33

Accutane and Psychiatric Adverse Events: The FDA Perspective

Over the years that Accutane has been on the market, more than 2500 reports have accumulated in the FDA database about patients who developed psychiatric problems associated with Accutane treatment. People have many questions about the numbers: the number of affected patients, the number who have taken Accutane and had no problems, the number of patients who have committed suicide.

The numbers in circulation do not answer these important questions because they are not real numerators as we think of them in the context of clinical trials. The vast majority of serious adverse events occurring in the course of drug therapy are never reported to the manufacturer or to the FDA. This is especially true for a drug that has been on the market for a long time. In addition, many of the less "serious" cases that *are* reported to FDA are not entered into the database due to resource constraints. And, of course, cases are not necessarily causally linked to Accutane just because they are reported and entered into the adverse events database.

Intuitively, one would think that suicide, at least, would not be under-reported because families seek a cause to explain this tragic event. If this were true, then it would be reasonable to conclude that there is no causal linkage with Accutane because the reported numbers associated with Accutane do not exceed the estimated background rate for suicide in the population.

In fact, after the labeling change about suicidal behavior was publicized in 1998, FDA received "old" cases that had previously been unreported. After the recent publicity about the death of Representative Stupak's son, FDA again received previously unreported cases of suicide. What does this tell us? It does not inform the causality question, but it confirms that all serious adverse events that occur in association with Accutane treatment are *not* reported.

Why is this?

Families, patients, and prescribers may not consider the possibility that an acne medication may cause psychiatric side effects. Many people do not realize that proof of causality is not a prerequisite for reporting. Some may not want to report suspected events because of privacy concerns, legal concerns, or time constraints.

In addition to under-reporting of recognized events, many events are not reported because they are not diagnosed. Depression can be especially difficult to ascertain in teens. This issue may be further complicated now that "the word is out" because patients suffering with severe acne understandably fear that their Accutane will be stopped if they acknowledge psychiatric symptoms.

What of the reports we do have? Can we answer questions about causality from this data?

The vast majority of spontaneous adverse event reports would be entirely unacceptable as case reports in a clinical trial. They contain whatever information the reporter chose to reveal or thought was important. Sometimes the reporters are not health care professionals. Sometimes they are, but the diagnosis is imprecise. Often, even the most basic information is missing, such as the indication, dosage, concomitant medications, past history, other risk factors for the event, the dates of drug therapy, and the date when the adverse event began and resolved.

Does this mean the reports are not valuable?

On the contrary, spontaneous reports are of immense importance to drug safety surveillance, even if incomplete. It is signals from concerned reporters that form the bedrock for hypothesis generation and further investigation.

What is it about the imperfect information at hand that has engendered FDA's concern?

For events with a high background rate, such as psychiatric disease, the absolute number of reports is less important than the qualitative nature of the information that is available. The concept of "contributory cause" requires a demonstration that the suspected cause precedes the effect and, usually, that perturbing the "cause" perturbs the effect, at least in some patients.

An accumulating subset of qualitatively rich reports suggests a pattern of temporal association between Accutane treatment and emergence of psychiatric symptoms. These reports describe patients, with no previous history of psychiatric illness and no identified concomitant risk factors, who developed significant psychiatric problems during the course of Accutane therapy. The problems resolved within a few days when the Accutane course was completed or discontinued (positive dechallenge). They recurred when Accutane was restarted (positive rechallenge). Resolution was again noted within a few days on subsequent discontinuation. Commonly reported signs and symptoms include mood swings/irritability, uncontrollable crying, aggressive personality changes, and frank depression.

These spontaneous reports prompted us to ask whether other information supports a possible causal relationship:

