

Celecoxib Plus PPI Protects Against NSAID Ulcers

BY BRUCE JANCIN
Denver Bureau

PARIS — Celecoxib plus a proton pump inhibitor is the superior gastroprotective strategy in patients who require chronic NSAID therapy for analgesia but have had a prior NSAID-associated bleeding ulcer, according to a randomized clinical trial.

The 13-month cumulative incidence of recurrent ulcer bleeding in this trial was 0% in subjects randomized to the combination therapy, compared with 8.9% in controls on celecoxib (Celebrex) plus placebo, Dr. Francis K. Chan said at a satellite symposium held in conjunction with the annual European Congress of Rheumatology.

The study participants were a consecutive series of 441 *Helicobacter pylori*-negative Hong Kong arthritis patients taking nonselective NSAIDs until they were hospitalized for upper GI ulcer bleeding. Randomization to celecoxib 200 mg plus esomeprazole (Nexium) 20 mg, both twice daily, or to celecoxib plus placebo took place after their ulcers healed, explained Dr. Chan, professor of medicine and chief of gastroenterology and hepatology at the Chinese University of Hong Kong.

He observed that, for those physicians who dismiss clinical trials as not reflecting real-world practice, it's worth noting that a marked reduction in the risk of recurrent upper GI bleeding with the combination

of celecoxib and a proton pump inhibitor (PPI) also was documented in a recent case-control study by Dr. Laura L. Targownik and her coworkers at the University of Manitoba, Winnipeg.

The Canadians matched 1,382 patients hospitalized for NSAID-associated upper GI complications to nearly 34,000 controls. They concluded that the combination of celecoxib and a PPI provided gastroprotection superior to a nonselective NSAID plus a PPI, a cyclooxygenase-2 inhibitor alone, or a nonselective NSAID plus misoprostol (*Gastroenterology* 2008;134:937-44).

Results of the Canadian study along with Dr. Chan's published clinical trial (*Lancet* 2007;369:1621-6) suggest a need to

revisit current American College of Rheumatology guidelines for the management of osteoarthritis. The guidelines recommend use of a COX-2 inhibitor or nonselective NSAID plus a PPI in patients at increased risk of ulcers, but these recent studies clearly show that is not adequate protection for the substantial group at very high risk, according to Dr. Chan.

The satellite symposium was supported by Pfizer Inc. Dr. Chan's study was solely supported by the Research Grants Council of Hong Kong, while Dr. Targownik's was supported by the Canadian Institutes of Health Research and the Manitoba Medical Services Foundation. Dr. Chan has received consulting fees from Pfizer. ■

Joint Distraction Eases OA Knee Pain, Enables Cartilage Repair

BY NANCY WALSH
New York Bureau

Joint distraction, a surgical technique that involves the placement of an external fixation frame around a degenerated joint, may offer a means of postponing the need for total knee replacement in young patients with severe osteoarthritis.

The cartilage in end-stage osteoarthritis (OA) is severely damaged, with fissuring; altered chondrocyte distribution and death; and a significant loss of extracellular matrix constituents. These changes in cartilage are accompanied by characteristic changes in periarticular bone and soft tissue. All these structural changes mean severe pain and functional limitations for patients, who typically rate their pain with a score of 80% out of a maximum of 100%, according to Dr. Floris P.J.G. Laféber, of the University Medical Center Utrecht (the Netherlands).

The standard treatment for these patients is total knee replacement, which poses a dilemma for relatively young patients. "Total knee prostheses don't last forever," Dr. Laféber said. "They last on average 15 years, so if you have one placed at age 60 you are likely to need a replacement at 75,

which is complicated and expensive, and the results are often disappointing. And then if you need another at age 90, the difficulties are really serious," he said.

The rationale for joint distraction lies in the hypothesis that osteoarthritic cartilage is capable of self-repair if the joint is unloaded and chondrocyte nutrition is maintained. Pins are drilled through the soft tissue and bone just above and below the joint, and when the frame is in place the distance between the cartilaginous surfaces of the joint is increased by 5 mm. This transfers the load and stresses on cartilage away from the joint, eliminating further wear and tear.

