Celecoxib Triggered Fewer Lower GI Events

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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.

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 in 32 countries.

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, a gastroenterologist and professor of medicine at 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, while 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.

The Study of Celecoxib or Diclofenac and Omeprazole for Gastrointestinal (GI) Safety in High GI Risk Patients With Arthritis (CONDOR) 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. Patient factors associated with a significantly increased risk included 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 rheumatoid arthritis 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 rheumatoid arthritis in upper GI events. Here we have a clear signal of lower GI sensitivity that warrants further study."

The analysis also showed an effect by race, with Hispanics and Asians having a significantly higher risk for GI events than whites. "I wouldn't make much of this until we look further," he said.

But these findings begin to give physicians guidance on which patients need more expensive treatment with a coxib rather than cheaper treatment with a nonselective NSAID plus a proton pump inhibitor.

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?" He said that a cost-effectiveness analysis should address these issues.

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. By design, CONDOR excluded patients on antiplatelet or anticoagulant drugs, including aspirin, and it also excluded patients with ischemic heart disease, heart failure, peripheral arterial disease, and cerebrovascular disease. "I can't comment on what's better for patients with cardiovascular disease. Cardiovascular events were not a significant finding in this trial."

An editorial that accompanied the article published in the Lancet 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 authors of the editorial, Dr. Elham Rahme and Dr. Sasha Bernatsky, from 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).

Dr. Goldstein replied that "it is premature to say [the CONDOR results] are important or unimportant. I'd say that we now have an opportunity to understand the importance" of lower GI events in patients on long-term NSAID treatment. ■

Data Lacking on Best Approach for Rotator Cuff Tears

BY SHARON WORCESTER

FROM ANNALS OF INTERNAL MEDICINE

Both operative and nonoperative approaches to the management of rotator cuff tears appear to result in substantial improvement, but a paucity of data from well-constructed studies means that no firm conclusions can be made about the best approach or the optimal overall management of the condition, according to authors of a meta-analysis of data from 137 studies.

The review showed that the benefits of being treated for a rotator cuff appear to outweigh the risks and that patients experience substantial improvement across all interventions.

Few differences of clinical importance were apparent in studies that compared interventions, and complications—most of which were not clinically important—occurred only rarely, reported Jennifer C. Seida of the University of Alberta, Edmonton, and her colleagues.

The authors searched 12 electronic databases, grey literature, trial registries, and reference lists to identify controlled and uncontrolled studies conducted between January 1990 and September 2009 that assessed the management of rotator cuff tears in adults.

All trials included in the meta-analysis were rated by a reviewer as having high risk of bias, and cohort and uncontrolled studies were, on average, rated as being of moderate quality.

No differences in reported functional outcomes were found in studies comparing open and mini-open repairs, mini-open and arthroscopic repairs, arthroscopic repairs with or without acromioplasty, and single- or double-row fixation.

However, earlier return to work occurred with mini-open compared with open repair; and with continuous passive motion plus physical therapy compared with physical therapy alone. Greater improvement in function was seen with open repairs compared with arthroscopic debridement, they said.

Still, they characterized the available evidence as limited and frequently low in quality across all interventions.

The lack of data on the best approach to management leaves physicians and patients uncertain about when nonoperative approaches should be aborted in favor of surgery, so future research should focus on comparing early with delayed surgical repair, they said.

"Investigators should use a streamlined approach in evaluating operative treatments, beginning with broad treatment questions before focusing on detailed procedures," they wrote, adding that a comparative study design and appropriate confirmation of the diagnosis of rotator cuff are important.

Researchers should provide detailed reporting of study methodology and interventions to allow for appropriate interpretation of the results and for replication of treatments, the authors said.

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