

Aspirin May Cut Thrombus Risk in COX-2 Users

On the negative side, daily aspirin may increase the likelihood for GI bleeding in patients on NSAIDs.

BY BRUCE JANCIN
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AMSTERDAM — Concomitant aspirin use may fully reverse the increased atherothrombotic risk associated with cyclooxygenase-2 selective NSAIDs, Dr. Gurkirpal Singh reported at the annual European Congress of Rheumatology.

In addition, aspirin may also reduce—albeit only partially in some instances—the cardiovascular risk conferred by most traditional nonselective NSAIDs, said Dr. Singh of Stanford (Calif.) University.

Although these findings from a large case-control study provide insight into the mechanism by which NSAIDs increase cardiovascular risk, he stressed that adding a daily aspirin in order to mitigate that cardiovascular risk is not a practical solution for arthritis patients seeking pain relief. That's because there is some evidence that concomitant use of aspirin and NSAIDs, whether COX-2 selective or not, appears to magnify the risk of NSAID-associated GI bleeding, he said.

Dr. Singh utilized the California Medicare database to identify all adults

with rheumatoid arthritis or osteoarthritis treated with a COX-2 selective or non-selective NSAID from 1999 through the first half of 2004.

During nearly 2.4 million patient-years of follow-up, 15,343 arthritis patients experienced an acute MI, 8% of which were fatal. Each MI patient was matched to four controls.

The adjusted relative risk of MI was increased by 31% in patients being treated with rofecoxib

and by 12% in patients being treated with celecoxib, compared with the rate in remote users of any NSAID. Both differences were significant.

The MI risk was also increased by 65% in current users of indomethacin, by 52% with meloxicam, and by 47% with sulindac, but was not significantly elevated in current ibuprofen users.

Concurrent use of aspirin completely reversed the increased MI risk associated with rofecoxib, celecoxib, meloxicam, and

sulindac. However, the increased risk in current users of indomethacin was only partially and nonsignificantly reduced, such that patients on concomitant aspirin and indomethacin still had a 20% increased risk, he explained.

In a separate presentation, Dr. Steven B. Abramson said he thought Dr. Singh's findings make a lot of sense. "My instincts are that there will be some cardioprotection be-

cause you're getting 24-hour inhibition of platelets with a single aspirin," added Dr. Abramson, professor of medicine and associate dean for clinical research at New York University.

Concurrent use of aspirin acted to reverse the increased MI risk associated with some COX-2s.

DR. SINGH



It has been shown that 500 mg of naproxen provides good platelet inhibition for close to 12 hours. Moreover, a recent large meta-analysis of trials comparing COX-2 inhibitors with nonselective NSAIDs, or drugs in either class with placebo, showed that while the COX-2 inhibitors were associated with a 42% relative increase in MIs and other vascular events relative to placebo, a comparable risk was present in patients on high doses of traditional

NSAIDs—except for those on naproxen at 500 mg b.i.d.

The metaanalysis, led by investigators at the University of Oxford, involved roughly 145,000 patients in 138 randomized trials, including some unpublished ones on file with manufacturers (BMJ 2006;332:1302-8).

"It still remains uncertain whether naproxen is cardioprotective, but it probably is at 500 mg twice per day," Dr. Abramson said. He was quick to add, however, that this will have to be shown in prospective clinical trials before the FDA would consider removing the warning of increased cardiovascular risk from naproxen's label, a warning currently applied to all COX-2 selective and traditional NSAIDs.

Dr. Abramson, who was a member of the FDA's special advisory panel on the COX-2 inhibitors' cardiovascular risk, criticized the European Union drug regulatory agency for limiting the label warning of increased cardiovascular risk to the COX-2 inhibitors. The available evidence, he said, strongly suggests the same risk applies to nonselective NSAIDs, with the likely exception of high-dose naproxen. He is concerned that this labeling may give many European physicians and patients a false sense of security about treatment with traditional NSAIDs. ■

Serum Urate Levels Kept Low

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"Maintaining serum urate at that level of less than 6 mg/dL looks like it's going to be able to resorb tophi," observed Dr. Schumacher, professor of medicine at the University of Pennsylvania and director of rheumatology at the Veterans Affairs Medical Center, Philadelphia.

Food and Drug Administration approval of febuxostat is expected imminently. The drug should be on pharmacy shelves later this year, according to Dr. Schumacher. If so, it would be the first new drug approved for gout in 40 years.

FOCUS participants started on once-daily febuxostat at 80 mg. During weeks 4-24 they were allowed to titrate to 40 or 120 mg/day in an effort to maintain serum urate levels in the target range or to address adverse reactions. Patients remained on their week-28 dose for the rest of the 4 years.