- Does Accutane reach the target organ of the observed adverse event (the brain)? Yes.
- Is Accutane associated with other central nervous system adverse events? Yes. Of all the organ systems classified in the spontaneous reporting database, the central nervous system has the largest number of serious adverse event reports for Accutane.
- In cases with positive dechallenge, is the average time to resolution of symptoms consistent with Accutane pharmacokinetics? Yes.
- Are there published reports of psychiatric adverse events associated with Accutane that pre-date the publicity of the 1998 warning? Yes.
- Are the temporal and clinical patterns in these reports similar to the patterns in the spontaneous reports? Yes.
- Are any other retinoids associated with psychiatric disturbance? Yes, including the "natural" retinoid, Vitamin A when consumed in excessive amounts.
- Are retinoid receptors and binding proteins found in adult mammalian brain? Yes.
- Have any well-conducted studies demonstrated a functional role for retinoids/receptors in the central nervous system of animals? Yes.
- Has a mechanism of action been established to account for the observed events? No. Delineation of the mechanism of action for drug side effects is often clinically useful, but the unknown is of no utility, especially when studies of possible mechanisms have yet to be conducted. Indeed, dermatologists have managed for many years the potentially serious psychiatric side effects of systemically administered corticosteroids without delineation of the mechanism.

The information available now does not allow a conclusion that Accutane is causally linked to serious psychiatric diagnoses. It also does not allow a conclusion that Accutane is not causally linked. It may be impossible to answer this question with a clinical trial due to numerous significant design problems (ethics of a placebo control, masking, etc.). Observational studies to date have been inconclusive. If the observed events are causally linked to isotretinoin, the

process of science will likely uncover the mechanism, but in the meantime, what should be done to maximize safe use of Accutane?

The Code of Federal Regulations stipulates that the package insert for a product should warn of possible serious health consequences if there is reasonable suspicion. Proof of causality is *not* required. However, according to the laws of common sense, we also have an obligation not to over-warn. In the case of Accutane, this common sense imperative is particularly focused because some experts believe that the indication for the drug, severe recalcitrant nodular acne, may itself be a risk factor for serious psychiatric illness. Although this hypothesis is unproven, it is an important consideration in risk management strategy, since Accutane is a highly efficacious acne treatment.

In early 1998 it was announced that the Accutane package insert was being amended to warn that there *may* be a causal link between serious psychiatric outcomes and Accutane. "Dear Doctor" letters were sent by the manufacturer to alert health care providers about the need to educate patients and take appropriate action if signs of psychiatric disturbance emerged in association with Accutane therapy.

Was this 1998 action effective?

We do not know because we don't know how many actual cases happened before the Warning, nor do we know how many cases are actually happening now. In fact, publicity alone can increase the number of reports in the absence of a true causal relationship. However, after the 1998 action, we continued to hear anecdotal reports of patients and parents who recalled no discussion about the possibility of serious psychiatric outcomes with Accutane use.

In May of 2000, the long-standing warning about "mood changes" on the Accutane box dispensed to patients was changed to specifically note the possibility of self-injurious behavior. This very limited space for multiple safety messages, including the well-established risk of severe birth defects, is far from an ideal venue for conveying the uncertain risk of self-harm. In September of 2000 the issues surrounding Accutane and psychiatric events were brought before a public hearing of the FDA advisory committee for dermatologic drug products. This panel consisted of committee dermatologists and invited specialists in psychiatry, medical ethics, pediatrics, and neurodevelopment.

The committee considered the inconclusive evidence to be cause for concern and recommended further study. In the interim, they recommended a Medication Guide for Accutane. Medication Guides are a relatively new risk management tool mandated by law under certain circumstances to provide consumers with pertinent information from the professional labeling, written in non-technical language. Medication Guides are FDA approved and must be dispensed by

pharmacists with each prescription filled. In addition, the committee recommended a new patient agreement/consent form directed at awareness of possible psychiatric adverse events.

These risk management tools are an important addition to the overall program for Accutane, but no tool can begin to replace the perspective that a well-informed prescriber offers patients. This perspective, unique for each patient, is even more critical when uncertain risk of grave events needs to be conveyed without failing the duty not to over-warn.

Despite the efforts of the manufacturer, the FDA, and the scientific community, a definitive answer to this complex question is unlikely to emerge soon. We urge prescribers to make use of the risk management tools available now, and to think critically about emerging information on the relationship between Accutane and serious adverse psychiatric effects. Patients undergoing treatment with Accutane are counting on it.

Notes:

We encourage you to report serious adverse events to either the manufacturer (Roche Medical Services 1-800-526-6367) or directly to the FDA MedWatch program (1-800-FDA-1088). You can also submit reports electronically via the FDA website: www.fda.gov/medwatch/index.html

Details about information discussed in this manuscript can be found via the FDA's Accutane webpage: www.fda.gov/cder/drug/infopage/accutane/default.htm