

## **What is the role of oral isotretinoin in the treatment of severe acne?**

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Severe, treatment-resistant acne is frequently treated with oral isotretinoin. Although its complete mechanism of action has yet to be elucidated, oral isotretinoin has been shown to decrease sebum excretion, keratinization, inflammation, and follicular colonization by *P. acnes* and other organisms, such as *Pityrosporum spp.*

### ***Efficacy***

The efficacy of systemic isotretinoin in the treatment of severe, cystic acne is well demonstrated. The Agency for Healthcare Research and Quality (AHRQ) systematic review identified 11 RCTs which evaluated the outcomes of isotretinoin therapy.<sup>1-11</sup> One trial<sup>11</sup> used sebum excretion rate (SER) as its only measure of drug efficacy, and included no results regarding clinical outcome (number of lesions, summated cyst diameter, severity of disease, etc.). It was therefore excluded from the RCTs listed on Table 1. Three other trials<sup>12-14</sup> were found through searching PubMed. At least nine of the 13 RCTs were investigator blinded, with three of the remaining four not indicating any blinding protocol.

Five RCTs<sup>2,3,8,10,13</sup> compared isotretinoin therapy with placebo or other traditional, first-line therapies (tretinate, tetracycline, dapsone, minocycline). In all cases, isotretinoin was found to be a more effective therapy than its comparators. One study

concluded that 0.5 mg/kg/day isotretinoin therapy for 16 weeks was significantly more effective than placebo, with a 97% overall decrease in number of cystic lesions at 41 months post-treatment.<sup>8</sup> Goldstein et al.<sup>2</sup> reported 1.0 mg/kg/day isotretinoin to be significantly more effective than 1.0 mg/kg/day etretinate after an 8-week course of therapy and at an 8-week post-treatment visit ( $p < 0.05$ ). Tetracycline performed equally well as isotretinoin by the end of a 16-week course of therapy in one RCT. However, at a 24-week visit (8-weeks post-treatment), isotretinoin therapy demonstrated a statistically significant decrease in the number of cystic lesions when compared to tetracycline therapy (85% overall reduction in number of lesions,  $p < 0.02$ ).<sup>3</sup> Isotretinoin therapy was significantly more effective than dapsone therapy, as demonstrated by one 16-week RCT.<sup>10</sup> Isotretinoin therapy resulted in significantly fewer lesions on both face and trunk at 20, 28 and 36 weeks (4, 12 and 16 weeks post-treatment respectively). Isotretinoin therapy also achieved a better clinical result over minocycline in one 20-week RCT.<sup>13</sup>

Eight RCTs compared various isotretinoin dosage regimens ranging from 0.1 mg/kg/day to 2.0 mg/kg/day.<sup>1,4-7,9,12,14</sup> All doses studied resulted in a significantly decreased number of lesions. However, no dose-related clinical response could be detected among the doses tested. Only one trial<sup>9</sup> reported (somewhat anecdotally) that higher doses of oral isotretinoin resulted in better clinical outcomes. However, no statistics were available to substantiate this claim.

Several studies have also demonstrated significantly decreased SER,<sup>1,2,4,6-8,10,14</sup> free fatty acid excretion<sup>1</sup> and bacterial<sup>1,10</sup> and yeast<sup>1</sup> colonization with isotretinoin therapy. SER was shown to be significantly reduced in both a dose-dependent<sup>4,6,7,12,14</sup> and dose independent<sup>1</sup> manner in several studies, but was also found to resume near-normal

levels following termination of treatment at a rate that was inversely proportional to isotretinoin dosage.<sup>4,6,8,10</sup> In other words, higher doses of isotretinoin resulted in a more prolonged decrease in SER. One study reported a significant decrease in SER at 16 weeks post-treatment with 1.0 mg/kg/day ( $p < 0.0025$ ).<sup>6</sup> The mechanism of decreased SER seems to be related to sebaceous gland atrophy, which begins to occur after three weeks of isotretinoin treatment.<sup>8,15,16</sup> Decreases in bacterial and yeast colonization were also noted in several studies.<sup>1,10</sup> One study noted a statistically significant, dose independent decrease in anaerobic bacteria colonization after 16 weeks of treatment, but not of aerobic bacteria.<sup>1</sup> The same study also noted statistically significant, dose independent decreases in *Pityrosporum spp.* at 16 weeks. Another study noted a statistically significant decrease in both aerobic and anaerobic bacteria colonization during treatment with isotretinoin.<sup>10</sup> It is hypothesized that the decreases in colonization is an indirect result of alterations in the microenvironment necessary for the survival of skin-surface microorganisms, rather than a direct antimicrobial effect.<sup>1,17-18</sup>

