Anticoagulant Backed After Hip, Knee Surgery

BY ELIZABETH MECHCATIE

ADELPHI, MD. — A federal panel agreed that data on the oral anticoagulant rivaroxaban indicate that the drug's benefits in preventing venous thromboembolic events after hip and knee replacement surgery outweigh its potential risks of excess bleeding and potential risk of severe hepatotoxicity.

At a meeting of the Food and Drug Administration's Cardiovascular and Renal Drugs Advisory Committee, the panel voted 15-2 that data from four clinical trials demonstrated that rivaroxaban has a favorable risk-benefit profile for the proposed indication—the prophylaxis of venous thromboembolism, in patients undergoing hip or knee replacement surgery. The recommended dosage is 10 mg once daily for 35 days (after hip surgery) or 14 days (after knee replacement).

Most of the panelists agreed that potential hepatoxicity should not preclude approval, although long-term data to assess hepatoxicity were critical. Panelists were concerned about off-label use of the drug and emphasized the importance of advising clinicians to avoid prescribing the drug for longer periods and for other uses, and of continuing to follow patients on rivaroxaban in clinical trials and clinical practice for hepatoxicity.

If approved, rivaroxaban, an oral, direct Factor Xa inhibitor manufactured by Johnson & Johnson Pharmaceutical Research & Development LLC, would be the first oral anticoagulant approved for these indications, as well as the first oral anticoagulant approved since warfarin.

The FDA usually follows the recommendations of its advisory panels.

The proposed regimen was compared with enoxaparin in four international studies of more than 12,000 patients (6,183 patients on rivaroxaban) after total hip or knee replacement surgery. Patients with significant liver disease were excluded. In the four studies, the composite end point of venographic evidence of deep-vein thrombosis (DVT), nonfatal pulmonary embolus (PE), or death was significantly lower among those treated with rivaroxaban, but patients on the drug had a higher rate of bleeding. In an analysis of pooled data from the four studies, the major bleeding rate was 0.4% among those on rivaroxaban, compared with 0.2% among those on enoxaparin. The one bleeding-related death in all four studies was in a patient on rivaroxaban.

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There was also a greater number of serious ALT elevations (0.3% vs. 0.2%) among those on rivaroxaban, which was not a significant difference. A composite marker of liver injury—an ALT greater than three times the upper limit of normal with a total bilirubin greater than two times the upper limit of normal—was also more common among those on rivaroxaban (0.15% vs. 0.11%), but this was not a statistically significant difference.

The consumer representative on the panel was Dr. Sidney Wolfe, director of the Public Citizen Health Research Group. He voted no on the risk-benefit question and said he was concerned about the bleeding risk and was "very uncomfortable about the certainty of long-term use and the absence of long-term safety data on hepatoxicity." Because there is no need for a regular blood test, as there is with warfarin, he expects it will be used "massively" for off-label indications for which there are no data.

If approved, Johnson & Johnson plans to market rivaroxaban as Xarelto. ■

Collaborative Care Improves Chronic Pain Outcomes

BY MARY ANN MOON

A collaborative intervention designed to help primary care practitioners improve management of chronic pain was found to be modestly but significantly effective, according to data from a cluster randomized trial.

The intervention resulted in greater use of adjunctive pain medications and treatments, which meant that practitioners were acting in better accordance with guidelines for chronic pain management, said Dr. Steven K. Dobscha of the Portland Center for the Study of Chronic, Comorbid Mental and Physical Disorders at the Portland (Ore.) Veterans Affairs Medical Center and his associates.

The investigators assessed the collaborative intervention in three urban and two rural primary care clinics of the VA medical center. A total of 22 physicians, internal medicine fellows, and nurse practitioners were randomly assigned to provide usual treatment to 214 chronic pain patients, and 20 practitioners were assigned to provide care according to the collaborative intervention to 187 patients.

All patients had a diagnosis of moderate or severe musculoskeletal pain with a median of 10 years' duration, and two-thirds had more than one such diagnosis. The mean patient age was 61 years. Depression, PTSD, and panic attacks were common.