The majority of patients reduced their serum urate level to below 6 mg/dL—the generally accepted saturation point, and a level at which crystals would be expected to dissolve—within 7 days. The proportion of patients with a serum urate level below 6 mg/dL climbed from 78% at year 1 to 90% at year 4. Even among the handful of patients on 40 mg/day, which isn't expected to be a recommended dose, 86% had a serum urate below 6 mg/dL.

However, nobody on 40 mg/day got their serum urate level to less than 4 mg/dL, a range in which tophi

dissolve more rapidly. In contrast, 30% of patients on 80 or 120 mg of febuxostat once daily had serum urate levels consistently falling below 4 mg/dL.

The mean number of gout flares per year declined sharply over time: an average of 2.22 in year 1, 0.44 in year 2, 0.26 in year 3, and 0.18 in year 4.

Prophylaxis against gout flares was provided by concomitant colchicine at 6 mg/day for the first 4 weeks of FOCUS. Upon discontinuation of the drug, however, the flare rate temporarily went up. This suggests that maintaining prophylaxis for longer than 4 weeks is warranted in clinical practice, Dr. Schumacher said.

Allopurinol, the only FDA-approved serum urate-lowering drug, is a problematic agent with numerous side effects, particularly in patients with renal insufficiency, a common comorbidity. Several studies have demonstrated that patient compliance with allopurinol is "abysmal," he said.

Fifty-five patients quit FOCUS, most due to disenchantment with the paperwork and frequent office visits.

No serious adverse events were attributed to febuxostat. The most common adverse event was transient, mild to moderate elevation of liver function test results. This occurred in 14 patients; however, 3 were alcohol abusers and 9 others were on concomitant medications having hepatotoxic effects, including acetaminophen, colchicine, and NSAIDs. ■

No Uptick Seen in Visits to MD After Diagnosis of Fibromyalgia

BY BRUCE JANCIN
Denver Bureau

AMSTERDAM — The diagnosis of fibromyalgia is not followed by a surge in physician office visits, according to Dr. Ernest H.S. Choy, speaking at the annual European Congress of Rheumatology.

A recent study using data from the U.K. General Practice Research Database, led by Dr. Simon Wessely, a King's College psychiatrist, compared health care utilization from 10 years before through 4 years after diagnosis of fibromyalgia in 2,260 patients and a group of age- and gender-matched controls, said Dr. Choy, of King's College London.

The investigators found that the rates of office visits, prescriptions, and medical tests were markedly higher and rising in the years prior to diagnosis in fibromyalgia patients, compared with control patients.

In the year prior to diagnosis, patients averaged 25 office visits and received 11 prescriptions, compared with 12 office visits and 4.5 prescriptions during the same year for controls. The most common reason for pre-diagnosis office visits by fibromyalgia patients was depression, followed by fatigue, chest pain, headache, and disrupted sleep.

Diagnosis of fibromyalgia was not followed by a surge in illness behavior and health care utilization. In fact, health care utilization declined for 2-3 years following the diagnosis before climbing back up, probably because the patients were not getting effective treatment, according to the investigators (Arthritis Rheum. 2006;54:177-83).

"Patients demand less tests and have less consultations after the diagnosis is made," Dr. Choy commented.

Fibromyalgia is a high-cost medical condition, he noted. A classic University of Kansas 7-year prospective study determined that the mean annual per-patient cost was \$2,274 in 1996 dollars. "That is a phenomenal cost. It's comparable to inflammatory arthritis. These patients are consuming a vast amount of health care resources," he said at the congress sponsored by the European League Against Rheumatism (EULAR).

Another recent large observational study undercuts claims that fibromyalgia is simply part of a single larger, ill-defined somatization disorder that also includes conditions like chronic fatigue syndrome, irritable bowel syndrome, and regional pain disorders. This study involved 18,122 U.K. patients diagnosed by their primary care physician as having a fatigue syndrome during 1988-2001.

The key finding was that outcomes differed significantly for patients with various diagnostic labels, being best for those with postviral fatigue syndrome, worst for myalgic encephalomyelitis and chronic fatigue syndrome, and intermediate for those with fibromyalgia (Fam. Pract. 2005;22:383-8).

As for treatment options, Dr. Choy presented new EULAR evidence-based recommendations for fibromyalgia management. The recommendations, to be published later this year, identified a number of interventions with what he termed "moderate to good" effectiveness, including drugs, exercise, and cognitive-behavioral therapy. ■