Also May Reflect Therapeutic Response

Progression *from page 1*

(PIIANP) and the urinary excretion of cross-linked C-telopeptide (CTX-II) are associated with disease progression. To investigate the longitudinal changes of these measures and their relationships with radiologic progression, Dr. Garnero and coinvestigators at the University of Bristol in England followed 84 patients with early osteoarthritis in one or both knees for 5 years. All of the patients, mean age 62 years, had experienced persistent pain in one or both knees for more than 3 months, and 39% presented with a Kellgren-Lawrence score of less than 2.

'These collagen biomarkers may offer a more consistent, sensitive method for determining which patients are at greatest risk for progression.'

Using specific ELISA assays, the investigators measured each patient's PIIANP and CTX-II levels and obtained knee radiographs at baseline and at 2, 3, and 5 years. The radiographs were read by two independent readers. "Of interest," said Dr. Garnero, independent readings showed that "about 60% of the patients had Kellgren-Lawrence scores lower than 2 and about 42% had scores below zero, suggesting a large proportion of this cohort had very early disease."

For the study, "we defined disease progression as either a reduction in the tibiofemoral joint space by at least 2 millimeters or total replacement of either knee during the 5-year follow up," Dr. Garnero said. Based on these criteria, 24 had progressive disease and 60 did not.

In the overall cohort there was a "slight but significant" mean PIIANP increase of 1.6% per year and no increase in urinary CTX-II levels during the 5-year follow up, said Dr. Garnero. When patients with and without progressive disease were considered independently, however, there were substantial differences. "Both measures were significantly higher throughout the study in the 24 patients with progressive disease compared with the remaining 60 patients," said Dr. Garnero. Even so, he noted, "we could not differentiate the two groups according to x-ray measurements," suggesting that detectable biomarker changes precede radiologic progression.

When classified by quartile of mean 5-year levels for both PIIANP and CTX-II measures, patients in the highest quartile of PIIANP and in the two highest quartiles for CTX-II were associated with increased risk for progression, said Dr. Garnero. The odds ratio for increased progression risk for the highest quartile PIIANP measures alone and the two highest quartiles for CTX-II measures alone were 3.2 and 3.4, respectively, compared with 11.8 for the combination of both markers.

The sensitivity and specificity of the PIIANP top quartile alone were 42% and 82%, respectively, compared with 71% and 58% for the CTX-II top two quartiles. "Combined, the sensitivity and specificity for both markers was 92% and 52%, respectively," said Dr. Garnero. Because progression of joint damage likely results primarily from an imbalance between degradation and reparative processes, "combining these two markers is more effective in predicting progression than the measurement of a single marker," he said.

Predicting progression in osteoarthritis is notoriously difficult "because the outcomes vary substantially from patient to patient even if other considerations are the same," said Dr. Garnero. "Measuring these collagen biomarkers may offer a more consistent, sensitive method for determining which patients are at greatest risk for progression, and it may be useful for monitoring response to treatment."

Because the investigation included a relatively small number of patients overall, "the number of patients identified with progressive disease was quite low, and thus the findings need to be validated in a larger study," Dr. Garnero said. ■

COX-2 Inhibitors Found No Safer Than NSAIDs for GI

Cyclooxygenase-2 inhibitors were found to be no safer than nonselective NSAIDs in averting adverse gastrointestinal events in a large observational study conducted in the United Kingdom.

The finding is important "given that enhanced gastrointestinal safety has been one of the main justifications for these drugs," wrote Dr. Julia Hippisley-Cox and her associates at the University of Nottingham (England). The COX-2 inhibitors were developed to relieve pain without inducing the GI side effects common with NSAIDs, but long-term safety data are lacking.

The researchers calculated the risk of GI events in patients who took these prescription pain relievers between 2000 and 2004. After reviewing the medical records in a database of more than 7 million patients treated at general practices throughout England, Scotland, and Wales, the investigators identified 9,407 who had an adverse GI event and matched them with more than 88,000 controls who had no such events (BMJ 2005;331:1310-6).

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Patients with GI events were more likely to have taken either prescription NSAIDs (odds ratio 1.69) or prescription COX-2 inhibitors (odds ratio 1.89) than were control subjects.

The researchers also found that the concomitant use of ulcer-healing drugs reduces the GI risks of COX-2 inhibitors, which suggests "that there is some risk to protect against." Taken together, these results indicate that COX-2 inhibitors "may not be as safe as originally thought," the authors said.

Celecoxib was the only agent out of 27 pain relievers used by the study subjects to show no link with adverse GI events. However, the number of celecoxib users was very small, so this finding remains "difficult to interpret," the researchers noted.

