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Isotretinoin Regulation:
Do the Ends Justify the Means?

There is little doubt of isotretinoin's effectiveness, but now dermatologists question whether associated risks justify additional regulatory burden and whether that burden will impact prescribing practices.

With the launch of the iPLEDGE program looming, concerns continue to mount as dermatologists prepare themselves for the strict limitations and measures of the program that lay ahead in 2006. But this "strengthened risk management program for isotretinoin," as the US Food and Drug Administration (FDA) calls it, is not the only substantial issue regarding isotretinoin—the highly effective acne treatment best known as Accutane. Isotretinoin comes with many serious warnings and concerns not just about birth defects but about a possible link with depression and suicide, as well.

Depressing Results

If you were to perform a Yahoo! search for "Accutane," the search results would include numerous law firm websites recruiting patients adversely affected by the drug. The sheer volume of these sites highlights the incredible number of legal actions related to isotretinoin. Interspersed among these law firm sites are numerous web pages documenting personal accounts of patients who claim to have been damaged by isotretinoin. Couple these findings with the relentless media coverage of real and apparent isotretinoin risks, and it would seem that the drug is a harmful medicine that should not even be on the market. Yet, in reality, isotretinoin is a commonly prescribed and highly effective treatment for acne. Many recent studies have found no greater likelihood of depression in patients taking isotretinoin, which in addition to Accutane is marketed as Sotret, Amnesteem, and Claravis, but it's still hard to ignore the warnings of depression and suicide associated with the agent.

Among the findings in favor of isotretinoin, a study published in a recent issue of the *Archives of Dermatology* (141: 557- 560) concluded that the use of isotretinoin is actually associated with a decrease in depressive symptoms among acne patients. The principal investigator of the study, Elaine Siegfried, MD, Clinical Associate Professor of Dermatology at St. Louis University and in private practice in St. Louis, notes that it "was designed to assess the clinical impression of most dermatologists," namely, if isotretinoin is associated with an increased risk of depression or suicide, the adverse effect is rare and idiosyncratic. Though many studies in recent years support the notion that isotretinoin is not linked with depression, this study is particularly interesting because it provides data that treatment with isotretinoin is much more often associated with improved mood than with depressed mood.

Richard G. Fried, MD, PhD a dermatologist and psychologist practicing in Yardley, PA, shares the opinion that isotretinoin is actually more likely to improve mood in treated acne patients. "The reality is that the data remains consistent and robust that isotretinoin is a safe, well tolerated medicine," says Dr. Fried. "Freeing an individual from the burden of acne has an antidepressant affect," he adds. Yet, almost any description you can find of isotretinoin, whether from academic, encyclopedic, or mainstream sources, inevitably mentions—usually in bold lettering—the potential risk of depression and suicide associated with taking isotretinoin. Many dermatologists understand these warnings to be born of caution rather than a prevailing consensus regarding a clear risk.

Media Frenzy

Dr. Fried and Dr. Siegfried seem to voice the views of the general dermatology community in claiming that isotretinoin is a safe and extraordinarily effective drug, which begs the question: if most dermatologists know that isotretinoin is unlikely to be associated with depression or suicide, why is the issue so well-recognized? "The publicity surrounding isotretinoin and depression reflects politics much more than science," Dr. Siegfried says. The most important political issue is the drug's teratogenicity, and the potential link to pregnancy termination.

The controversy surrounding isotretinoin and depression has been a secondary issue that reached a new level in 2000, when Congressman Bart Stupak very publicly proclaimed that Accutane, which his son B.J. had been taking, caused the teen to commit sui-

By Ted Pigeon, Associate Editor

cide. Furthermore, in 2002, 15-year old Charles Bishop flew a light aircraft into a building in Tampa, FL. He had reportedly taken Accutane, and his parents alleged that the drug had caused severe psychosis in the boy. These two events were instrumental in prompting the media whirlwind concerning isotretinoin, even though the claims made in both cases were practically unfounded. Referring to this, Dr. Fried recalls the old adage, "never let the facts stand in the way of a good story."

