

Celecoxib Shown Safer Than NSAIDs in Osteoarthritis

The COX-2 inhibitor was as effective as naproxen and diclofenac, while causing fewer upper GI events.

BY DOUG BRUNK
San Diego Bureau

Celecoxib is just as effective as naproxen and diclofenac for treating osteoarthritis, but it causes significantly fewer serious upper gastrointestinal events, compared with the other agents, according to data from a large international study.

The finding “shows conclusively that celecoxib does reduce the risk of upper GI complications, compared to conventional NSAIDs,” the study’s lead author, Dr. Gurkirpal Singh, said. “Up until now managed care has been saying there is no evidence in a randomized, clinical trial that celecoxib is better than NSAIDs in reducing GI bleeding. But here it is; these are level 1 data that conclusively prove that.”

However, Dr. Brennan M.R. Spiegel noted that while the difference favoring celecoxib reached statistical significance in the study, the actual difference was a matter of 1 patient per 100 patient-years, which “is a tiny difference that to me is not enough to warrant spending as much money as we do on COX-2 inhibitors,” said Dr. Spiegel, of the division of digestive diseases at the University of California, Los Angeles.

He added that the study is “notable because it’s very large, [but] I believed it before that GI events are less common with

coxibs than with NSAIDs. I didn’t need another study to demonstrate that.”

In a trial called the Successive Celecoxib Efficacy and Safety Study-1 (SUCCESS-1), Dr. Gurkirpal and his associates randomly assigned 13,194 osteoarthritis patients from 39 countries to double-blinded treatment with celecoxib 100 mg b.i.d., celecoxib 200 mg b.i.d., or nonselective NSAID therapy for 12 weeks. The NSAID therapy consisted of diclofenac 50 mg b.i.d. or naproxen 500 mg b.i.d. (Am. J. Med. 2006; 119:255-66).

Patients with a history of two or more episodes of active peptic ulceration were excluded from the study, as were those with gastrointestinal bleeding or recurrent gastric or duodenal ulcers and those with an esophageal, gastric, or duodenal ulcer within a month prior to randomization. Patients with active gastrointestinal disease or any condition that required NSAID therapy were also excluded from the study.

The mean age of study participants was 62 years, 76% were women, and 80% were white, reported Dr. Singh, of the division of gastroenterology and hepatology in



the department of medicine at Stanford (Calif.) University. The mean duration of osteoarthritis was 8 years.

Instruments used to measure efficacy included the Patient’s Assessment of Arthritis Pain-Visual Analog Scale, Patients’ Global Assessment of Arthritis, and the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index. Serious GI events were evaluated by two independent committees that were blinded to patient randomization.

The researchers reported that the primary efficacy measures for both doses of celecoxib were equally effective as the NSAIDs in treating osteoarthritis.

There were 37 confirmed upper GI events: 19 in the patients who took the NSAIDs and 18 in the patients who took celecoxib. That translated into a rate of 2.1 per 100 patient-years for patients who took the NSAIDs vs. a rate of 1.0 per 100 patient-years for those who took celecoxib. The difference was statistically significant with a P value of .023.

A key limitation of the study, Dr. Singh said, is the fact that it was not powered to detect differences in terms of cardiovascular adverse events. “So we can’t make any conclusion about that,” he said. “We did not see any statistically significant dif-

ferences [between treatment groups], but at the time the study was designed, [concerns about COX-2 inhibitors and risk of] myocardial infarction were not an issue, so that’s not something we followed.”

To tease that information out, he added, “you’d need a larger study over a longer period of time, perhaps in a high-risk population that has had myocardial infarction. I’d probably want to do it for at least 2 years.”

Dr. Spiegel said that the current standard of care for older patients with osteoarthritis has “overtaken” the overall impact of the SUCCESS-1 study findings.

“The reality is that people are moving to adding a proton pump inhibitor to an NSAID when [osteoarthritis] patients exceed the age of 65 or if they’re put on aspirin,” he said. “They’re not moving to COX-2 inhibitor, and this study doesn’t give me any more reason to put someone on a COX-2 inhibitor as opposed to just adding a PPI to an NSAID, which is overall a cheaper thing to do. [That approach] is more relevant because it’s cheaper, it’s cost effective, and there’s no risk of MI as there is with COX-2 inhibitors. In fact, there’s less overall dyspepsia in patients who are on an NSAID plus a PPI, compared to [those on] a COX-2 inhibitor.”

Dr. Singh disclosed that he received research support from Searle Pharmaceuticals, Pharmacia, Pfizer, Merck & Co., Boehringer Ingelheim, TAP Pharmaceuticals, Wyeth, Altana Pharma, Glaxo-SmithKline, Novartis Pharmaceuticals Corp., and Centocor Inc. ■

Glucocorticoid Use May Elevate Tuberculosis Risk Fivefold

BY KERRI WACHTER
Senior Writer

Patients currently taking a glucocorticoid have nearly a fivefold increased risk of developing tuberculosis that is independent of other risk factors.