A team including a full-time psychologist care manager and an internist implemented the intervention, which included leading workshops to introduce both clinicians and patients to the intervention, assessing patients and their barriers to treatment, screening for comorbid psychiatric disorders, developing individualized functional goals, providing patient support, and providing feedback to the clinicians.

Patients in the intervention group were more likely to be prescribed adjunctive medications such as antidepressants, NSAIDs, and capsaicin, and were more likely to receive long-acting rather than standard opioids. They also were more likely to receive physical therapy than were those in the usual-care group.

After 1 year, patients in the intervention group reported "generally modest" but significant decreases in pain intensity and in pain-related disability, compared with those in the usual-care group.

A total of 22% of the intervention patients showed 30% reductions in measures of pain and disability, compared with 14% of the usual-care patients, Dr. Dobscha and his colleagues said (JAMA 2009;301:1242-52).

The intervention was similarly effective in the subgroup of chronic pain patients who had concomitant depression, showing that "improvements in pain intensity and disability can be achieved even among patients with depression," the researchers noted.

However, there were no differences between the two treatment groups in health-related quality of life, satisfaction with health care treatment, or subjective assessments of treatment effectiveness.

The authors had no financial disclosures relating to this study. ■

Many With Controlled RA Experience Uncontrolled Pain

BY MICHELE G. SULLIVAN

Despite having clinically well-controlled disease, more than half of patients with rheumatoid arthritis experience moderate to severe pain, and few take the medications necessary to control it, according to findings from a prospective study.

Patients and physicians share the responsibility for inadequate pain control, Dr. Mary-Ann Fitzcharles and her colleagues found. Physicians tend to ignore pain in favor of focusing on disease control, whereas patients are afraid of the very medications that could help control pain, wrote Dr. Fitzcharles of McGill University in Montreal (J. Pain 2009;10:300-5).

"Our patients were very, very cautious about pain medication. They are scared of addiction, they dislike taking even more pills, and they worry about drug interactions, side effects, and masking disease progression. … We have not appreciated the importance of pain to these patients and simply don't ask about it," she said in an interview.

The study comprised 60 patients with RA who attended a specialist rheumatology practice. In all, 54 (90%) were women; their mean age was 57 years. They had been diagnosed with RA for a mean of 14 years. Most (54, or 90%) were taking disease-modifying antirheumatic drugs.

Patients were asked to complete several questionnaires about pain and quality of life. They were also asked about potential barriers to pain control with medications.

A seeming contradiction appeared almost immediately, Dr. Fitzcharles said. Despite 39 (65%) patients' reporting satisfaction with their pain control, 28 (47%) reported a desire for additional pain relief, and 32 (53%) reported experiencing moderate to severe pain. Almost half (45%) reported that the pain caused them moderate to severe distress, and the same percentage reported that pain exerted a moderate to severe interference with their daily activities.

"This was most striking," she said. "They believed their pain was controlled, yet they were still having pain. And most were not using any modality to reduce the pain. Of the 60 patients, only 4 were taking anything stronger than acetaminophen."

Patients expressed a high degree of concern about taking pain medications. More than half of the group (55%) expressed at least three barriers to taking such drugs. In all, 48 (80%) were worried about the side effects; 38 (63%) disliked taking even more pills; 34 (57%) worried about drug interactions; 21 (35%) had concerns about addiction; and 16 (27%) thought that controlling pain might mask disease progression. The higher the patient's pain level, the more barriers the patient felt toward controlling that pain.

Patients with RA seem to believe that pain is "an inevitable symptom," and that little can be done about it, Dr. Fitzcharles and her colleagues wrote. "The importance of pain may also take second place to other effects of RA, including the impact on self-esteem due to deformity, the systemic effects of fatigue and depression, and functional limitations due to mechanical joint dysfunction."

Physicians, on the other hand, often fail to address the symptom of pain. "Physicians may pay more attention towards the complexities of control of the underlying disease and neglect day-to-day comfort issues for the patient." ■