The bad publicity that has plagued isotretinoin for the past several years has heightened public concern about the drug's risks, and no less than a large, prospective, double-blind, placebo-controlled, multi-center study demonstrating safety will ever fully restore the drug's image. As Dr. Siegfried observes, "The media focus has blown the risks of isotretinoin way out of proportion, generating a huge amount of distrust regarding the drug." And because neither government nor industry is interested in supporting a definitive safety study of isotretinoin, she suggests, funding is not available.

Widespread reports and subsequent public awareness of the depression controversy strongly affects the emotional response of patients and dermatologists, many of whom are aware that risk is minimal. Due to the controversy thus far, it is impossible for clinicians to recommend isotretinoin without discussing the issue of depression in a degree of detail disproportionately greater than the presumed risk. Some mention of the possible association is certainly warranted. Dr. Fried notes, "idiosyncratically, any medicine can make any person feel unwell physically or emotionally at any time." Both he and Dr. Siegfried suggest that there are several confounding factors that must be taken into account when considering a possible association.

Confounding Factors

Dr. Siegfried notes that one of the most significant factors in examining the relationship of isotretinoin and depression is age. "There are roughly 100,000 prescriptions written a month for isotretinoin, the majority for patients aged 15 to 25, a cohort commonly experiencing new-onset depression. And suicide is the number three cause of death in this age group," notes Dr. Siegfried. "The frequent spontaneous reports of depression and suicide may represent an epi-phenomenon rather than cause and effect."

Dr. Fried stresses that depression in teenagers and young adults is often exacerbated by acne. "The incidence of clinical depression in adolescents in the US is 11 percent," he says. "If you add acne to that, the percentage increases." Dr. Fried points out the simple fact that an adolescent with acne is more likely to be unhappy or depressed due to acne alone. "Acne is physically and emotionally scarring. Adolescents are at an increased likelihood for depression simply by having acne."

Although a few recent studies suggest a potential link between isotretinoin and depression (see the feature article by J. Douglas Bremner, MD on page 28), Dr. Siegfried and Dr. Fried suggest numerous confounding factors prevent studies from demonstrating causality. "Teens by definition do impulsive things," says Dr. Fried, "so there is going to be a small portion of teens doing impulsive things on isotretinoin. That is inevitable." This doesn't mean that isotretinoin *causes* that depression or behavior, according to Dr. Fried. He further warns, "Taking it off the market would guarantee an increase in depression and suicide amongst acne patients and would also risk potential functional impairment."

Dr. Siegfried suggests that additional studies are needed to help define any pre-disposing factors for the rare subset of people who may be negatively affected by isotretinoin, including the role of possible predictive factors such as a personal or family history of depression, impulsivity, substance abuse or other psychological illnesses. Dr. Fried feels that "money would be better spent on studies focusing on the positive effects of isotretinoin as opposed to the lack of negative effects," Dr. Fried suggests.

Interests in iPLEDGE

As Dr. Fried and Dr. Siegfried both point out, most dermatologists seem to agree about the issue of isotretinoin and depression, viewing the drug as a good treatment that improves mood and quality of life. Recently, another substantial issue related to isotretinoin use has overshadowed the depression controversy: iPLEDGE.

The iPLEDGE program has caused quite a stir in the dermatology community. The program becomes mandatory on January 1, 2006, and is designed to prevent patients of childbearing potential from getting pregnant while using the drug. The program came at the strong recommendation of the Drug Safety and Risk Management and Dermatologic and Ophthalmic Drugs Advisory Committees. According to the FDA website, the program is a "technology based, closed system of registered wholesalers, prescribers, pharmacies, and patients that addresses the need for improvements in the isotretinoin risk management program to strengthen processes to ensure pregnancy testing and counseling of patients before and during treatment to reduce the risk of fetal exposure."

The risks of isotretinoin to an unborn baby have been known for quite some time, with programs established in the past to ensure pregnancy prevention. The original program, developed by Roche, was known as the "System to Manage Accutane Related Teratogenicity", or SMART, and was initiated in response to FDA concern that the rate of pregnancy among isotretinoin-treated patients was higher than zero. But the program did not reduce the already low rate of isotretinoin-exposed pregnancy. This fact coupled with the loss of patent protection and need for multiple pregnancy prevention programs by multiple pharmaceutical companies ultimately led to the push for the iPLEDGE program.

