Coxibs Found to Trigger Fewer GI Events in RA

VITALS

Major Finding: In patients with rheumatoid arthritis or osteoarthritis on long-term NSAID treatment, daily celecoxib produced a 0.9% rate of lower gastrointestinal bleeding events, significantly less than the 3.6% rate in patients treated with diclofenac plus omeprazole.

Data Source: Multicenter, randomized trial with 4,484 patients.

Disclosures: The study was sponsored by Pfizer. Dr. Goldstein said that he has received grant support and honoraria from Pfizer. He also disclosed financial relationships with AstraZeneca, TAP, Takeda, Novartis, Pozen, Logical Therapeutics, Procter & Gamble, PLX, Wyeth, Astellas, Amgen, Given, GlaxoSmithKline, and Merck.

BY MITCHEL L. ZOLER

FROM THE ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY

ROME — Daily treatment with a selective cyclo-oxygenase-2 inhibitor triggered significantly fewer lower gastrointestinal adverse events than did a nonsteroidal anti-inflammatory drug plus a proton pump inhibitor, in a randomized trial with more than 4,000 patients.

Results from many studies have already shown that small bowel ulcers, obstruction, perforations, and bleeding can all occur during treatment with a nonsteroidal anti-inflammatory drug, although at a lower rate than in the upper gastrointestinal tract. The new findings "give us an idea of what is the relative risk up and down the gastrointestinal tract," Dr. Jay L. Goldstein said while presenting a poster at the meeting.

"Upper GI tract [adverse events] are still more common, but injury in the small bowel is a real phenomenon. This is the first study to systematically address the issue of these events in a prospective, randomized control trial," said Dr. Goldstein of the University of Illinois at Chicago.

He acknowledged that upper GI bleeds usually have a more acute and dramatic onset, often causing vomiting and even shock, whereas the anemias resulting from the lower GI bleeds in this study had a more insidious course. The lower GI events "are not immediately life threatening, but when you see a drop in hemoglobin, it's a call to action," Dr. Goldstein said in an interview.

CONDOR (Study of Celecoxib or Diclofenac and Omeprazole for Gastrointestinal Safety in High GI Risk Patients With Arthritis) ran at 196 centers in 32 countries during 2005-2009. The study randomized patients expected to need regular NSAID treatment for at least 6 months to either the cyclo-oxygenase-2 inhibitor (coxib) celecoxib at 200 mg b.i.d, or to a slow-release formulation of the nonselective NSAID diclofenac at 75 mg b.i.d. plus the proton pump inhibitor omeprazole at 20 mg once daily. The study was sponsored by Pfizer, which markets celecoxib (Celebrex).

"It makes sense that a proton pump inhibitor will only protect the upper GI tract. The concept was that we wanted to be sure that the patients [in the control arm] had upper GI protection to find out what goes on beyond the upper GI tract," Dr. Goldstein said.

The study's primary end point was the composite incidence of clinically significant events occurring throughout the gastrointestinal tract during the first 6 months of treatment. The investigators confirmed 20 primary end points among 2,238 patients on celecoxib (0.9%), and 81 events among 2,246 patients on diclofenac plus omeprazole (3.6%). The difference in event rates between the two treatment arms was statistically significant. The main driver behind this difference was a higher incidence of patients with a hemoglobin decrease of at least 20 g/L: 15 patients in the celecoxib arm and 77 in the control arm.

These primary results from the trial appeared in an article published simultaneously with Dr. Goldstein's poster report at the meeting (Lancet 2010;376:173-9).

A new analysis that he presented in his poster identified risk factors linked with the increased risk for GI events in CONDOR, including age of 65 or older, which boosted the risk by 40% compared with younger patients; a history of gastritis, which boosted the risk by 50% compared with patients without this history; having rheumatoid arthritis, which raised the risk by 90% compared with osteoarthritis; and a C-reactive protein level at baseline of more than 1 mg/dL, which raised the risk by 50% compared with patients with lower C-reactive protein levels.

"We know that age is a risk factor for upper GI events; now we're suggesting that it's also a risk factor for lower events. And patients with prior GI problems may also be at risk," Dr. Goldstein said. The increased risks linked with RA and elevated C-reactive protein "may be very similar things," reflecting the effect of a chronic, underlying inflammatory disease. "The evidence is split on a role [for RA] in upper GI events. Here we have a clear signal of lower GI sensitivity that warrants further study."

The findings suggest that an otherwise healthy 55-year-old patient with no history of gastritis who needs long-term NSAID treatment would face a relatively low risk for GI bleeds on a nonselective NSAID, Dr. Goldstein said. But in a similar, 65-year-old patient, "I'd use a coxib or add a proton pump inhibitor," he said.