Six RCTs included post-treatment evaluation in order to determine rates of long-term disease remission/relapse. Several studies noted a further decrease in acne severity during the post-treatment follow-up period.<sup>2-5,8,10</sup> Furthermore, one study noted that the degree of disease remission was significantly greater in patients who had been treated with higher doses of oral isotretinoin.<sup>5</sup> In one 20 week study, 40% of patients treated with 0.1 mg/kg/day needed to be retreated, while only 10% of patients who had been treated with 1.0 mg/kg/day needed retreatment.<sup>5</sup> Another study reported similar findings.<sup>8</sup>

### ***Adverse effects***

The teratogenic effect of isotretinoin is well documented.<sup>19</sup> None of the trials reported pregnancies, births or birth defects. Most trials either excluded women with childbearing potential from the study or advised women to take adequate contraceptive measures.

Significant side effects of oral isotretinoin therapy were identified in all RCTs. In general, side effects were limited to the mucocutaneous membranes. Side effects were generally more severe with higher doses of isotretinoin therapy and generally resolved within one month of discontinuance of therapy. The most frequently cited side effects included cheilitis, xerosis, pruritus, facial dermatitis, epistaxis and desquamation.<sup>1-10,12,13</sup> Hair loss,<sup>2,4,5,7,13</sup> arthralgia,<sup>5,6,8,9,12</sup> and decreased appetite<sup>5,8,13</sup> were reported in a small percentage of patients. Most patients chose to live with side effects in order to benefit from the effect of isotretinoin on the clearance of their acne. Very few patients discontinued therapy because it was unmanageable.

Several studies have investigated the relationship between depression/suicidal behavior and isotretinoin-treated acne patients.<sup>20-29</sup> However, these studies have not identified an association between depression/suicidal tendencies and isotretinoin therapy. Despite these negative findings, a consensus regarding the potential association has not been reached, primarily due to limitations (sample size, study design, etc.) of the studies.

Additionally, oral isotretinoin was found to cause a steady increase in serum triglyceride levels during treatment in several studies.<sup>3-9,12,13</sup> However, triglyceride levels were shown to decrease to normal levels after drug cessation.<sup>3-8,12,13</sup> Other laboratory findings included slight, transient elevations in serum protein,<sup>3,4,12</sup> serum glutamic oxaloacetic transaminase (SGOT),<sup>3,4,6-9,12</sup> serum glutamic pyruvic transaminase

(SGPT),<sup>3,7,8</sup> alkaline phosphatase,<sup>7</sup> and serum cholesterol.<sup>9,10</sup> These elevations resolved either during or soon after cessation of treatment.

### ***Comment***

In an effort to eliminate fetal exposure to isotretinoin in the United States, all isotretinoin distributors, distributing pharmacies, prescribers and patients (both male and female) are required to register with the iPledge Program.<sup>30</sup> Female patients are required to report that two forms of contraception are being used simultaneously to their physician, as well as the results of a monthly pregnancy test. These protocol must be followed for one month prior to and one month following isotretinoin therapy. Male patients are not required to report contraceptive use, however, as there is not yet any evidence that isotretinoin therapy in males can cause teratogenic effects in fetuses. The iPledge Program was initiated in March 2006, and its efficacy in reducing fetal exposure to isotretinoin has yet to be fully determined.<sup>31</sup>

### ***Implications for practice***

Due to the myriad potential side effects of oral isotretinoin, its use should ideally be reserved for the treatment of severe, recalcitrant acne. The many potential side effects of oral isotretinoin, including teratogenicity, mucocutaneous complaints, elevated lipids, elevated serum protein or liver transaminases, arthralgia, decreased appetite, and the possibility of depression with suicidal ideation, require close monitoring of the patient at regular intervals. Patient education should also be an integral part of isotretinoin therapy.

The teratogenicity of oral isotretinoin requires that extra care should be taken when prescribing the drug to female patients and demands that adequate methods of contraception should be insisted upon in order to prevent birth defects. Laboratory monitoring should include pregnancy screening for female patients and periodic serum triglyceride, cholesterol and liver function tests may be indicated for all patients during isotretinoin therapy.

Lastly, more prolonged course of therapy (16-20 weeks) with a relatively low dose of isotretinoin ( $\leq 1$  mg/kg/day) may provide an optimal balance between long term outcomes and side effects.

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