Tips for Patient Screening:

In the best interest of patient health, question adolescents about the possible effects that acne is having on them and attempt to identify patients who may be at risk for depression. When screening patients, Dr. Fried suggests that you ask the patient about and attempt to observe the following:

- *Change in mood i.e. increased lability, blunted affect*
- *Marked change in eating and sleeping habits*
- *Change in academic functioning*
- *Withdrawal from school activities*
- *Withdrawal from friends*
- *Morbid verbalizations i.e. talking about death, futility*

Like the previous programs, outcomes data for the iPLEDGE design are lacking, so enhanced pregnancy protection from this new approach has yet to be proven. Many people who were involved in the negotiations have doubts that this or any program can prevent pregnancy with 100% efficacy. "iPLEDGE is a program that was designed without any prior outcomes data to predict its efficacy," Dr. Siegfried says. "Pregnancy prevention was pretty successful even before the SMART program—with a pregnancy rate lower than that seen with routine use of birth control pills—and it didn't improve further with SMART."

iPLEDGE is more intricate than any of the programs that preceded it, and it requires much more effort on the part of patients, pharmacists, and physicians. All three participants must register by phone or on-line; patients are then closely tracked while on the drug. But despite the numerous requirements and strict guidelines, many speculate about the success of iPLEDGE. "I can't speak for all dermatologists, but I think that most people are in favor of the spirit of the program," says Dr. Fried. "For educational purposes, I think it is excellent. I don't think it will change very much, however." While an increased educational foundation and stricter guidelines may help, he points out that they could very well have no impact at all. There will inevitably be failures, according to Dr. Fried, especially with regards to contraception. Not only is there no way to prove if patients are using them, there is no guarantee that a contraceptive will even work.

But one thing is certain, according to Dr. Siegfried: the program will require much time and money. "I know who will need to spend the time—doctors, pharmacists, and patients. The financial burden of operating the iPLEDGE program will be bourne by the pharmaceutical companies. Ultimately, costs are usually transferred to consumers," she remarks. Some worry that doctors may negatively view the program based on how cumbersome it ultimately will be on them as well as patients. "I only hope that the burden of iPLEDGE does not discourage doctors from prescribing isotretinoin," notes Dr. Fried.

Perhaps the point of iPLEDGE is to some extent its complicated and somewhat intimidating nature. After all, it fundamentally cannot ensure pregnancy prevention. But the process lends a level of gravity to use of isotretinoin that may translate to patients approaching treatment with sincerity. It remains unclear how the FDA or anyone else will gauge the "success" or "failure" of iPLEDGE, but some wonder what will happen if the program fails to meet its goals. Regarding the success of iPLEDGE and the future of isotretinoin, Dr. Fried says, "I am fearful that if iPLEDGE is not successful, isotretinoin is at serious risk of being withdrawn from the market. I am hopeful that the ongoing accumulation of data supporting isotretinoin's safety and marvelous efficacy taken together with the serious short and long term risks of allowing scarring to occur will outweigh the risks of unwanted pregnancy and teratogenicity."

A Risk Worth Taking

Both the controversy over depression and the new iPLEDGE program have created a substantial burden for patients taking isotretinoin and the doctors prescribing it. This raises the question: Is isotretinoin worth the risks, concerns, and the overall burden for doctors and patients? Although the drug's image has been tarnished, it's 25 year history of widespread use, unparalleled efficacy, and generally manageable adverse effects have proven a very favorable risk/benefit ratio. No one really knows what will result from iPLEDGE, making the future of isotretinoin uncertain. Nevertheless, many dermatologists remain optimistic. Like Dr. Fried, they firmly believe in isotretinoin and think it is a cause worth fighting for. "It is a privilege to offer patients a drug with that degree of safety and effectiveness," he says. "Isotretinoin is a life-enhancing medicine. I don't know what [dermatologists] would do without it."