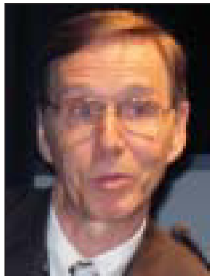
Tegaserod's CV Risk May Have Been Exaggerated

BY BRUCE JANCIN
Denver Bureau

MUNICH — Results of a large case-control study suggest the irritable bowel syndrome drug tegaserod (Zelnorm) may have gotten a bum deal when the Food and Drug Administration suspended its marketing in March 2007 because of cardiovascular concerns.

"Our results suggest that a prior observation of a differential increase in cardiovascular events with tegaserod may be due to chance rather than causal," Dr. Jeffrey L. Anderson concluded in presenting the study findings at the annual congress of the European Society of Cardiology.



The 'increase in cardiovascular events with tegaserod may be due to chance rather than causal.'

DR. ANDERSON

The FDA approved tegaserod in 2002 for treatment of irritable bowel syndrome (IBS) of the constipation-predominant subtype, then later granted an added indication for treatment of chronic idiopathic constipation in patients under age 65.

Tegaserod, a selective serotonin-4 receptor agonist, was the only drug approved for treatment of IBS with constipation until it was yanked from the market. However, in April 2008, Takeda Pharmaceutical's chloride channel activator lubiprostone (Amitiza) received FDA approval for IBS with constipation and for chronic idiopathic constipation.

Tegaserod sales were halted when a Novartis review of more than 18,000 patients in its database turned up 13 cardiac ischemic events in 11,614 treated patients, compared with just 1 case in 7,031 placebo-treated controls, explained Dr. Anderson, professor of medicine at the University of Utah and associate chief of cardiology at LDS Hospital, both in Salt Lake City.

All cases occurred in individuals who had a history of cardiovascular disease or were at increased cardiovascular risk. And when Dr. Anderson was asked to conduct a follow-up independent review of the Novartis data, he determined that three reported events in the tegaserod group were false-positives and another five involved "soft" anginal episodes. That left five hard cardiovascular events in the tegaserod group and one in the placebo group, a minimal difference that did not approach statistical significance.

Furthermore, no consistent relationship was seen between cardiovascular events and tegaserod dose or timing. And tegaserod had shown no ECG or other cardiovascular effects in the three randomized trials totaling nearly 2,500 women with IBS that led to the drug's approval.

IBS is a common and burdensome disorder in young women. On the basis of Dr. Anderson's largely reassuring review of the Novartis database along with the lack of a known vascular mechanism, he and his coinvestigators decided to conduct a prospective study free of any industry support. They turned to the Intermountain Healthcare database, which contains comprehensive hospital, outpatient, and prescription information on the Utah-based health plan's 1.2 million enrollees.

They identified 2,603 tegaserod-treated patients and matched them by age and gender with 15,618 untreated controls. In keeping with IBS demographics, the tegaserod group averaged 38.6 years of age, and 94% were women. Duration of therapy was 2 months in IBS patients, in accordance with the product labeling, and up to 4 years in those with chronic idiopathic constipation.

The composite end point comprising cardiac death, acute MI, cerebrovascular event, or hospitalization for unstable angina occurred in 12 tegaserod-treated individuals and 54 controls during an average 2.3 years of follow-up. This translated to very similar event rates of 0.46% and 0.35%, respectively. The most common events were cerebrovascular accidents, occurring in 10 tegaserod-treated patients and 36 control patients. All six cardiovascular deaths occurred in the control group.

The cardiovascular event rates in this study—roughly 3 per 1,000 person-years in both groups—were actually lower than the expected rate of about 5 per 1,000 person-years in a population of mostly premenopausal women, Dr. Anderson noted.

Dr. Dan Atar, professor of cardiology at the University of Oslo, commented that if one were searching for a plausible mechanism of vascular effects for tegaserod, platelet function would be the place to start. At least 14 different serotonin receptors have been identified to date, and while tegaserod is relatively selective for the type 4 receptors in the gut, the drug could, in theory, act on other serotonin receptors promoting platelet activation.

Dr. Anderson agreed, although such an effect has not been found to date. He added that cardiovascular event rates are so low in women under age 40—the typical IBS population—that a formal randomized trial of tegaserod with cardiovascular end points would have to be so huge as to be impractical.

"It raises the question of what should be required of a drug like this that treats relatively young women who are highly symptomatic with this disease, when if there is a cardiovascular risk it's very, very small," the cardiologist observed.

The Intermountain Healthcare study was funded by the Deseret Foundation. ■

Ileal Pouch Anal Anastomosis Works for Some Crohn's Patients

BY BRUCE JANCIN
Denver Bureau

NEW YORK — Ileal pouch anal anastomosis has an unexpectedly good long-term retention rate in highly selected Crohn's disease patients, according to a single-center study of more than 200 patients.