"Our findings show a clear advantage for the coxib, but the question is, is it worth it [the additional cost]? Is it economically feasible?" Dr. Goldstein also stressed that the results from CONDOR do not apply to patients with an elevated cardiovascular risk, including those on a chronic aspirin regimen.

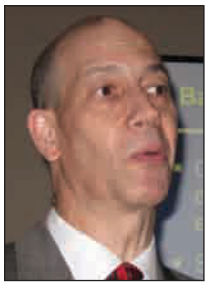
An accompanying editorial agreed that the CONDOR study is "the first large, double-blind, randomized clinical trial to assess upper and lower gastrointestinal events in patients needing chronic NSAID therapy." The editorial authors, Dr. Elham Rahme and Dr. Sasha Bernatsky of McGill University in Montreal, called the 6-month duration of CONDOR "short" and "a drawback" that "hinders extrapolation to long-term treatment. The editorial also called "premature" the suggestion by Dr. Goldstein and his coauthors to revise existing recommendations for selecting NSAID therapy based on CONDOR's results (Lancet 2010;376:146-8). ■

Daily Celecoxib Prevented Osteoarthritis Flares in Study

BY MICHELE G. SULLIVAN

FROM WONCA 2010, THE CONFERENCE OF THE WORLD ORGANIZATION OF FAMILY DOCTORS

CANCUN, MEXICO — Osteoarthritis flares were reduced by 42% in patients who took 200 mg of celecoxib daily, compared with those who took the medication only when they experienced a disease flare, judging from findings from a randomized, placebo-controlled trial.



The continuous users of celecoxib had a mean of 0.54 flares per month, vs. 0.93 flares for the intermittent users.

DR. SANDS

Osteoarthritis patients who took the drug daily were no more likely than intermittent users to have either new-onset hypertension or an aggravation of existing hypertension, Dr. George Sands reported.

"Over the 22-week treatment period, continuous daily celecoxib was more effective in terms of fewer osteoarthritis flares, less pain, and less stiffness than intermittent celecoxib, with no difference in overall adverse effects or in hypertension," said Dr. Sands, senior medical director at Pfizer Inc., which sponsored the study.

The study group comprised 875 patients with hip or knee osteoarthritis. All patients had to be taking a daily NSAID to control their disease. The study had three phases: In phase I, patients stopped their NSAID until they had a flare at their index joint. In phase II, patients with flares received open-label celecoxib until the flare resolved. Phase III consisted of the 22-week randomized, placebo-controlled study. Patients had two study medications, one for daily use and one for use during a flare. Half of the patients (440) received celecoxib every day and a placebo during the flare. The rest of the group (435) received daily placebo and celecoxib during the flare. Treatment continued for 22 weeks.

"Only patients who had resolved flares could be entered into the trial," Dr. Sands said. "This is different from the usual arthritis studies, where they stop their NSAID, get worse, and are treated. In this study, patients were randomized after a successful treatment of a flare."

The patients' mean age was 58 years; 30% were 65 or older. Their mean weight was 83 kg. Most (80%) had knee osteoarthritis; the hip was the affected joint in the remaining 20%. The baseline WOMAC (Western Ontario and McMaster Universities) Osteoarthritis Index score was 25 in both groups. Hypertension was present in 45%. Most of the continuous-use patients (80%) and 74% of the intermittent-use patients completed the trial.

VITALS

Major Finding: Among 875 patients with osteoarthritis, those who took 200 mg of celecoxib every day had significantly fewer flares than those who took the drug only during a flare.

Data Source: A three-phase randomized, placebo-controlled trial.

Disclosures: Pfizer Inc. sponsored the study; the data were reported by Pfizer employee Dr. Sands.

The primary end point was the number of flares occurring during the randomized portion of the study. The median time to first flare was significantly longer in the continuous-use group than in the intermittent-use group (16 days vs. 8 days, respectively). "This is not surprising, since in this part of the study, before anyone had a flare, you were testing celecoxib against placebo," noted Dr. Sands.

By the end of the 22-week treatment period, continuous users had a mean of 0.54 flares per month, significantly fewer than the mean 0.93 flares experienced by the intermittent users. This translates into 42% fewer flares per month, or about two fewer flares per month, Dr. Sands said.

At the end of the treatment period, WOMAC scores were significantly better in the continuous-use group. The change in total WOMAC score was 1.6 in the continuous users vs. 4.99 in the intermittent users.

At the final visit, 23% of the continuous-use group and 11% of the intermittent-use group had been flare free—a significant difference. Adverse events occurred in 57% of the continuous users and 59% of the intermittent users. ■