Isotretinoin, Suicide, and Depression: Monitoring Acne Patients is a Joint Effort

Data fail to show a direct relationship between isotretinoin and depression or suicide, but the cumulative evidence suggests patients with severe acne require careful monitoring.

By Joshua Zeichner, MD

The controversial alleged association between isotretinoin and depression and/or suicide has dogged the medical community for more than a decade. Despite several studies that failed to show a negative correlation1-3, a few inconclusive studies and reports suggesting a risk for depression4-5 plus several high-profile instances of suicide by patients taking isotretinoin raised concern about the drug among both physicians and patients.

A warning regarding risk for depression and suicidal ideation was added to the isotretinoin label in 1998, and prescribers have been advised to caution patients about possible depression associated with use of the drug.6-7 Yet a causal relationship between isotretinoin use and depression or suicide had not been definitively established. Specialists have noted that acne itself, rather than isotretinoin use, is associated with depression, anxiety, and diminished quality of life (QoL).8-9 In fact, a new study shows a correlation between acne severity and depression and that acne treatment improves QoL.10 Furthermore, a new, large study has failed to identify a link between isotretinoin use and suicide and found that the attempted suicide risk in severe acne patients actually was lower during treatment compared to after treatment.11

Fewer pediatricians prescribe isotretinoin since the launch of the iPLEDGE prescriber/patient enrollment program. However, pediatricians commonly refer patients to dermatologists. The latest findings show that pediatricians should continue to play an active role in monitoring isotretinoin-treated patients—and all acne patients—in order to identify those most psycho-socially impacted by the disease.

Recent Findings

Conventional dosing of isotretinoin ranges from 0.5 to 1.0mg/kg per day to reach a total cumulative dose of 120 to 150mg/kg, usually obtained in 16-32 weeks. To

Take-Home Tips. Accumulating evidence suggests that severe acne is associated with significant psychological and quality of life influences that may have more impact on suicide risk than isotretinoin does. All patients with severe acne require comprehensive monitoring, including by family members and all physicians.
minimize the risk of adverse events (including skin dryness and irritation, cheilitis, etc.), low-dose isotretinoin (ranging from 0.25 to 0.5mg/kg/day) has been widely adopted. A recent comparative study found no statistical difference in efficacy between patients treated with traditional isotretinoin doses (0.5-1mg/kg/day) and those treated with low dose isotretinoin doses (0.25-0.4mg/kg/day). However, there was higher patient satisfaction in the low dose group. Moreover, both continuous dosing regimens were significantly more effective than an intermittent dosing regimen (0.5-0.7mg/kg/day) for one week every four weeks.12

An Australian retrospective review of more than 1,700 patients treated with isotretinoin for acne confirmed a lower rate of adverse events (AEs) with lower doses. Among patients receiving 10-20mg isotretinoin daily, there were no serious AEs reported. The most common side effect reported among all isotretinoin-treated patients were cheilitis (which was dose-dependent), eczema, and mood changes. Each AE occurred significantly less frequently among those patients receiving a dose less than 0.25mg/kg/day compared to more than 0.75mg/kg/day (Table 1). Most mood change was preceded by tiredness and was self-reported as mild in most cases. In total, 13 patients discontinued isotretinoin due to mood changes.

A recent Swedish study assessed risk for suicide associated with isotretinoin therapy and failed to identify a causal relationship. The investigators evaluated 5,756 patients ranging in age from 15 to 49 years who received isotretinoin for severe acne and evaluated attempted suicide risk before, during, and after treatment.3 In total, 128 patients were admitted to the hospital for attempted suicide. However, analysis showed that the incidence of suicide was raised before initiation of therapy. In the year before treatment, the risk of attempted suicide began to rise in severe acne patients. Moreover, the risk of attempted suicide was even higher in the six-month period after therapy with isotretinoin was completed. Only after three years post-isotretinoin therapy did the attempted suicide risk reflect that of the general population. The authors concluded that collectively, these observations do not support a causal relationship between isotretinoin and depression.

