Dabigatran Curbs Bleeding in VTE Prophylaxis

BY PATRICE WENDLING

NEW ORLEANS — Dabigatran etexilate had comparable efficacy and significantly lower or comparable bleeding rates to warfarin in patients with acute venous thromboembolism, according to data from the RE-COVER trial.

The direct thrombin inhibitor is among several emerging oral anticoagulants that might replace warfarin, which has accumulated a notorious safety record over its 60-year history and requires frequent dose adjustments. Dabigatran, which is approved as Pradaxa in 40 countries for the primary prevention of VTE in patients who have undergone total knee or hip replacement, is not approved for use in the United States.

Dabigatran met this phase III study's primary end point, showing noninferiority to warfarin for preventing recurrent or fatal VTE. After 6 months, 2.4% of 1,274 patients randomized to dabigatran and 2.1% of patients assigned to warfarin experienced recurrent VTE or related death (hazard ratio 1.10), Dr. Sam Schulman reported at the annual meeting of the American Society of Hematology.

Major bleeding events occurred in 1.6% of dabigatran patients and 1.9% of warfarin patients (HR 0.82). Dabigatran reduced the risk of any bleeding event at 6 months by 29% (HR 0.71). Fatal bleeding occurred in one patient in each arm; intracranial bleeding was seen in no patients on dabigatran and three on warfarin.

"Dabigatran etexilate provides a convenient, oral fixed-dose treatment for acute VTE that offers an alternative to warfarin in the treatment of VTE," said Dr. Schulman, professor of medicine at McMaster University, Hamilton, Ont., and director of the clinical thromboembolism program at Hamilton General Hospital.

Liver function abnormalities, which caused the only previously available oral direct thrombin inhibitor, ximelagatran, to be denied FDA approval, were infrequent in both groups. A combination of elevated alanine aminotransferase level three times the upper limit of normal and bilirubin two times the upper limit of normal occurred in two dabigatran patients and four warfarin patients.

The number of MIs was similar with dabigatran and warfarin (four vs. two), he said. In the RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trial in patients with atrial fibrillation, dabigatran at the same 150-mg twice-daily dose was associated with lower rates of stroke, compared with warfarin, and a slight but significant increase of MI (N. Engl. J. Med. 2009;361:1139-51).

When this point was raised by reporters at a press briefing, Dr. Schulman said the number of MIs with dabigatran was too small to support conclusions. He speculated that it may be an issue of dose dependence, based on data from the phase II RE-DEEM study of dabigatran in patients with acute coronary syndrome.

"As always, it is a question of finding the right dose," he said. "Whether in general oral thrombin inhibitors increase the risk of MI, I don't think we can say that. I know there was a rumor of this with ximelagatran in orthopedic studies" based on "very vague data."

Dr. Schulman suggested that the price to treat VTE would be about double that for the orthopedic indication, which is about $7 per day for dabigatran versus $8 a day plus lab monitoring costs for low-molecular-weight heparin.

Press briefing moderator Dr. Bradford Schwartz, regional dean of the college of medicine at the University of Illinois at Urbana-Champaign, said oral dabigatran will "simplify the management of a feared disorder."

Dr. Mary Cushman of the University of Vermont in Burlington, who introduced the formal study presentation, said anticoagulation is underutilized in the United States because of the difficulties in managing warfarin, such that 50% of elderly patients eligible for treatment are not treated and remain at risk for stroke. Dabigatran meets some of the requirements for an "optimal new anticoagulant," she added, in that it is an oral agent that does not require lab monitoring and has few drug and food interactions.

Patients in the double-blind multinational trial had symptomatic VTE for a maximum of 14 days and were given initial parenteral anticoagulation therapy and warfarin or placebo until they reached an international normalized ratio (INR) of 2.0 or more on 2 consecutive days; they were randomized to dabigatran 150 mg b.i.d. or warfarin dose-adjusted to an INR of 2.0 and 3.0. Patients with a creatinine clearance rate less than 30 mL per minute, who were excluded from the study, should not be treated with dabigatran, Dr. Schulman advised.