The 10-year pouch retention rate was 85% or higher in patients diagnosed with Crohn's disease before or immediately after the procedure, and about 50% in those whose Crohn's diagnosis was delayed 3 months or more postoperatively.

Ileal pouch anal anastomosis (IPAA) surgery also won very high patient satisfaction marks from individuals with long-term pouch retention, Dr. Genevieve B. Melton reported at the annual meeting of the American Surgical Association.

IPAA is widely considered the procedure of choice in ulcerative colitis patients whose inflammatory bowel disease requires surgery. However, IPAA is a controversial treatment for Crohn's patients because of concerns that the pouch itself may develop active Crohn's disease, as well as a lack of long-term outcome data, said Dr. Melton of the Cleveland Clinic Foundation.

Dr. Melton reported on 204 Crohn's disease patients who underwent IPAA at the Cleveland Clinic. Just how cautious and selective the clinic's surgeons are is evident from the fact that these 204 were the only Crohn's disease patients in the clinic's database of nearly 2,900 inflammatory bowel disease patients on whom the procedure was performed.

Moreover, only 10% of the 204 patients were known to have Crohn's disease at the time IPAA was scheduled. Another 47% were diagnosed with Crohn's disease immediately after surgery, based on surgical pathology, while in 43% the diagnosis was delayed a median of 3 months postoperatively.

The overall 10-year pouch retention rate was 71%. It was 85% among patients with known Crohn's disease at the time of IPAA, 87% in those whose Crohn's was diagnosed immediately after surgery, and significantly worse (53%) in those with a delayed diagnosis.

In a multivariate analysis, pouch loss was associated with delayed diagnosis of Crohn's disease, abdominopelvic sepsis, and pouch-vaginal fistula, but not with extraintestinal disease manifestations, smoking, postoperative infliximab or corticosteroid therapy, or preoperative pathology, Dr. Melton said.

At follow-up, patients with pouch retention reported a median of seven bowel movements per day. In all, 72% reported perfect or near-perfect continence, and 68% reported rare or no urgency symptoms.

Postoperative manifestations of Crohn's disease were common. Perianal fistula, pouch-vaginal fistula, IPAA stricture, and pouchitis occurred in 11%-40% of patients without a delayed diagnosis of Crohn's disease and were two- to fourfold more common in those with delayed diagnosis.

Nonetheless, patients with a retained pouch at follow-up rated their quality of life as a median 9 out of a possible 10 and their happiness with the surgery as a 10.

"The functional outcomes aren't as good as for the pouch in ulcerative colitis patients, but one of the take-home messages of this study is that Crohn's patients are perhaps willing in some cases to accept less than perfect outcomes," she said. "These patients—if they retain their pouch—are reporting a happiness with surgery of 10 out of 10."

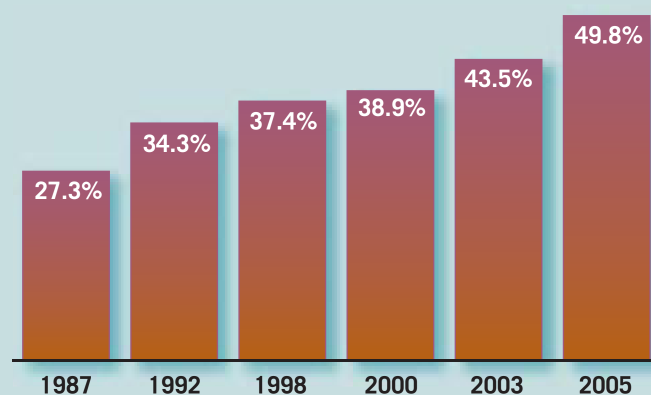
Why do patients with a delayed diagnosis of Crohn's disease do so much worse following IPAA? The answer is unknown, but it's likely they have a phenotypic variant of the disease that, over time, tends to include small-bowel and/or anal involvement, Dr. Melton said.

Audience members were eager to learn whether this study's results will prompt Cleveland Clinic surgeons, who are very experienced with IPAA, to suggest a large-scale broadening of the selection criteria for the procedure.

"We're reluctant to offer it to patients with known Crohn's disease," Dr. Melton replied. Their current selection criteria include Crohn's disease confined to the colon with no anal, perianal, or small bowel involvement; stable disease for several years; and a thorough patient understanding of the risks of recurrence. ■

DATA WATCH

Percentage of Adults Aged 50 and Older Who Have Ever Had a Colonoscopy Is Rising



Source: Centers for Disease Control and Prevention

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