

# On Dosage and Diet:

## Isotretinoin 101

Isotretinoin is one of the most essential agents in the treatment of acne, but dietary and dosage considerations must be made to maximize efficacy.

BY JOSHUA ZEICHNER, MD

For the past three decades, isotretinoin has been one of the most effective treatments on the market for severe acne. Since 2006, the brand name Accutane has no longer been available on the market, and several other generic isotretinoin formulations have emerged. This article will provide a summary of the use of isotretinoin for acne and examine the effects of dosing and diet on treatment efficacy.

### PHARMOKINETIC PROPERTIES

Isotretinoin is an oral retinoid indicated for the treatment of severe, recalcitrant, nodular acne not responsive to traditional therapies. Unlike other therapies, it addresses all of the known acne pathogenic factors, including sebum production, follicular hyperkeratinization, bacterial proliferation, and inflammation. It is a lipophilic molecule, which enhances its penetration to the sebaceous glands.

The accepted target treatment goal is a cumulative dose of 120-150mg/kg, with a typical dosing of 0.5mg/kg for the first month, followed by 1mg/kg thereafter.<sup>1</sup> In the initial clinical trials with Accutane, 85 percent of patients cleared after doses in that range.<sup>2</sup> Among the reasons given that patients did not clear were the presence of macrocomedones, ovarian dysfunction, and other “unknown factors.”<sup>2</sup> While initial dosing regimens were given over 15-20 weeks, some patients may require longer treatment durations, especially given variations in bioequivalence of different substituted generics. Moreover, absorption is influenced by dosing (daily versus twice daily) and by the presence of a fatty meal.

### DIET AND ISOTRETINOIN

For optimal absorption, isotretinoin must be taken with high-fat, high-calorie meals.<sup>3</sup> The FDA defines “high fat” as 50 percent of total caloric intake of the meal, while “high calorie” refers to 800 to 1,000 calories (150 from proteins,



The Baconator (830 calories, 50.1 grams of fat) is an example of a “high-fat, high-calorie” meal required for maximum absorption of isotretinoin.

250 from carbohydrates, 500-600 from fat).<sup>4</sup> Clinical trials evaluating the efficacy and safety of isotretinoin are all performed under those conditions. In the real world, where many patients do not even eat three meals a day, let alone high-fat, high-calorie meals, absorption of isotretinoin may be much lower. Moreover, many dermatologists are not educating patients on the true dietary needs of patients on this medication.

Studies support that this “high fat” is not typical for patients on isotretinoin. One study showed that 10-30 percent of teenagers regularly skip meals.<sup>5</sup> According to the American Dietetic Association, more than 50 percent of teenage boys and more than 66 percent of teenage girls do not eat

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breakfast on a regular basis.<sup>6</sup> The reason for this is that many teenage girls believe that skipping meals is the best approach to lose weight.<sup>7</sup> One in 10 girls (14-15 years) often go without breakfast and lunch each day.<sup>7</sup>

## RECURRENCE AND INSUFFICIENT DOSING

The goal of isotretinoin treatment is to give patients both a short-term improvement and long-term remission. Relapse rates are low, but re-treatment is not uncommon. Several risk factors for relapse have been identified. One study followed 299 severe acne patients treated with isotretinoin for five years post-treatment.<sup>8</sup> Investigators reported that the majority of recurrences developed within the first year after the initial isotretinoin course. Of relapsed patients, 17 percent required two courses, five percent required three courses, and one percent required more than three courses.<sup>8</sup> In addition, 22 percent of patients were not adequately treated and not totally clear after the first course.

Risk factors for relapse include Male gender,<sup>9</sup> Truncal involvement,<sup>9,10</sup> Macrocomedone predominance,<sup>2,11</sup> Ovarian dysfunction,<sup>2,12</sup> More severe disease,<sup>9,10</sup> Longer isotretinoin therapy (>121 d),<sup>13</sup> Younger age,<sup>10-12</sup> Linear lesions (sinus track disease),<sup>5</sup> Insufficient dosing,<sup>2,9,14</sup> Hemorrhagic PG type/acne fulminans,<sup>12</sup> Urban setting.<sup>13</sup>

One of the major, modifiable risk factors for relapse is insufficient dose. Prescribers must acknowledge that non-adherence to prescribed regimens and under-dosing are common. Patient-related factors cannot be controlled, but prescribers must make sure that the target cumulative doses are reached. Low doses of isotretinoin are often prescribed; patients cannot be discontinued after the standard 15-20 weeks of therapy, as adequate cumulative drug levels will not have been reached.

Diet and number of doses per day can both affect drug absorption. Plasma levels of isotretinoin in the fasting state have been shown to be nearly 60 percent lower than levels in the fed state.<sup>3</sup> Moreover, twice-daily dosing is a more effective regimen than once-daily dosing. In addition, trough levels of twice-daily dosing with isotretinoin actually exceed once-daily peak levels. Currently, 63 percent of prescriptions are for twice-daily dosing.<sup>15</sup>

It is important to evaluate our patients with each visit to the office. If their skin and lips are not dry, they may not be satisfactorily absorbing their medication. Is the patient taking the medication? If so, is the patient absorbing it? Why not? In addition to giving out a prescription, we must educate our patients on how to take the medication. High-fat, high-calorie meals maximize absorption, and twice daily dosing is superior to single dosing regimens, if your patient will be adherent with taking it. ■

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