The Swedish investigators concluded that isotretinoin should not automatically be withheld from a patient with severe acne and a history of depression. In the study, the incidence of suicide was already increased in severe acne patients before isotretinoin therapy initiation. They interestingly found that patients who had attempted suicide before treatment made fewer attempts during treatment compared to those who had not made previous attempts. These findings lend support to the argument that acne itself increases an individual’s risk for suicide. Moreover, other investigators have shown that isotretinoin treatment for severe acne actually alleviates depressive symptoms and improves acne-related QoL.14

Data supporting the theory that acne confers its own mental health risks was gathered in a recent Norwegian questionnaire-based study. Approximately 3,700 patients between 18-19 years old were surveyed on the effect of acne and their mental and social functioning. The investigators found that substantial acne was associated with a higher risk of suicidal ideation and mental health problems. Additionally, these patients had a lower level of social functioning, particularly a low attachment to friends, not thriving in school, and an impairment of romantic relationships.15

**Clinical Implications**

As noted above, ample data document an association between acne and depression and decreased QoL. Findings from the currently available studies show that patients with severe acne are at increased risk of suicide even before initiating isotretinoin and that this risk continues after completion of isotretinoin therapy. Severe acne itself may correlate with increased depression and suicide risk, and treatment with isotretinoin may improve symptoms of depression from poor quality of life as a result of severe acne. While a causal relationship cannot be established
between isotretinoin and depression, all severe acne patients should be carefully monitored for suicidal behavior before, during, and after treatment. Non-dermatologic care providers may be particularly effective in monitoring patients post-therapy.

So why is continued monitoring after treatment so important? Why was the risk of attempted suicide highest in the six month period after completion of isotretinoin in the Swedish study? Perhaps this, too, relates to QoL. Response to isotretinoin therapy can be dramatic and rapid. However, the social benefits of clear skin may not be as quickly evident. Patients who have unrealistic expectations of treatment outcomes—including associated social and QoL improvements—may be particularly prone to psychological distress if those expectations aren’t met. Consider, too, that severe acne is associated with risk of scarring, which can be disfiguring. While treatment with isotretinoin can help prevent the formation of new scars, it does not improve existing scars. Therefore, patients whose acne responds to oral isotretinoin may still suffer psychological sequelae from scarring even after the acne improves. Fortunately, fractionated laser therapies can improve these scars.

The Take Away
The true relationship between severe acne, isotretinoin, and depression is still be elucidated. Despite newer data, prescribers cannot dismiss the association between isotretinoin and depression, given that the drug may modulate serotonin signaling in the brain. Regardless of the treatment selected, all involved in the patient’s care must assess and monitor the psychological health of all acne patients, especially those with severe acne. Monitoring beyond the active treatment period is essential.

Last November, the AAD updated its position on isotretinoin, noting in part:

• “A correlation between isotretinoin use and depression/anxiety symptoms has been suggested but an evidence-based causal relationship has not been established. Other studies give evidence that treatment of acne with isotretinoin was accompanied by improvement of both depressive and anxiety symptoms, as well as improved quality of life…”

• “The Association concludes that the prescription of isotretinoin for severe nodular acne continues to be appropri-ate as long as prescribing physicians are aware of the issues related to isotretinoin use, including IBD or psychiatric disturbance, and educate their patients about these and other potential risks. Physicians also should monitor their patients for any indication of IBD and depressive symptoms.”

In light of these findings and recommendations, clinicians must focus on careful monitoring of all patients with severe acne, especially those treated with isotretinoin. Patients should be monitored throughout treatment and for up to one year after. In addition to the prescribing dermatologist, the family physician or pediatrician, the patient’s family, and the patient him/herself should be recruited to participate in monitoring and reporting of psychological symptoms, including change in mood, depression, or suicidal ideology or behavior. Open communication between the patient and care providers and between various care providers is essential. Referring physicians should always feel comfortable contacting the prescriber to discuss the patient’s care or voice concerns.

Establishing appropriate expectations of treatment for acne of any severity is crucial. Patients must understand that medications can treat and prevent acne lesions but will not treat existing scars.

Treatment, while generally associated with improved QoL, does not ensure any social benefits. ■