Isotretinoin-IBD Connection Is Unsupported

BY BRUCE JANCIN AND MICHELE G. SULLIVAN

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

Neither found a basis for allegations of an increased risk of IBD in patients who were treated with isotretinoin. "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, the investigators concluded (Am. J. Gastroenterol. 2009;104:2774-8).

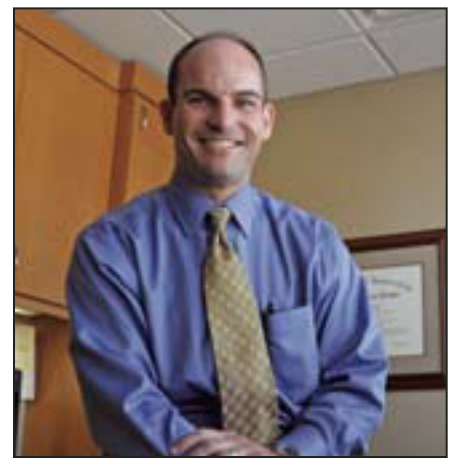
Dr. J. Mark Jackson of the University of Louisville (Ky.) characterized the Manitoba study as "a really well-done study coming at a critical time," conducted by physicians who deal with IBD and, therefore, have no stake in protecting a drug that could cause it.

The second study was a seven-country, systematic data search led by gastroenterologists at the University of North Carolina at Chapel Hill. 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've 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.



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Dr. J. Mark Jackson talks with patients before he prescribes isotretinoin.

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." 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 how many audience members have fielded questions from their patients regarding a putative isotretinoin-IBD link, the majority of dermatologists' hands shot up.

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 at Chapel Hill.

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.*

Trunk Fat Tops BMI, Waistline as Predictor of Elevated ALT

BY DENISE NAPOLI

Increased trunk fat on dual-energy x-ray absorptiometry was independently associated with elevated serum ALT levels, a measure of liver injury—more so than was extremity fat, body mass index, or waist circumference, reported Dr. Constance E. Ruhl and Dr. James E. Everhart.

The findings "support the hypothesis that liver injury can be induced by metabolically active intra-abdominal fat," the authors wrote, noting that "obesity is an important risk factor for liver injury" (Gastroenterology 2010;138:1346-56).

VITALS

Major Finding: Each step up in trunk fat quintile conferred a 1.7 increased odds ratio for elevated ALT in men and a 1.4 increased OR for women.

Data Source: 11,821 participants (5,918 men and 5,903 women) in NHANES between 1999 and 2004.

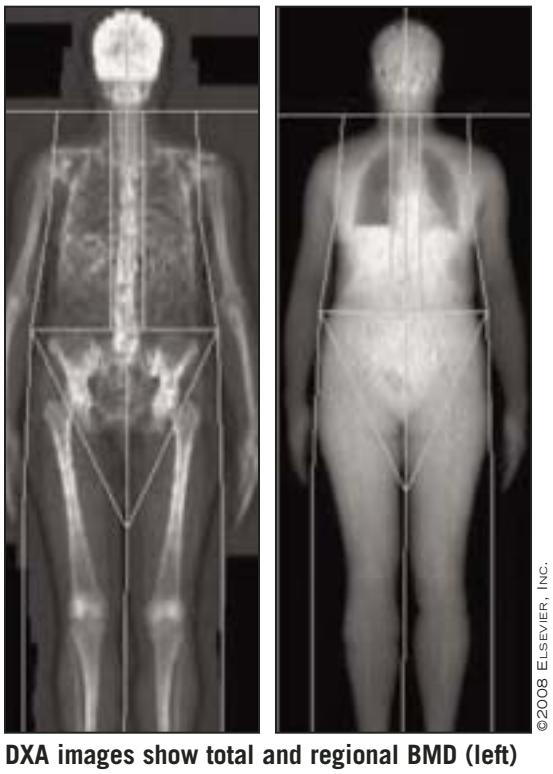
Disclosures: Dr. Ruhl and Dr. Everhart reported having no conflicts of interest. The study was supported by the National Institute of Diabetes and Digestive and Kidney Diseases, a division of the National Institutes of Health, where Dr. Everhart is employed.

Dr. Ruhl of Social & Scientific Systems Inc., a research support company, and Dr. Everhart of the National Institute of Diabetes and Digestive and Kidney Diseases studied data from patients in the National Health and Nutrition Examination Survey. In all, 11,821 participants (5,918 men and 5,903 women) in NHANES in 1999-2004 were ultimately included in the analysis. Study participants had DXA measurements to determine trunk fat, trunk lean mass, extremity fat, and extremity lean mass, and were then divided into quintiles within each category. Missing DXA measurements were imputed by the National Center for Health Statistics. Serum ALT levels, a marker of liver damage, were considered elevated above 44 U/L in men and above 31 U/L in women.

"The prevalence of elevated ALT was 11.1% among men and 10.1% among women," wrote the authors. Among men, each step up in trunk fat quintile conferred a 1.7 increased odds ratio for elevated ALT (*P* less than .001). In women, each step up in trunk fat quintile was associated with a 1.4 increased OR (*P* less than .001). The results were adjusted for ethnicity, age, glucose status, serum total cholesterol, cigarette smoking, and alcohol consumption.

In contrast, having an increased amount of extremity fat actually was protective against elevated ALT. Among men, every increased quintile conferred a 0.87 OR of elevated ALT ($P = .002$), and for women, each increasing quintile conferred a 0.86 OR ($P = .001$). Trunk lean mass and extremity lean mass, on the other hand, showed no significant relationship with ALT concentration.

"Having established that elevated ALT was most strongly associated with trunk fat, we considered its effect on the association of BMI and waist circumference with elevated ALT," wrote the authors. "When trunk fat, BMI, and waist circumference were included together in multivariate-adjusted models, higher trunk fat remained independently associated with elevated ALT among both men [$P = .002$] and women [$P = .011$], but BMI and waist circumference were not."



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DXA images show total and regional BMD (left) and body composition (fat, muscle mass; right).

Regarding the "unexpected" finding that extremity fat was protective against elevated ALT, the researchers postulated that the "uptake and storage of free fatty acids by femoral adipose tissue could lead to protection of other organs such as the liver from exposure to fatty acids and ectopic fat deposition."

The authors conceded that DXA measurements of abdominal fat are not as accurate as CT or MRI, and the use of ALT levels alone as a marker of liver damage cannot be entirely accurate. "Participants were included in the elevated ALT group who would not have been, had repeat ALT measurements been available." ■