CRITICAL VIEWS IN GASTROENTEROLOGY & HEPATOLOGY

Isotretinoin, Acne, and Crohn's Disease: A Convergence of Bad Skin, Bad Science, and Bad Litigation Creates the Perfect Storm

Brian G. Feagan, MD, and **Reena Khanna, MD,** spoke with *Gastroenterology & Hepatology* about the controversial issue of inflammatory bowel disease (IBD) and litigation regarding isotretinoin use. Were malpractice lawsuits justified, how did the situation get so out of control, and why do litigation claims persist even though the link between IBD and retinoid use has been debunked? Dr Feagan and Dr Khanna answer these questions in the following editorial. Dr Feagan is a professor and Dr Khanna is an assistant professor in the Division of Gastroenterology at the University of Western Ontario in London, Canada. Dr Feagan is also director of the Clinical Trials Research Group at the Robarts Research Institute at the University of Western Ontario.

The consequences of the once proposed, but now discredited, causal relationship between inflammatory bowel disease (IBD) and isotretinoin use is a social tragedy on multiple levels. Specifically, patients with severe acne have been denied access to effective therapy, physicians and pharmaceutical companies have been subjected to unwarranted and reckless litigation, and patients treated with retinoids are fearful of IBD. These unfortunate, yet preventable, circumstances should be examined from both scientific and societal perspectives.

Bad Skin

Acne is a common condition that occurs in 35% to 90% of adolescents.[1] In this population, severe acne is associated with an increased risk of mental illness, poor social functioning, and suicide.[2] Accordingly, acne cannot be considered a trivial condition. Although multiple topical and oral therapies are used to treat acne, isotretinoin is the most effective drug currently available,[3,4] and since it received US Food and Drug Administration (FDA) approval in 1982,[5] it has revolutionized treatment. Isotretinoin improves quality of life,[6,7] psychiatric symptoms,[8] and social function.[8] However, in the past 30 years, concerns have been raised that isotretinoin use can lead to the development of IBD. Recently, successful civil litigation based on this proposed relationship has occurred that has made physicians fearful of prescribing isotretinoin to their patients.

Bad Science

The causes of most chronic diseases are complex, multifactorial, and poorly understood. Therefore, it is not surprising that incorrect conclusions regarding causation are relatively common. Gastroenterologists will recall the "no acid–no ulcer" dogma of the pre-*Helicobacter* era or the proposed relationship between measles immunization and the development of Crohn's disease (CD). Physicians should have a basic understanding of the levels of evidence needed to establish causation because this knowledge is highly relevant to clinical practice. Patients are often concerned about the development of a disease or complication after learning of a hypothetical risk factor in the media. Unfortunately, these associations are frequently based on poor-quality evidence and are ultimately determined to be false. "Association" describes an exposure and outcome that occur more frequently than would be expected by chance alone. In contrast, "causation" is a specific term that is only used when an association is scientifically proven and additional criteria are met (Table).[9] Proving causation is usually a difficult task.

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What are the basic tools that epidemiologists use to determine whether a valid association exists between a given disease and a candidate risk factor? Case reports or series are the lowest form of evidence available. Essentially, these reports are anecdotes. No control group exists; a case series cannot establish whether or not an association beyond chance exists. A more methodologically rigorous design is the case-control study in which a group of patients with a given condition are retrospectively matched for important variables, such as age and gender, to controls without the disease. Relative exposure to the risk factor is then determined. This design features a control group that allows determination of the strength of association through calculation of an odds ratio (OR). However, case-control studies are highly vulnerable to bias, both in selection of controls and determination of exposure to the risk factor. Cohort studies provide stronger evidence for association. In this design, a group at risk for the disease of interest is prospectively followed. Exposure to the risk factor is determined, and the relative risk for the development of the disease is compared in exposed and unexposed persons. The cohort design eliminates many of the problems of bias inherent in the case-control study and allows adjustment for known confounding variables. Consequently, the cohort study is usually the best means of establishing causation in human diseases. Finally, randomized controlled trials that differentially eliminate a risk factor can be powerful instruments for establishing causation; however, this approach is frequently impracticable for either ethical or pragmatic reasons.[10,11]

Based on these considerations, what evidence exists to support a causal relationship between exposure to isotretinoids and IBD? The first case reports that proposed this relationship described either patients in whom IBD developed following initiation of retinoid therapy or those with an established diagnosis of IBD who experienced a disease flare after treatment.[12-15] Subsequently, reports submitted to the FDA through the MedWatch system were collected and reviewed according to the Naranjo adverse drug reaction probability scale.[16] Of the 85 cases of IBD available, 5% were rated as having "high probability" of being linked to isotretinoin, 68% as "probable," 27% as "possible," and 0% as "doubtful."[17] However, the evidence provided by this case series is problematic because it is based exclusively on spontaneous reporting of adverse events by physicians, which is highly susceptible to bias, does not have a control group, and provides no information on the strength of association. Nevertheless, this report, which does not even meet the minimum standard for proving association, let alone causation,[18] provided the basis for a subsequent tsunami of litigation directed towards physicians and pharmaceutical companies.

