Isotretinoin-IBD Link Challenged by Two Studies

BY BRUCE JANCIN AND MICHELE SULLIVAN

WAIKOLOA, HAWAII — Two studies—both conducted by gastroenterologists—dispute the notion that isotretinoin causes inflammatory bowel disease.

Neither found a basis for allegations of an increased risk of inflammatory bowel disease (IBD) in patients who were treated with isotretinoin.

"There has been a lot of concern about this. You can't say anything with certainty in life, but at least thus far the data we have are very reassuring that there is no association," Dr. Sheila Fallon Friedlander said at the annual Hawaii Dermatology Seminar sponsored by Skin Disease Education Foundation.

She cited a retrospective, nested case-control study by investigators at the University of Manitoba, Winnipeg, who used the comprehensive provincial IBD database to demonstrate that patients with IBD were no more likely to have used isotretinoin before diagnosis than were matched controls. "Although there may be anecdotes of isotretinoin causing acute colitis, our data suggest that isotretinoin is not likely to cause chronic IBD," the investigators concluded (Am. J. Gastroenterol. 2009;104:2774-8).

Dr. J. Mark Jackson of the University of Louisville (Ky.) characterized the Manitoba study as "a really well-done study coming at a critical time," conducted by physicians who deal with IBD and therefore have no stake in protecting a drug that could cause it.

The second study was a seven-country, systematic data search led by gastroenterologists at the University of North Carolina at Chapel Hill, who found "no clear relationship" between the use of isotretinoin and IBD. Unlike the earlier study, this analysis used the rigorous Chapel Hill criteria designed to weigh the strength, consistency, specificity, and plausibility of scientific evidence, and on that basis, the investigators determined no causal association had been established (Am. J. Gastroenterol. 2009;104:2387-93).

"We now have some very good data reviews showing that IBD is not overrepresented in patients who use isotretinoin," Dr. Jackson said in an interview. "When this issue comes up [in prescribing], we need to make people aware that this rumor has not been validated."

Personal injury lawyers seized on an earlier study that concluded it was "highly probable" that isotretinoin was the cause of four cases of IBD reported to the Food and Drug Administration's MedWatch program, with the oral retinoid being deemed the "probable" cause of another 58 (Am. J. Gastroenterol. 2006;101:1569-73). Trial investigator Dr. Sunanda Kane of the University of Chicago was contacted for an interview, but was unable to comment because of pending litigation. The other three study investigators never responded to interview requests.

"This is a situation where there are conflicting data, but a bottom line of interest to all of us is that a New Jersey jury has awarded $12.9 million to patients who have taken isotretinoin and developed IBD," said Dr. Friedlander, a dermatologist who is a clinical professor of pediatrics and medicine at the University of California, San Diego.

Lawyers shooting for claims have found isotretinoin to be an easy mark for years. The finding that it could increase birth defects by up to 30% left it "an open target," Dr. Jackson said. "It's always been on the legal radar because of this past issue, and it tends to get put back in the forefront frequently—it's an easy medicine to beat up."

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"This rumor has not been validated," Dr. J. Mark Jackson said.

He said he makes it a practice to discuss reports of these issues with patients before prescribing isotretinoin. "I bring it up with my patients because I don't want them hearing it from some other source first," he said.

At the meeting, when Dr. Jackson asked for a show of hands as to how many audience members have fielded questions from their patients regarding a putative isotretinoin-IBD link, the majority of dermatologists' hands shot up. "It's amazing how isotretinoin continuously gets brought to the forefront of the legal realm. There's always something going on," he said.

Dr. Seth D. Crockett, a coauthor of the University of North Carolina study, tried to bring some perspective to the issue in an interview with this news organization. "Our study was a critical appraisal of the literature and an assessment of causality. Basically we found that the only published evidence is case reports, which generally is considered poor evidence to establish causality. The best evidence is from epidemiologic studies such as the University of Manitoba study," he said.

"It's important to recognize that the absence of published evidence does not mean the absence of an association; it just means that there's insufficient evidence in the scientific literature thus far to support a causal connection between isotretinoin and IBD," added Dr. Crockett of the division of gastroenterology and hepatology at the University of North Carolina.