“Our results suggest that glucocorticoid use is associated with a substantially increased risk of developing tuberculosis and that the risk increases with increasing daily dose,” said Susan S. Jick, Sc.D., of Boston University, and her colleagues.

Although chronic corticosteroid use is common among patients with rheumatic diseases, the number of such patients in the study population was too small to say definitely whether use of corticosteroids specifically for arthritis and other rheumatic diseases was associated with an increased risk for TB.

Low body mass index (BMI), diabetes, current smoking, and obstructive pulmonary disorders were also determined to be important risk factors for tuberculosis in a review of 497 new cases of tuberculosis and 1,966 matched controls during the period 1990-2001 (Arthritis Rheum. 2006;55:19-26).

The researchers based their study on data available from the U.K.-based General Practice Research Database. Patients were included if they had a first-time diagnosis of tuberculosis followed by treatment with at least three different antituberculosis medications and if treatment lasted at least 6 months. As many as four control subjects were matched to each patient based on age, gender, the practice attended, and the patient’s index date along with the control’s visit to the practice that corresponded in time to the patient’s index visit.

Assessment of glucocorticoid use was based on prescription data. Patients were classified as currently exposed

if they had received a prescription for any oral glucocorticoid and if the supply had lasted until within 120 days prior to the index date. Recent exposure was defined as use that ended 121-180 days before the index date. All other use more than 180 days prior was considered past use.

The researchers also assessed current exposure to antirheumatic drugs or immunosuppressants and the presence of pulmonary disorders, rheumatic disorders, inflammatory bowel diseases, dermatitis, silicosis, renal failure, gastrectomy, and jejunoileal bypass surgery (diagnosed prior to the index date).

Patients currently using corticosteroids were 4.9 times more likely to develop tuberculosis than were nonusers, even after adjusting for the effects of BMI, smoking, disease-modifying antirheumatic drug use, and history of diabetes and pulmonary disease. The risk for tuberculosis remained elevated (OR 4.3) in patients who had recently stopped using corticosteroids.

First-time users were 3.2 times more likely to get tuberculosis than were never users. Patients with longer-term use, extending over two to nine consecutive prescriptions, saw their risk increase sevenfold.

The effect of corticosteroid use on risk for TB increased with increasing dose. The OR was 2.3 in people taking daily doses of prednisone equivalents less than 7.5 mg daily (physiologic) versus those taking supraphysiologic doses of 7.5 mg or more daily (OR 7.0, based on the highest daily dosage received by current users).

Both the American Thoracic Society and the Centers for Disease Control and Prevention agree that more than 15 mg/day of prednisone or its equivalent administered for 1 month or longer is a risk factor for tuberculosis. In light of this, the researchers evaluated the impact of daily dosage using this cutoff. The adjusted odds ratio was 2.8 for those using less than 15 mg of prednisone

equivalents per day, while those using 15 mg of prednisone equivalents per day or more had an adjusted odds ratio of 7.7.

“We found that current smoking was associated with a 60% increased risk of tuberculosis. . . . Although this effect is relatively low, because smoking is prevalent in this study population 17% of all cases are attributable to smoking compared with only 8% of cases attributable to glucocorticoid use in this population,” the researchers said. Those with a BMI less than 20 kg/m² also had an elevated risk (OR 2.8), while those with a BMI greater than 25 had an odds ratio of 0.5, compared with patients with a BMI of 20-25.

Prior pulmonary diagnoses were also associated with an increased risk of tuberculosis that was independent of other risk factors. A diagnosis of rheumatic disease and use of antirheumatic agents are purported to be risk factors for tuberculosis as well.

However, the number of patients taking antirheumatic drugs in this analysis was low—only 12 patients were currently exposed. Overall 17 participants (cases and controls) had rheumatoid arthritis, 1 had lupus, 12 had polymyalgia rheumatica, and 7 had arteritis. “Despite the large number of tuberculosis cases in this study, the prevalence of antirheumatic agent use was low . . . and therefore the independent effects for patients taking antirheumatic agents could not be reliably evaluated,” the researchers said.

In an accompanying editorial, Dr. Loreto Carmona observed that “the truth is that the report says little about the risk of TB in patients with rheumatic disease who are treated with glucocorticoids” (Arthritis Rheum. 2005;55:1-2). Dr. Carmona heads the research unit of the Spanish Foundation of Rheumatology in Madrid. It’s unclear how much of the risk of tuberculosis is due to rheumatic diseases—for which corticoids are taken—and how much is due to the glucocorticoids. ■