Easing the mechanical stress is only one therapeutic aspect of the process of joint distraction. Springs within the distraction frame cause changes to occur in fluid pressure in the joint, with increases during loading and normalization with unloading. This continuous change in fluid pressure is important for the cartilage, because chondrocytes depend on synovial flow for nutrition, Dr. Laféber explained.

The loading onto the frame also results in periarticular osteopenia, which in turn permits the sclerotic, osteoarthritic bone to become more flexible and the mineral



A patient's knee is shown before treatment (left). At 2 years after joint distraction treatment, the repaired cartilage allows for greater space within the joint.

content to normalize once the frame is removed. Furthermore, the periarticular bone turnover results in the release of multiple growth factors that can help repair the cartilage.

In collaboration with his center's orthopedic department, Dr. Laféber and his colleagues in the department of rheumatology and clinical immunology began exploring this technique in a proof-of-concept study with ankle distraction. Although ankle OA is much less common than knee OA, in the case of failure an arthrodesis could be performed without much risk, he said.

A total of 73 patients underwent ankle distraction for 3 months, with the result that pain scores—rated at an average of 75% of a maximum of 100%—fell to 20%, while scores for function and clinical condition rose from approximately 25% at baseline to 80%. Some of these patients now have been followed for as long as 10 years, with continuing benefits.

The researchers next did a feasibility study that included three patients with knee OA, and found similar results on pain and function scores as well as on stiffness scores. They then undertook a larger prospective study in which 19 patients with severe knee OA (mean age, 48 years) have been treated with 2-month periods of distraction. Thus far, six have been followed for up to 2 years. Functional ability and clinical condition, poor at the onset with scores of 39% and 32%, respectively, increased to 82% and 81%.

Serum and urinary biomarkers of cartilage turnover were measured throughout a 12-month follow-up period. During the distraction phase there was an enormous turnover, with elevations of markers of both synthesis and breakdown, but after

the distraction phase there was a gradual decrease of breakdown markers and a gradual increase in the markers of synthesis, indicating repair of the cartilage, Dr. Laféber said.

Imaging studies also demonstrated improvements. In seven patients who have been followed for more than 12 months, joint space width shown on x-rays increased from slightly greater than 2.5 mm to more than 3.5 mm. "And on MRI studies done after 1 year and read in a blinded fashion in collaboration with Prof. Felix Eckstein, who is one of the leading researchers in this field, the amount of subchondral bone covered with cartilage was shown to have increased by 40%, cartilage volume increased by 50%, and cartilage thickness over the bone increased by 5%," Dr. Laféber said. ■



An external fixation frame is shown here around the degenerative joint.

The Iowa Ankle Experience Compares

Ankle distraction also has been performed and is being evaluated in a randomized study led by Dr. Annunziato Amendola of the University of Iowa, Iowa City.

"We are interested in posttraumatic osteoarthritis of joints, and the ankle in particular," said Dr. Amendola, professor in the department of orthopedics and rehabilitation.

The study, which was funded by the National Institutes of Health, prospectively enrolled about 40 patients with posttraumatic ankle OA. They used the same ankle distraction technique as did Dr. Laféber's group, but patients were randomized to distraction alone or to distraction plus continuous passive joint motion.

"There's lots of evidence indicating

that motion is beneficial to a healing joint," he said. During the course of the study, patients were evaluated clinically and radiographically, and with a special three-dimensional CT scanning technique to look at cartilage regeneration.

All but three patients have now undergone 2- and 3-year evaluations, and the results thus far have been comparable to the results they have had in Utrecht in terms of relief of pain, according to Dr. Amendola. Additional improvements have been seen over time, and patients in the motion group did significantly better at every time point than did the nonmotion group.

"I think this is quite an intriguing technique, and I'm sure you will be hearing more about it in the next few years," Dr. Amendola said.