Rivaroxaban Assessed

Anticoagulant *from page 1*

who were concerned about off-label use of the drug, 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 made by Johnson & Johnson Pharmaceutical Research & Development LLC, would be marketed as Xarelto. It would be the first oral anticoagulant approved for these indications, as well as the first oral anticoagulant approved since warfarin. The drug works by inhibiting direct Factor Xa, which lowers thrombin production and prolongs prothrombin time. 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. The composite end point of venographic evidence of deep vein thrombosis (DVT), nonfatal pulmonary embolus (PE), or death was significantly lower in those treated with rivaroxaban, but patients on the drug had a higher rate of bleeding. The major bleeding rate was 0.4% in those on rivaroxaban and 0.2% in those on enoxaparin. The one bleeding-related death in the studies was in a patient on rivaroxaban.

Serious ALT elevations were more common with rivaroxaban (0.3% vs. 0.2%), as was 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, in 0.15% vs. 0.11%), but these were not significant differences.

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.

The panel chair, Dr. A. Michael Lincoff, professor of medicine at the Cleveland Clinic Foundation, who was among the majority in favor of the risk-benefit profile, said that "the liver issue is not completely resolved, but I believe the signal for liver injury is very weak" but should be followed.

Rivaroxaban is also being studied for other indications in ongoing trials, including acute coronary syndromes, secondary prevention and long-term treatment of patients who have had a DVT or PE, and prevention of stroke and noncentral nervous system embolism in patients with nonvalvular atrial fibrillation. ■

ADVISER'S VIEWPOINT

Anticoagulation in Hospitalized Patients

Once the oral anticoagulant rivaroxaban becomes available, I believe it will revolutionize the way that U.S. hospitalists manage patients who require an anticoagulant in the hospital.

The drug, already approved in Canada and the European Union, is expected to be approved by the Food and Drug Administration following a 15-2 vote by the FDA's Cardiovascular and Renal Drugs Advisory Committee that the drug has a favorable risk-benefit profile for prophylaxis of venous thromboembolism (VTE) in patients undergoing hip or knee replacement surgery. This is the first indication reviewed by the FDA; other indications are being studied in phase III trials, including a multinational study of VTE prevention in medically ill hospitalized patients. I am familiar with rivaroxaban in my role as principal investigator in this study at the University of Miami, one of the study sites.

BY AMIR K. JAFFER, M.D.

The drug is important for hospitalists because we work closely with orthopedic surgeons in caring for patients undergoing hip and knee replacement. It will provide an alternative to existing drugs for preventing VTE, a common complication in these patients, including warfarin (Coumadin); low-molecular-weight heparin (LMWH), such as enoxaparin sodium (Lovenox); and fondaparinux sodium (Arixtra). About half of these patients receive LMWH for prophylaxis, about 30%-40% receive warfarin, and a smaller proportion receive fondaparinux .

Promising data were reported in a study published last year, which compared rivaroxaban to enoxaparin after hip arthroplasty. The VTE rate was a little over 3.5% among those on enoxaparin, but was closer to 1% among those on 10 mg of rivaroxaban a day, a significant difference. Rivaroxaban was associated with an absolute risk reduction in VTE of approximately 2.6%, and the number of patients needed to treat to prevent one case of VTE was about 38 (N. Engl. J. Med. 2008;358:2765-75).

In addition to its efficacy, a great benefit of this drug is that it's taken once daily and, unlike LMWH, is not given parenterally. Compliance decreases when patients must take a drug twice a day or more often. Also, no monitoring is needed, so rivaroxaban has several advantages over warfarin, the only other oral anticoagulant available. Warfarin has a narrow therapeutic index, requires regular INR monitoring, interacts with many drugs and with some food, and is cleared by the cytochrome P450 system.

More patients are undergoing surgery than ever before, and joint replacement surgeries are becoming ever more frequent, so rivaroxaban holds great promise for our aging population.

Excess bleeding and potential hepatoxicity were the adverse events considered in the FDA panel's discussion of the drug's risk-benefit profile. Although the risk of major bleeding may be slightly increased, the rate of major bleeding in pooled clinical trials was 0.4% in those on rivaroxaban and 0.2% in those on enoxaparin, which was not a significant difference. Signs of potential hepatoxicity also were uncommon (0.15% in rivaroxaban-treated patients vs. 0.11% in those on enoxaparin, not a significant difference). I don't believe that hepatoxicity will be an issue with this drug.

