Oral Isotretinoin
New Developments Relevant to Clinical Practice

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KEYWORDS

• Isotretinoin • Acne • Dosing • Relapse • Adverse events • Mechanism

KEY POINTS

- Isotretinoin has multiple mechanisms of action in acne, including sebocyte apoptosis, inhibition of toll-like receptor 2, and suppression of certain hormones implicated in pathogenesis.
- With increasing acne severity, higher cumulative doses of isotretinoin are required to achieve clearance.
- There is no moderate-grade or high-grade evidence supporting the cumulative isotretinoin dose range of 120 to 150 mg/kg.
- Depression and suicidal risk are associated with acne; isotretinoin may confer a slight increase in depression risk.
- Recommendations to avoid acne scar repair procedures within 6 months after isotretinoin should be reconsidered.

INTRODUCTION

Since its introduction 3.5 decades ago, oral isotretinoin has been the single most effective treatment of acne.[1] Although its potential for side effects and monitoring requirements restrict its use, it has resulted in profound improvement in the lives of the patients treated. Nevertheless, this medication continues to be controversial regarding the potential for an array of adverse effects and the risk of birth defects. Although there are multiple recent reviews on oral isotretinoin in the literature, most focus on the pregnancy risk and pregnancy prevention programs; mental health disorders, including depression and suicidal risk; and bowel disease.[2–6] Aside from considerations of risk, there have also been advances in the use of this medication to enhance tolerability while maintaining effectiveness, measures to enhance bioavailability, clarification of the outcomes of different dosing routines and cumulative threshold dosing, and other evidence-based applications for the use of this medication. This article focuses on these advances to provide a perspective on dosing considerations relevant to maximize improvement while minimizing the potential for harms. Specifically, the objective is to provide a practical update relevant to clinical

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practice in the use of oral isotretinoin, including new findings regarding mechanism of action; means to enhance bioavailability, including a new formulation of oral isotretinoin; dosimetry to optimize acne clearance while minimizing the risk of avoidable adverse events; evidence regarding cumulative threshold dosing of oral isotretinoin 120 to 150 mg/kg; and current information on the timing of scar correction procedures after isotretinoin treatment.

Mechanism of Action

Isotretinoin, the cis-isomer of transretinoic acid, is converted in vivo to all-trans retinoic acid. The latter is the active effector molecule inducing cellular effects via binding to nuclear retinoic acid receptors, retinoid X receptors (RXRs), and retinoid acid receptors (RARs).[7] The pathogenic mechanisms of acne involve sebum hypersecretion, intraductal epithelial hyperkeratinization, *Propionibacterium acnes* proliferation, and inflammation. Although isotretinoin has been shown to affect these pathogenic factors, only recently have the mechanisms been understood.

Isotretinoin has been shown to have direct effects on sebocytes, leading to sebum suppression, and on inflammation by inhibiting innate immune system activation. In sebocytes, isotretinoin induces cell cycle arrest and apoptosis by a mechanism independent of RAR binding. This effect likely contributes to its sebosuppressive activity and ameliorative effect on acne.[8] Sebocyte apoptosis was shown to be mediated by tumor necrosis factor–related apoptosis-inducing ligand[9] and neutrophil gelatinase-associated lipocalin (NGAL).[10] The latter functions in innate immune defense against gram-negative bacteria. In patients with acne treated with isotretinoin, increased skin surface NGAL levels have been observed; an effect that precedes sebum suppression and reduction in *P acnes*.[11] It is speculated that reduction in the level of *P acnes* may be caused by the combined effect of these outcomes.

Peripheral blood monocytes from patients with acne have been shown to express higher levels of toll-like receptor 2 (TLR-2) and show greater expression of TLR-2 following exposure to *P acnes*. Isotretinoin at 1 week reduced monocyte TLR-2 expression and inflammatory cytokine release induced by *P acnes*. Note that this effect persisted to 6 months posttreatment, implying that TLR-2 modulation may be involved in the long-term therapeutic response to isotretinoin.[12]

Recently, oral isotretinoin was found to result in significant changes in various hormones, including some implicated in acne pathogenesis, such as insulin-like growth factor 1 and growth hormone, in a dose-dependent manner. In 105 patients with acne divided into 3 isotretinoin dosing groups (0.5–1 mg/kg/d, 0.2–0.5 mg/kg/d, and intermittent 0.5–1 mg/kg/d for 1 week per month) hormone levels were measured at 3 months. Levels of luteinizing hormone, prolactin, total testosterone, adrenocorticotropic hormone, cortisol, insulin-like growth factor 1, growth hormone, and free T3 and T4 were reduced, whereas levels of dehydroepiandrosterone sulfate increased. The greatest effects were seen with the highest of the 3 dose regimens (0.5–1 mg/kg/d). The smallest effect was observed for the intermittent dosing of 0.5 to 1 mg/kg/d for 1 week per month. Although the investigators suggested that changes in some of these hormone levels may be one of the mechanisms of action of isotretinoin in acne, some of these effects may also contribute to potential adverse effects, particularly because most treatment courses extend beyond 3 months.[13] Further study of these hormonal changes is a priority.

Enhancing Bioavailability

Isotretinoin, a derivative of vitamin A, is highly lipophilic and bioavailability is enhanced with fat coingestion. Hence the standard practice recommendation of ingestion with food, particularly a high-fat meal, to enhance absorption. Initial pharmacokinetic studies of oral isotretinoin involved ingestion of a standardized high-fat meal comprising 1000 calories with 50% from fat.[14] The bioavailability of standard oral isotretinoin formulations is approximately 60% lower in fasted conditions than after fatty meals, as described earlier.[15]

It is inconceivable that such a meal will be taken on a daily basis by patients on oral isotretinoin in usual practice. Thus, recommendations in standard practice for coingestion of oral isotretinoin include foods with high fat content (**Table 1**). Almost 1 in 3 adolescents do not have breakfast.[16] Thus, inconsistent eating habits and inadequate fat content of coingestants may result in suboptimal and varying bioavailability.

A related issue is that the standard for bioequivalence of generic formulations is 80% to 125% of the innovator product Accutane (Roche Laboratories). Immediately before and for 2 decades after its approval for use in the United States in 1982, studies on dosing in acne clearance and potential for remission were done with the innovator, generic formulations being available in the United States only since 2002.[17] If a cumulative threshold dose, as recommended by other investigators, is used as a therapeutic end point, there is a potential for underdosing while using generics.[18]