Isotretinoin is now available only in generic form. ■

Disclosures: *Dr. Jackson and Dr. Friedlander indicated that they are longtime prescribers of isotretinoin in severe cases of acne. Dr. Jackson has received support from Roche Pharmaceuticals (manufacturer of Accutane). Dr. Crockett had no relevant conflicts of interest. SDEF and this news organization are owned by Elsevier.*

Common Lab Tests Can Predict Thiopurine Response in IBD

BY ROBERT FINN

Algorithms based on common laboratory values outperformed expensive metabolite testing in determining which patients with inflammatory bowel disease are likely to respond to thiopurine therapy, Dr. Akbar K. Waljee and his colleagues reported.

Thiopurines are known to be effective immunomodulators in patients with inflammatory bowel disease (IBD) who have failed 5-aminosalicylic acid therapy. The problem is that thiopurines have a narrow therapeutic index, and individuals vary widely in how they metabolize these agents.

Experienced clinicians can use inexpensive complete blood count and standard blood chemistry values to balance efficacy and risk in individual patients, but this takes expert judgment, and there are no established algorithms.

A more reproducible approach is to measure the metabolites 6-thioguanine (6-TGN) and 6 methylmercaptopurine (6-MMP). Unfortunately, monitoring these metabolites is expensive, and the sensitivity and specificity of this approach are only 62% and 72%, respectively.

In an effort to resolve this dilemma, Dr. Waljee and his colleagues from the University of Michigan, Ann Arbor, used a machine learning technique to tease out the most accurate algorithms based on CBC and blood chemistries (Clin. Gastroenterol. Hepatol. 2010 [doi: 10.1016/j.cgh.2009.09.031]).

The investigators used data collected in 774 cases from 346 individuals who were seen at the University of Michigan between May 2004 and August 2006. To be included in the study, the patients had to have had thiopurine metabolite analysis, CBC, and a comprehensive chemistry panel within the same 24-hour period.

Using a randomly selected 70% of the cases, investigators used a statistical technique called the "random forest" method to derive the most accurate algorithms based on data from the CBC and chemistry panels. They then tested that algorithm on the remaining 30% of the cases, comparing the accuracy to that of thiopurine metabolite analysis.

Their primary outcome measure was the area under the receiver operating characteristic curve (AuROC), a standard measure of accuracy.

The random forest algorithm differentiated clinical response from nonresponse with an AuROC of 0.856, compared with 0.594, for 6-TGN levels, a difference that was highly statistically significant.

The most important independent variables in differentiating responders from nonresponders were neutrophil count, alkaline phosphatase, red-cell distribution width, age, and white blood cell count.

The investigators also derived a random forest algorithm that would predict patient nonadherence, and another that would predict which patients were likely to have unfavorable pharmacodynamic responses to thiopurine therapy. Both of those algorithms proved to be significantly better than thiopurine metabolite analysis.

They also developed a simple prediction rule that was reasonably accurate at differentiating responders from nonresponders. Patients with a ratio of mean corpuscular volume (MCV) to white blood cell count (WBC) of 12 or more had a 67% likelihood of having a clinical response, while those with a ratio less than 12 had a 35% likelihood of having a clinical response. This simplified algorithm was significantly worse than the more complex algorithm, but it was still significantly better than metabolite analysis.

The investigators hypothesized that the algorithms based on common laboratory tests serve as surrogate markers for immune system changes induced by effective thiopurine therapy.

"It seems likely that patients with inadequate responses in these parameters are underdosed and that some patients, even at high doses, will not achieve these physiologic changes, due to differences in pharmacodynamics," the investigators wrote. "We speculate that the eventual clinical utility of this machine learning approach, depending on a positive outcome of a prospective clinical trial, will be in guiding thiopurine dosing and timely changes to a different class of therapy." ■

Disclosures: *The investigators disclosed that the Regents of the University of Michigan, along with several of the study's coauthors, have applied for a patent on the application of machine learning to the prediction of clinical response to thiopurines.*