Closer Look Reassuring on Tegaserod's Safety

All 13 events in 11,614 patients occurred among those who were at an increased cardiovascular risk.

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 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, Salt Lake City, and associate chief of cardiology at LDS Hospital, also 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 sex with 15,618 untreated controls. 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 3/1,000 person-years in both groups—were actually lower than the expected rate of about 5/1,000 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.

The results suggest that observations of cardiovascular events with tegaserod may be due to chance.

DR. ANDERSON

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. ■

DNA-Based Colon Cancer Screening Assay Hits 80% Sensitivity

BY MITCHEL L. ZOLER
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PHILADELPHIA — A newly available, noninvasive screening test for colorectal cancer based on detecting a cancer-specific form of DNA had a sensitivity and specificity of greater than 80% in studies with a total of 363 people.

The indication for this screening test, known as ColoSure, is "people who refuse to have a colonoscopy," Dr. Sanford Markowitz said at a conference sponsored by the American Association for Cancer Research.

"If we use this test, it has the potential to substantially lower the morbidity and mortality from colon cancer," said Dr. Markowitz, a professor of cancer genetics at Case Western Reserve University in Cleveland.

The new genetic test is "lousy, compared with colonoscopy" as a screen for colon cancer, Dr. Markowitz noted, but many Americans older than age 50 years avoid colonoscopy screening despite the many guidelines that promote it. The new test is a better alternative than fecal occult blood testing (FOBT), he said.

Although a head-to-head comparison between the ColoSure test, which also involves testing a stool specimen, and FOBT has not yet been done, ColoSure was significantly more sensitive than a first-generation genetic-based stool test, PreGen-Plus; PreGen-Plus was previously shown to be significantly better than FOBT (N. Engl. J. Med. 2004;351:2704-14). This pair of findings is highly suggestive that when a head-to-head study is eventually done, ColoSure will prove to be more sensitive than FOBT, Dr. Markowitz said.

Marketing of the ColoSure test, made by Exact Sciences Corp., began last July. The test is offered by two companies: Laboratory Corporation of America (LabCorp), which requires a physician's prescription and charges about $240 as the retail price; and by DNA Direct, which charges $399 for the test but will accept specimens directly from patients without a physician's involvement. The test is licensed by Case Western Reserve University, and Dr. Markowitz and his associates who developed the test receive royalty payments through Case Western.

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DR. MARKOWITZ

Although Medicare coverage for the screen was still pending in late September, colorectal cancer–screening guidelines published in May by the American Cancer Society, the U.S. Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology said that "there now are sufficient data to include sDNA [stool DNA] as an acceptable option for CRC [colorectal cancer] screening" (CA Cancer J. Clin. 2008;58:130-60).

The ColoSure test is based on finding a hypermethylated form of the gene that codes for vimentin, a filament protein that helps form cell structure. This hypermethylated form of the gene that's been found in roughly 80% of colorectal cancers probably has no direct relevance to the pathogenic process that results in colon cancer. "It's a marker that is probably downstream from cancer-causing changes," Dr. Markowitz said in an interview.

The screening test requires that patients send the testing laboratory a complete bowel movement with at least 36 g of stool. Immediately after the specimen is collected it is treated and stored in a preservative solution that aids in maintaining the DNA content of the specimen. Once in the preservative solution, the specimen can be stored and shipped at room temperature.

Evidence for the efficacy of the stool test based on the vimentin gene was published online by Dr. Markowitz and his associates in August. They reported results from a two-phase study that involved 82 people aged 50 years or older who were known to have colorectal cancer based on a recent coloscopy examination, and 281 people who were free of colorectal cancer based on a recent screening colonoscopy.

The sensitivity of the ColoSure test in combined results from both phases of the study was 83%, and the specificity was 82% (Am. J. Gastroenterol. 2008 Aug. 27 [doi:10.1111/j.1572-0241.2008.02088.x]). Sensitivity levels were similar regardless of tumor stage or location in the colon.

In the paper, Dr. Markowitz and his associates also said that the false positives they found in the study may actually represent early detection of neoplasia before it becomes visible on colonoscopy. Although this notion will require confirmation, they suggested that if an apparently false-positive result from stool-DNA testing is encountered in clinical practice, then the patient may need repeat screening by the stool-based test or by colonoscopy sooner than the generally recommended screening interval.

Work is also underway to find one or more additional DNA-based screening markers that could be added to the hypermethylated vimentin gene to boost the sensitivity of the DNA-based screen closer to 100%. Dr. Markowitz said he was optimistic that useful, additional markers will be found. ■