Table. Bradford–Hill Criteria for Establishing Causation[9]

Criterion	Description
Strength	Larger associations are more likely to represent causal relationships than smaller observations.
Consistency	Similar findings by multiple investigators, in different populations, strengthens the probability of a causal link.
Specificity	The likelihood of a causal relationship is increased if no other plausible explanation for the phenomenon exists.
Temporality	Exposure to the cause must occur prior to the effect at an appropriate interval to induce the response.
Biological gradient	Greater exposure to the cause should lead to a higher incidence of the effect.
Plausibility	A credible mechanism between the cause and effect lends support to a causal relationship.
Coherence	Consistent results from multiple sources of data (such as epidemiology and laboratory findings) increase the likelihood of a causal link.
Experiment	Experimental evidence provides greater evidence of a causal effect than observational data.
Analogy	The possibility of a causal relationship is strengthened when similar factors produce the same effect.

> . . . attorneys have grossly inflated reporting of isotretinoin-associated IBD.

An article by Stobaugh and colleagues that was recently published in the *Journal of the American Academy of Dermatology* illustrates the magnitude of the problem of using case reports as an epidemiologic tool.[19] Their analysis of the Food and Drug Administration Adverse Event Reporting System database found that attorneys have grossly inflated reporting of isotretinoin-associated IBD. Of the 2214 cases of isotretinoin-associated IBD accumulated between 2003 and 2011, remarkably 87.8% were reported by attorneys, compared with only 6% by physicians and 5.1% by consumers. In contrast, attorneys filed only 3.6% of the total 2,451,314 reports of all adverse drug reactions received by the agency during this period. These data underscore the susceptibility of conventional pharmacovigilance systems to bias.

Critical Views

Important data from high-quality observational studies do not support an association between exposure to isotretinoin and the development of IBD.[20-23] Two registry-based case-control studies compared patients with IBD with age-, sex-, and geographically matched controls. In a study by Bernstein and colleagues, isotretinoin use was observed in 1.2% of the 2008 IBD cases and 1.1% of the 19,814 controls (OR, 1.16; 95% CI, 0.73-1.77).[20] Similarly, there was no difference in isotretinoin exposure for cases with ulcerative colitis (UC) (OR, 1.16; 95% CI, 0.56-2.20) or CD (OR, 1.15; 95% CI, 0.61-2.02) compared with controls. In the second study, 8189 cases of IBD were matched with 21,832 controls.[21] Isotretinoin use was noted in 0.29% and 0.16% of these groups, respectively, which resulted in ORs of 1.68 (95% CI, 0.98-2.86) for IBD and 0.68 (95% CI, 0.28-1.68) for CD. However, a positive association was observed (OR, 4.36; 95% CI, 1.97-9.66) for UC. The contribution of confounders, such as disease severity and exposure to antibiotics and other medications, casts doubt on this finding.[24,25] Subsequently, these factors were controlled for in a nested, case-control study of women who were receiving oral contraceptives.[23] In this population, 10 (0.46%) of the 2159 IBD cases and 191 (0.44%) of the 43,180 controls were exposed to isotretinoin (relative risk [RR], 0.99; 95% CI, 0.52-1.90). Similarly, there was no excess risk of CD (RR, 0.91; 95% CI, 0.37-2.25) or UC (RR, 1.10; 95% CI, 0.44-2.70) with isotretinoin exposure. Finally, additional data are now available from a retrospective population-based cohort study that evaluated 46,922 patients treated with isotretinoin, 184,824 patients who received topical acne medications, and 1,526,946 untreated controls. In this study, there was no association observed between exposure to isotretinoin and the risk of IBD (rate ratio, 1.14; 95% CI, 0.99-1.41).[22] These results were confirmed in a meta-analysis of 5 studies that demonstrated a pooled RR of 0.94 (95% CI, 0.65-1.36).[23]

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In summary, a large amount of high-quality evidence now exists that disproves the relationship between isotretinoin and the risk of IBD. Nevertheless, the legal tsunami continues unabated.

Bad Litigation

In epidemiology and medicine, the *P*-value, or alpha error, is specified to minimize the risk of making an error of commission; ie, a "false-positive" conclusion. Conventionally, a *P*-value of <.05—or a 5% chance that the result occurred by chance alone—is considered appropriate. It is relevant to compare this benchmark with corresponding standards for establishing culpability in criminal and civil law. In the former case, a higher level of evidence, "beyond a reasonable doubt," is required for conviction because of the serious consequences for both the accused and society of a false-positive judgment. This might relate to a *P*-value of <.001. However, a different situation exists in the case of civil litigation. Here, the standard is much lower such that the plaintiff needs only to establish that the "balance of probabilities" favors his or her case. This standard literally translates into a *P*-value of .49!

When we consider the consequences of a false-positive conclusion in this particular situation, it is difficult to conclude that this is an appropriate benchmark. The magnitude of the isotretinoin litigation industry is enormous and has the potential to bankrupt the manufactures of the drug. It is estimated that over 7000 personal injury lawsuits have been filed against drug manufacturers.[26] This situation could end in serious harm to patients who will be denied access to effective treatment for a serious condition. Based on the strong evidence now available that disproves the proposed association between isotretinoin and IBD, this would be a tragic result for both patients and society. The responsibility for interpreting the scientific evidence regarding causation currently resides in the hands of judges and jurors. We can only hope that they understand the relevant scientific principles, are aware of the enormous consequences of making incorrect rulings, and are respectful of the health of the millions of people not in their courtroom who will be affected by their judgments.

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Critical Views