The use of ulcer-healing drugs such as proton pump inhibitors reduced the risk for GI events in users of both COX-2 inhibitors and NSAIDs, again suggesting that the GI risks of the two types of pain relievers are similar, they added.

—Mary Ann Moon

New & Approved

Orencia, Boniva Injection

BY ELIZABETH MECHCATIE, SENIOR WRITER

Orencia

(abatacept, Bristol-Meyers Squibb)

A novel biologic agent that inhibits activation of T cells, for reducing signs and symptoms, inducing major clinical response, slowing progression of structural damage, and improving physical function in adults with moderately to severely active rheumatoid arthritis (RA) and an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs), such as methotrexate or tumor necrosis factor (TNF) antagonists.

▶ **Recommended Dosage:** IV infusion over 30 minutes at a weight-based dose at 0, 2, and 4 weeks, then every 4 weeks thereafter.

▶ **Special Considerations:** Orencia may be used as monotherapy or with DMARDs. Although Orencia works differently than do TNF antagonists, it should not be used with those agents. In studies, rates of infection and serious infection were greater in patients on Orencia and a TNF antagonist than in those on a TNF antagonist alone; there was no evidence that the combination was more effective. In studies, infection was more common with Orencia than with placebo; over a median of 12 months, the overall rate of malignancy was similar with Orencia and placebo. In patients with chronic obstructive pulmonary disease, adverse events were greater with Orencia than with placebo.

▶ **Comment:** Unanimously recommended for approval by the FDA's arthritis advisory panel, Orencia is a recombinant fusion protein that selectively modulates T-cell activation and "affects key mechanisms of inflammation and progressive joint destruction in RA," according to Bristol-Meyers Squibb.

Approval was based on placebo-controlled studies. In one study of over 600 patients with inadequate responses to methotrexate, 73% of those on Orencia and methotrexate had at least a 20% improvement in American College of Rheumatology criteria (ACR 20 response) at 12 months vs. a 40% improvement by those on methotrexate alone. At 12 months, ACR 50 and ACR 70 responses were 48% and 29%, respectively, with Orencia and methotrexate vs. 18% and 6% with methotrexate alone.

Boniva Injection

(ibandronate injection, Hoffmann-La Roche)

An injectable form of the bisphosphonate for treating osteoporosis in postmenopausal women. The first intravenous treatment for osteoporosis, and the third Boniva formulation approved by the FDA.

▶ **Recommended Dosage:** 3 mg administered IV over 15-30 seconds once every 3 months, by a clinician. Daily calcium and vitamin D supplementation necessary.

▶ **Special Considerations:** Overall safety and tolerability of the IV dose was similar to that of the daily oral dose in a trial comparing them, with arthralgia, abdominal pain, and back pain among the most commonly reported side effects. Some patients develop a mild flu-like syndrome after the first injection, which is easily suppressed by aspirin, acetaminophen, or an NSAID, said Dr. Robert Recker, an investigator in the trial. IV bisphosphonates have been associated with renal toxicity, so serum creatinine should be checked before each dose; patients with severe renal impairment should not receive the drug. No cases of acute renal failure were reported in controlled trials. The drug will be available "early this year," according to Roche.

▶ **Comment:** Like other bisphosphonates, Boniva inhibits osteoclast-mediated bone resorption, reducing bone turnover. Approval was based on a study of 1,358 women with postmenopausal osteoporosis; at 1 year, bone mineral density (BMD) of the lumbar spine increased by a mean of 4.5% with IV treatment once every 3 months vs. 3.5% with 2.5 mg of oral Boniva daily, a highly significant difference. Increases in total hip, femoral neck, and trochanter BMD were also greater with IV Boniva. The 2.5-mg daily formulation was shown to reduce the risk of new vertebral fractures over 3 years in studies that led to that formulation's approval, so antifracture efficacy data on IV Boniva were not required for approval.

Bypassing the esophagus and stomach—eliminating the need to sit upright without drinking anything but plain water or eating for 30-60 minutes after taking an oral bisphosphonate to reduce the risk of esophagitis and gastritis—is the most obvious advantage of the IV formulation, said Dr. Recker, director of the Creighton University Osteoporosis Research Center, Omaha, Neb. IV Boniva can also be used by people who cannot swallow well, and having the patient come to the office once every 3 months for an injection ensures compliance, he added. To get the most benefits from the drug, it's important to take a daily absorbable calcium supplement and a vitamin D supplement, said Dr. Recker, a consultant to Roche, and to manufacturers of other osteoporosis therapies. ■