The recommended dose of rivaroxaban is 10 mg a day, its onset of action is anywhere from 2.5 to 4 hours, it lasts for 24 hours, and it has a half-life of 6-9 hours. It is cleared by the kidneys, and patients with creatine clearances under 3 mL/min were not enrolled in trials. Rivaroxaban should be avoided in patients on drugs that inhibit the cytochrome P450 3A4 (CYP 3A4), such as ketoconazole and protease inhibitors, and vice versa. Rivaroxaban should be avoided in patients with severe renal disease (creatinine clearance below 30 mL/min) or severe liver disease.

We have just enrolled our first patient in the study that is comparing 10 mg of rivaroxaban a day (for up to 39 days) with 40 mg of enoxaparin once a day (for up to 14 days) for preventing VTE in medically ill hospitalized patients. Also, as one of the sites for a study of rivaroxaban for treating deep vein thrombosis and pulmonary embolism, we plan to start enrolling patients in that trial soon. For now, the FDA is looking at approving rivaroxaban only for VTE prevention in patients undergoing hip or knee replacement. But this indication itself will make the drug the first new oral anticoagulant since warfarin was discovered to treat VTE more than 50 years ago. ■

DR. JAFFER *is chief of the division of hospital medicine at the University of Miami Miller School of Medicine. He has received research funding for the rivaroxaban study from Bayer HealthCare AG, which is working with Johnson & Johnson to develop rivaroxaban, and has served as a consultant and a speaker for enoxaparin manufacturer Sanofi-Aventis. He had no other disclosures to report.*

Panel Supports Prasugrel Approval With Few Conditions

BY ELIZABETH MECHCATIE

SILVER SPRING, MD. — With unanimous support by an expert panel of prasugrel, the Food and Drug Administration is poised to approve the antiplatelet drug for treating patients with acute coronary syndrome who present with unstable angina, non–ST-segment elevation myocardial infarction, or ST-elevation MI.

All nine voting members of the FDA's Cardiovascular and Renal Drugs Advisory Committee agreed that prasugrel, a thienopyridine developed by Eli Lilly & Co. and Daiichi Sankyo Inc., has a favorable benefit-to-risk profile, based on clinical trial data.

Prasugrel, given as a 60-mg loading dose followed by 10 mg/day, was compared with clopidogrel, administered at a 300-mg loading dose followed by 75 mg/day, in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI 38), an international double-blind study of 13,608 patients with moderate to high-risk ACS, scheduled to have percutaneous coronary intervention. They had unstable angina, non–ST-segment elevation myocardial infarction (NSTEMI), or STEMI. All patients were on aspirin.

Over a mean of 12 months, the primary end point—a composite of cardiovascular death, MI, or nonfatal stroke—occurred in 12.1% of patients on clopidogrel and 9.9% of those on prasugrel, a significant reduction.

The rate of strokes in both groups was 0.9%. The overall risk of cardiovascular death was also not significantly different between the two groups.

The main risk was bleeding. The rate of major bleeding was 2.2% in those on prasugrel, compared with 1.7% in those on clopidogrel; the rates were 1.3% and 0.8% for life-threatening bleeding, including fatalities; 0.3% and 0.1% for fatal bleeding; and 0.3% and 0.2% for intracranial hemorrhage.

An FDA analysis showed that for every 1,000 patients with ACS treated with prasugrel, the treatment prevents 21 nonfatal MIs and 3 cardiovascular deaths, with no strokes, but at a cost of 2 fatal hemorrhages, 3 nonfatal major hemorrhages, 5 minor hemorrhages, and 19 minimal hemorrhages.

All panelists agreed that labeling should discourage physicians from prescribing prasugrel to treat patients with a history of stroke or TIA.

Among patients over age 70 years, bleeding was not more common with prasugrel, but the sequelae were more serious. The company has proposed that a lower dose be used in patients over age 75 years, and in people who weigh less than 60 kg, who also were at a greater risk of hemorrhage.

The panel recommended that the drug not be taken around the time of CABG.

The FDA usually follows the recommendations of its advisory committee. If approved, prasugrel will be marketed as Effient. ■