The trial results were published simultaneously in the New England Journal of Medicine (2009;361:2342-52 [doi:10.1056/NEJMoa0906598]). The study was sponsored by Boehringer Ingelheim. Dr. Shulman has received honoraria from AstraZeneca, Bayer Healthcare, Boehringer Ingelheim, GlaxoSmithKline and Sanofi-Aventis, lecture fees from LeoPharma and Sanofi-Aventis, and an unrestricted grant from Bayer. ■

MY TAKE

Clinicians Eager to Replace Warfarin

A replacement for warfarin has been on just about every clinician's wish list for the last decade. The direct thrombin inhibitors currently hold the most promise.

DR. TANGALOS

Let's keep our fingers crossed that this class of drugs carries the same benefit as warfarin, with far fewer complications and far less monitoring.

Such a breakthrough would have instant impact. Early in my career I struggled with managing hyperlipidemia in my patients until statins appeared. Later, treating depression was a struggle until the SSRIs showed up.

This would be even bigger.

In his book "The Youngest Science," Dr. Lewis Thomas wrote about promising opportunities in medicine that began developing more than 60 years ago. Those physicians now retired or long passed were astounded when antibiotics first became available and were put into practice.

Perhaps the next generation of practitioners will marvel that so many of us for so long anticoagulated our patients with "rat poison."

Exciting times are still upon us.

ERIC G. TANGALOS, M.D., *is a professor of medicine at the Mayo Clinic in Rochester, Minn. He reports no relevant conflicts of interest.*

Fixed-Dose Rivaroxaban Slashes Risk of Recurrent VTE

BY SUSAN LONDON

NEW ORLEANS — Rivaroxaban, an oral anticoagulant that does not require monitoring, produced a dramatic long-term decline in recurrent venous thromboembolism in results from the EINSTEIN-Extension Study.

Patients treated with rivaroxaban had an 82% reduction in the risk of a recurrence, compared with their counterparts treated with placebo—without an increase in the risks of major bleeding or hepatotoxicity, according to a late-breaker presentation at the annual meeting of the American Society of Hematology.

Rivaroxaban has been approved in several countries, according to a statement from Bayer HealthCare, a partner in the drug's development. Despite a Food and Drug Administration advisory panel vote favoring approval in the United States, an application is on hold pending additional data.

Rivaroxaban is a direct factor Xa inhibitor, with pharmacokinetics and other characteristics that give it several advantages over vitamin K antagonists such as warfarin (Coumadin), said Dr. Harry R. Büller, a vascular medicine specialist at the Academic Medical Center in Amsterdam. Namely, this drug does not require regular laboratory monitoring, dose adjustments, or dietary restrictions.

He and his coinvestigators enrolled patients from 28 countries who had completed 6-12 months of anticoagulant therapy for a confirmed symptomatic VTE and did not have any clear indication for either continuing or discontinuing this therapy.

Patients treated with rivaroxaban had an 82% reduction in the risk of a recurrence, compared with placebo—without an increase in the risks of major bleeding or hepatotoxicity.

The patients were randomly assigned to double-blind treatment for an additional 6-12 months with a placebo or rivaroxaban at a fixed dose of 20 mg once daily. Intent-to-treat analyses were based on 602 patients assigned to rivaroxaban and 594 patients assigned to placebo. They were 58 years old on average, and 58% were male.

The mean duration of anticoagulant therapy before trial entry was about 8 months, and the mean duration of treatment on the trial was about 6 months.

Compared with their counterparts in the placebo group, patients in the rivaroxaban group were less likely to experience symptomatic recurrent VTE—the composite of recurrent deep venous thrombosis, nonfatal pulmonary embolism (PE), fatal PE, or unexplained death where PE could not be excluded (1.3% vs. 7.1%).

The difference between groups corresponded to an 82% relative reduction in risk with rivaroxaban (hazard ratio, 0.18), Dr. Büller reported. The number needed to treat to prevent one VTE event was 15.

The incidence of major bleeding was essentially the same in the two groups (0.7% with rivaroxaban and 0% with placebo). No events were fatal or located in a critical site, he noted. However, patients in the rivaroxaban group were more likely to experience clinically relevant nonmajor bleeding (for example, prolonged nosebleeds, large skin hematomas, and macroscopic hematuria): 5.4% vs. 1.2%.

In 7-8 months, the results of EINSTEIN-DVT, a head-to-head comparison between rivaroxaban and warfarin, will be available, he said. ■

Disclosures: *Dr. Büller reported that he has received research funding from and been a consultant and advisory board member for Bayer HealthCare.*