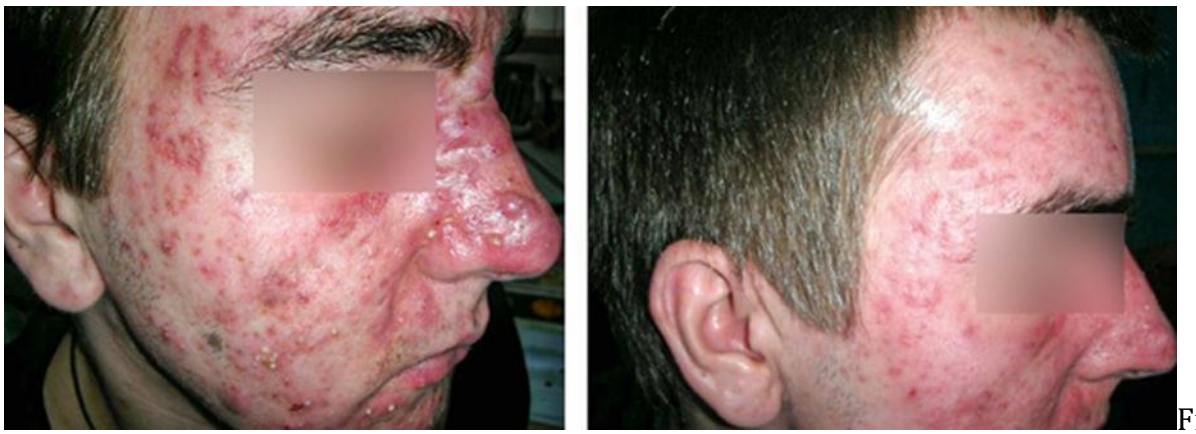

Figure 2. Clinical progression of Patient R with severe nodular acne: baseline and after 5 months of isotretinoin (Sotret) therapy.

Despite existing clinical guidelines for the use of isotretinoin, in real-world practice we still encounter cases where physicians prescribe vitamin A for the treatment of acne. The rationale behind this approach is the perceived greater safety of vitamin A compared to isotretinoin. However, literature reviews indicate that high doses of vitamin A can lead to serious adverse effects, including hepatic failure progressing to fibrosis, osteoporosis, and potentially toxic effects on the kidneys and lungs. Moreover, the effectiveness of vitamin A in acne treatment is highly questionable and cannot be compared to that of isotretinoin.

A newly identified mechanism of adverse reactions associated with vitamin A intake involves the inhibition of UDP-glucuronosyltransferases—key phase II drug-metabolizing enzymes responsible for the glucuronidation and elimination of various xenobiotics (e.g., drugs, herbal substances, environmental pollutants) and endogenous compounds (e.g., bilirubin, estrogen, bile acids). This inhibition leads to reduced metabolic clearance and increased toxicity of these substances in the body.

Therefore, the appropriateness of prescribing vitamin A for acne is highly questionable, and it should not be considered a substitute for isotretinoin therapy.

Relapse Prevention After Isotretinoin Therapy

Despite the high efficacy of systemic isotretinoin, the issue of acne relapse and its prevention remains relevant. According to current guidelines, topical adapalene is considered the drug of choice for maintenance therapy following a course of systemic isotretinoin.

Adapalene is a retinoid metabolite with comedolytic and anti-inflammatory properties. It normalizes keratinization and epidermal differentiation. Its mechanism of action is based on binding to specific gamma receptors in epidermal skin cells. As a result, adapalene reduces the adhesion of epithelial cells at the opening of the pilosebaceous follicle and decreases microcomedone formation. Adapalene has demonstrated anti-inflammatory activity both *in vitro* and *in vivo* by inhibiting leukocyte migration to the site of inflammation and suppressing arachidonic acid metabolism.

Clinical Case 1

Patient R., 16 years old, had been suffering from acne since the age of 13. He had received multiple prolonged courses of systemic antibiotics, topical treatments, and alcohol-based lotions, all without significant long-term improvement. At his most recent visit, he was prescribed high-dose vitamin A (retinol palmitate) at 200,000 IU per day. By day three of treatment, the patient developed right upper quadrant abdominal pain, scleral icterus,

pronounced skin and mucosal dryness, and worsening of acne symptoms. Biochemical tests revealed elevated liver transaminases and alkaline phosphatase.

On examination: severe acne, pronounced xerosis, cheilitis, and scleral icterus. Vitamin A was discontinued, and detoxification therapy was initiated. After a washout period of one month, isotretinoin (Sotret) was started at a dose of 0.5 mg/kg/day. One month later, after biochemical monitoring, the dose was increased to 0.7 mg/kg/day until a cumulative dose of 150 mg/kg was achieved. After 6 months of treatment, the patient reached clinical remission. Isotretinoin was discontinued, and the patient was switched to maintenance therapy with a 0.1% adapalene cream (Adaklin) for 6 months. Follow-up over 12 months showed no recurrence.

Clinical Case 2

Patient A., 18 years old, had a 7-year history of acne. She had previously undergone multiple courses of topical therapy and hormonal contraceptives, with only short-term improvements. Diagnosis: moderate papulopustular acne. Given the recurrent nature of the condition and absence of sustained remission, isotretinoin (Sotret) was initiated at 0.5 mg/kg/day for 6 months, with a cumulative dose of 120 mg/kg. Upon discontinuation of the drug, maintenance therapy with adapalene (Adaklin) was prescribed for 12 months. Follow-up over the next 12 months revealed no relapse.

Figure 3. Patient A. Moderate acne: before treatment with Sotret, and after 3 and 6 months of therapy.

Clinical Case 3

Patient C., 21 years old. After visiting a cosmetologist and undergoing mechanical facial cleansing for comedones, she developed acne lesions that were unresponsive to topical therapy. Diagnosis at presentation: severe acne (conglobate acne). Given the severity and sudden exacerbation, isotretinoin (Sotret) was prescribed at a dose of 0.7 mg/kg/day along with dexamethasone at 1.5 mg/day during the first month of treatment. The corticosteroid was then discontinued, and the patient continued isotretinoin at 0.7 mg/kg/day for 8 months until a cumulative dose of 150 mg/kg was achieved.

After completing the primary course of systemic isotretinoin and achieving clinical remission (absence of new inflammatory lesions), maintenance therapy with adapalene (Adaklin) was recommended for 12 months. Follow-up over the next 12 months revealed no relapse.

Conclusion

Currently, the key issues surrounding isotretinoin use in acne treatment include expanding its indications (e.g., for mild and excoriated acne), determining appropriate daily and cumulative dosages, treatment duration, and optimal post-treatment strategies to prevent relapse.

Our clinical experience demonstrates that isotretinoin is the drug of choice in cases of severe and moderate-to-severe acne. In such cases, clinicians should adhere to standard dosing regimens and treatment durations, as this significantly reduces the risk of relapse.

Another important topic of discussion is the relevance of maintenance therapy following a completed course of systemic retinoid treatment. Observational studies have shown the effectiveness of topical retinoid adapalene in reducing the risk of disease recurrence after isotretinoin therapy. Long-term use of adapalene—applied daily for 6 to 12 months—is considered appropriate in these cases.

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