FDA Says Bisphosphonates Not Tied to Atrial Fib

BY ELIZABETH MECHCATIE
Senior Writer

The Food and Drug Administration's safety review of bisphosphonates has not found a clear association between treatment with a bisphosphonate and atrial fibrillation.

"Based on the data available at this time, health care professionals should not alter their prescribing patterns for bisphosphonates and patients should not stop taking their bisphosphonate medication," the FDA stated on its MedWatch Web site.

The review compared data on 19,687 patients treated with a bisphosphonate with 18,358 patients who received placebo, who were followed from 6 months up to 3 years. These data, from the manufacturers of alendronate, ibandronate, risedronate, and zoledronic acid, were provided at the FDA's request in October 2007, after concerns about a possible association between bisphosphonates and an increased risk for serious atrial fibrillation were raised in a study and letter published 5 months earlier in the New England Journal of Medicine (2007;356:1809-22; 2007;356:1895-6).

The review found that cases of atrial fibrillation were "rare," with two or fewer cases reported in most of the studies. The absolute difference in rates of atrial fibrillation between each bisphosphonate and placebo arm ranged from 0 to 3 cases/1,000 people, according to the FDA.

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In a large zoledronic acid study, however, the rate of serious atrial fibrillation cases was significantly higher among treated patients. But "across all studies, no clear association between overall bisphosphonate exposure and rate of serious or nonserious atrial fibrillation was observed," the FDA statement said. In addition, increasing the dose or duration of treatment was not associated with an increased rate of atrial fibrillation. (The label for zoledronic acid, given intravenously once a year for osteoporosis, includes information about the increased risk for serious atrial fibrillation.)

The statement said that the FDA is aware of "discordant results" from the literature and epidemiologic studies of the incidence and clinical course of atrial fibrillation in patients taking bisphosphonates and is "exploring the feasibility of conducting additional epidemiologic studies to examine this issue." The FDA also continues to monitor postmarketing reports of atrial fibrillation in people treated with bisphosphonates, which are approved for treating osteoporosis, Paget disease, and some cancer-related indications.

In the 2007 studies, 1.3% of the women on Reclast and 1.5% of those on Fosamax developed serious atrial fibrillation (life threatening or resulting in hospitalization), compared with 0.5% and 1.0%, respectively, of those on placebo. When combined, rates of serious and nonserious cases of atrial fibrillation were not significantly different in the treatment and placebo groups. The patients were women aged 65-89 years with osteoporosis.

The bisphosphonates approved by the FDA are alendronate (Fosamax, Fosamax plus D), etidronate (Didronel), ibandronate (Boniva), pamidronate (Aredia), risedronate (Actonel, Actonel with calcium), tiludronate (Skelid), and zoledronic acid (Reclast, Zometa). ■

The FDA statement is available at www.fda.gov/medwatch/safety/2008/safety08.htm#bisphosphonates2. Serious or unexpected adverse events associated with bisphosphonates can be reported to the FDA's MedWatch program at 800-332-1088 or www.fda.gov/MedWatch/report.htm.

Closer Look at Cardiovascular Risk Of IBS Drug Tegaserod Reassuring

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 said at the annual congress of the European Society of Cardiology.

The prior observation of an increase in cardiovascular events 'may be due to chance rather than causal.'

DR. ANDERSON

The FDA approved tegaserod, a selective serotonin-4 receptor agonist, in 2002 for treatment of irritable bowel syndrome (IBS) of the constipation-predominant subtype, then later granted an added indication for chronic idiopathic constipation in patients under age 65.

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, versus 1 case in 7,031 placebo-treated controls, said Dr. Anderson, associate chief of cardiology at LDS Hospital in Salt Lake City.

All cases occurred in individuals who had a history of cardiovascular disease or were at increased cardiovascular risk. When Dr. Anderson was asked to conduct a follow-up independent review of the Novartis data, he found 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 nonsignificant difference.

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 of 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 conducted a prospective study free of any industry support.

Using 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. The tegaserod group averaged 38.6 years of age; 94% were women. Therapy duration 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 of cardiac death, acute MI, cerebrovascular event, or hospitalization for unstable angina occurred in 12 tegaserod-treated patients and 54 controls during a mean 2.3 years of follow-up, yielding similar event rates of 0.46% and 0.35%, respectively. The most common events were cerebrovascular accidents, occurring in 10 tegaserod patients and 36 controls. 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 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, said platelet function could be a plausible mechanism of vascular effects for tegaserod.

Dr. Anderson agreed, although such an effect has not yet been found.

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

Merck Trial Confirms Vioxx's CV Toxicity

BY MARY ANN MOON
Contributing Writer

Extended follow-up of patients in the Adenomatous Polyp Prevention on Vioxx trial confirms the initial finding that rofecoxib raises the risks of myocardial infarction and stroke.

"Small numbers prohibit detailed conclusions about when the increased risk begins and ends, but our data are compatible with an early increase in risk that seems to persist for about 1 year after 3 years of treatment," reported Dr. John A. Baron of Dartmouth Medical School, Lebanon, N.H., and associates (Lancet 2008 Oct. 14 [doi: 10.1016/S0140-6736(08)61490-7]).

The APPROVE trial, designed to assess whether rofecoxib (Vioxx) reduced the risk of recurrent colorectal neoplasia, was halted early (in 2004) because the drug appeared to double the risk of cardiovascular toxicity. Rofecoxib was soon withdrawn from the market. The trial, funded by Merck Research Laboratories, was criticized for flaws in its statistical analyses.

Dr. Baron and his associates extended the follow-up to at least 1 year after the drug was discontinued, to further assess rofecoxib's CV toxicity. Follow-up was completed for 1,092 subjects who had taken placebo and 1,074 who had taken rofecoxib.

Thrombotic events occurred in 76 rofecoxib patients and 46 on placebo (overall unadjusted hazard ratio, 1.7). After adjustment for age, sex, aspirin use, and CV risk profile at baseline, the hazard ratio was 1.72 for MI and 2.17 for stroke. Subgroup analyses suggested that rofecoxib particularly affected people already at risk for CV disease, but the data were not conclusive because the number of events was small.

Rofecoxib's cardiovascular toxicity "seems to be a class effect," since other studies have found similar results with different cyclooxygenase-2 inhibitors. Conventional non-aspirin NSAIDs "may share the same toxicity, to the extent that they are COX-2 selective," the investigators added.

"All these drugs are effective analgesic and anti-inflammatory agents, and seem to reduce risks of colorectal neoplasia. But these benefits will have to be weighed against their proven or possible cardiovascular risks in assessing their suitability in various clinical settings," they said.

Dr. Baron received consulting fees from Merck as a member of the trial's steering committee and is a consultant to, and has received research funding, from Bayer. ■