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Comment and Controversy
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Isotretinoin in retrospect

Ayse Serap Karadag, MD[a,*], Lawrence Charles Parish, MD, MD (Hon)[b], Wm Clark Lambert, MD, PhD[c]

[a]*Department of Dermatology, Istanbul Medeniyet University School of Medicine, Istanbul, Turkey*
[b]*Department of Dermatology and Cutaneous Biology, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, Pennsylvania*
[c]*Departments of Dermatology and Pathology and Laboratory Medicine, Rutgers–New Jersey Medical School, Newark, New, Jersey*

Introduction

When isotretinoin was introduced about 30 years ago, this oral retinoid was applauded as the answer for the treatment of acne. The side effects, for the most part, were recognized; however, indiscriminate use subsequently led to both government intervention and disappointment.

Oral isotretinoin, with FDA approval in 1982 in the United States and the following year in the European Union, has proven to be essential in treating many patients with acne, especially those young men and women with acne conglobata. In addition, it has a niche in the therapy of gram-negative folliculitis, pyoderma faciale, and acne fulminans when they become systemic with fever, weight loss, and musculoskeletal pain.[1,2] To date, no other therapeutic agent has exhibited the ability to induce both complete remission of acne vulgaris and sustain its therapeutic benefits, after completion of a therapeutic course.

A number of side effects, ranging from psychiatric disorders, hepatitis, and inflammatory bowel issues, have been observed in patients on an isotretinoin regimen; however, evidence establishing a strong relationship between them and treatment is limited. Aside from these risk considerations, advances have also been made to enhance tolerability while maintaining effectiveness, measures have been taken to enhance bioavailability, and clarification of the outcomes of different dosing routines and cumulative threshold dosing, and other evidence-based applications have been made.[3–6]

Dosage and duration

Appropriate treatment duration or cumulative dosage of isotretinoin therapy, that is, total dosage versus duration of treatment,[7] is not determined. Isotretinoin therapy may be used as high dose, the conventional/standard dose, or low dose in patients with acne vulgaris. The standard dose is 0.5-1 mg/kg/day, and the resultant cumulative dose is between 120 and 150 mg/kg.[2,3,6]

Although some evidence suggests that the cumulative dose is significant in the treatment of acne and prevents relapse, other studies suggest that relapse may be more directly attributed to prolonged sebosuppresion.[8] Whether sustained remission is best achieved through prolonged sebosuppression with low-dose administration or through apoptosis and sebaceous gland atrophy through a standard regimen remains unconfirmed.[3]

Does the required dosage and duration of treatment depend on the severity of acne?

Severe acne

The US standard guidelines suggest 1 mg/kg/day with a target cumulative dose ranging from 120 to 150 mg/kg for patients

* Corresponding author. Tel.: 000-000-000.
E-mail address: karadagaserap@gmail.com (A.S. Karadag).

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with severe acne vulgaris.[9] Dosing is not the same as the European guidelines, which recommend of a dosage of 0.3-0.5 mg/kg/day for severe papulopustular and moderate nodular acne and over 0.5 mg/kg/day only for acne conglobata. The US and European guidelines recommend treatment for a minimum of 6 months; however, with an insufficient response, the period may be prolonged. Current evidence is insufficient to make a strong recommendation for a cumulative dose needed for an optimal response or to ensure a low relapse rate.[7]

Further studies suggest that patients with severe acne need increased cumulative doses, ranging from 264 to 290 mg/kg; however, an analysis of other relevant studies suggests that a threshold dose surpassing 150 mg/kg is not necessary.[10,11] What appears to be confirmed is that age (≥20 years) and severe facial acne are predictive factors of a relapse, whereas an abundance of closed comedones often results in treatment failure.[12]

Comment and conclusions

That increased cumulative doses consistently produce fewer relapses in comparison to lower doses has been demonstrated in a systematic review[13]; therefore, a cumulative dose of at least 120-150 mg/kg should be completed in the treatment of severe acne. A dosage of systemic isotretinoin of 0.5-1 mg/kg can be used for severe papulopustular or nodular acne. A typical course of isotretinoin lasts for 20 weeks, but this is not absolute, and continued therapy, at least for several more weeks, may be offered.[2]

Truncal acne is known to have a delayed response in comparison to facial acne, requiring longer treatment and increased cumulative doses.[14] Patients with microcystic acne and women with endocrinologic problems, including polycystic ovarian syndrome, may require several courses and even then only partial remission may be achieved.[4,15]

Moderate acne

Isotretinoin has been used in patients with treatment-resistant or quick-relapsing moderate acne.[9] A dose of 0.25-0.40 mg/kg/day has been used successfully in patients with moderate acne. The effect of a low cumulative dose regimen is comparable to the conventional cumulative dose regimen.[9] The cumulative doses required for acne clearance seem to range from 66.8 to 90 mg/kg in these patients[13,16,17]; a low-dose regimen is not useful for severe acne, where the relapse rate may also be high.[18]

Maintenance dosing

A number of studies have analyzed the efficacy of combination and maintenance therapy of low-dose isotretinoin with treatments that include pulsed topical and/or systemic antimicrobials, topical retinoids, benzoyl peroxide, azelaic acid, and adapalene. These combined treatments effectively control the acne relapse, increase the effects, and lower the cumulative dosage.

Comment and conclusions

Low-dose isotretinoin (0.25-0.4 mg/kg/day) and low cumulative dose regimens are effective in the treatment of moderate acne. Combination therapies are useful to reduce the cumulative dose and provide maintenance in the posttreatment period. Intermittent dosing is not beneficial, where the relapse rate may be very high.

New formulations

Isotretinoin is marketed in the United States as seven generically based agents; the brand Accutane® was withdrawn in 2009. All but one of these seven formulations have similar features. In the fasting state, standard oral isotretinoin formulations may cause plasma levels to have approximately a 60% lower absorption with food.[19]

To combat this, a new formulation was developed, utilizing lipid agents to encase the lipophilic drug, providing more tolerability, less gastric irritation, rapid absorption, and protection against oxidation.[19,20] Both formulations seem to be bioequivalent, although fasting has permitted the isotretinoin-lidose formulation to achieve 66.8% absorption, whereas the original isotretinoin formulation only reached 39.6% absorption when observed with a fatty meal.[20]

Because of the limited number of published studies concerning these different formulations, we are unable to compare all side effects between them, although one study has confirmed no differences in the effect of two formulations of isotretinoin on spine bone density after 6 months of treatment.[21]

Comment and conclusions

It is quite conceivable that earlier relapse may occur if patients often consume conventional oral isotretinoin on an empty stomach[6]; however, the standardization of cumulative dose with the new formulation is easier than that with conventional oral isotretinoin because it has better absorption in empty stomach. We need to do further studies to investigate advantages and disadvantages of these formulations.

Laboratory testing: how ımportant?

The common side effects of isotretinoin are elevated blood lipid and hepatic enzyme levels, which seem to occur in the early weeks of therapy.[22,23] A new meta-analysis concluded that any isotretinoin effects on lipid and liver enzyme levels are mostly mild, transient, and reversible. Discontinuation of the treatment is usually not necessarry.[24] This meta-analysis determined that changes in total cholesterol and TG levels had similar alterations from baseline to 8 or 20 weeks.[24] The recommendations include performing laboratory monitoring at baseline and within the first 1-2 months of isotretinoin therapy rather than continuing monitoring throughout the course of treatment.[25]

A large population-based study has shown abnormalities in transaminase level to be both less common and transient (>79%) during isotretinoin treatment. Abnormalities in