Anticoagulant Outdoes Warfarin

Dabigatran *from page 1*

professor of medicine at McMaster University in 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function abnormalities, which caused the only previously available oral direct thrombin inhibitor, ximelagatran, to be withdrawn from European markets and to be denied FDA approval, were infrequent in both groups.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 during the meeting, Dr. Schulman responded that 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."

Price was a key issue raised during both the press briefing and the discussion following the formal study presentation. Dr. Schulman told the audience that it was unclear what the price would be for the treatment of VTE, which has a different dosage than for VTE prevention in orthopedic patients. During the press briefing, he 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; for example, 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; then 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.

Results of the trial 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 disclosed receiving 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

New Anticoagulants Hold Promise

Safer oral anticoagulants are needed, and this study highlights an emerging option for replacing warfarin.

However, this study design didn't address the important potential for new oral anticoagulants to meet both the acute and chronic anticoagulation indications for VTE. This study treated VTE acutely with traditional inpatient parenteral anticoagulants.

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For hospitalists, the value in these new anticoagulants will be the potential to write a prescription for oral therapy straight from the emergency department, essentially turning uncomplicated acute VTE into an outpatient condition.

Hospitalists will be on the front lines in managing possible complications of new anticoagulants. Renally impaired patients were excluded from this study, yet patients on these medications might develop acute kidney injury and require hospitalization unexpectedly. How will we reverse this agent if needed? This will be uncharted territory for hospitalists.

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Many Patients at Risk Never Receive VTE Prophylaxis

BY PATRICE WENDLING

NEW ORLEANS — Nearly two-thirds of 9,675 medical patients at risk for venous thromboembolism received no inpatient pharmacologic prophylaxis and more than 98% received no outpatient prophylaxis, a retrospective analysis showed.

The analysis is unique in that it assessed both inpatient and outpatient pharmacologic venous thromboembolism (VTE) prophylaxis in medical patients at risk of VTE, Dr. Alpesh N. Amin and his associates reported in a poster at the annual meeting of the American Society of Hematology.

"Further efforts to improve VTE prevention in medical patients are required, with particular emphasis needed on the transition to outpatient prophylaxis," the authors concluded. Most hospitalized medical patients have at least one VTE risk factor, with the risk persisting for several weeks after discharge. In addition to hospitalization for a medical illness, VTE risk factors in the study included age at least 60 years (40.5% of patients), malignancy (28%), and obesity (19%).

Overall, 6,185 patients (64%) did not receive any pharmacologic VTE prophylaxis while hospitalized, reported Dr. Amin, executive director of the hospitalist program and professor and chair of medicine at the University of California at Irvine, and his associates. Lack of thromboprophylaxis was most apparent in patients with cancer, occurring in about 70% of 2,544 patients.

Among the 3,490 patients who received pharmacologic VTE prophylaxis, 2,045 received enoxaparin and 1,044 received unfractionated heparin. Enoxaparin was the most commonly prescribed prophylactic agent in patients with heart failure, severe lung disease, or infectious disease; heparin was the most commonly prescribed agent in patients with cancer.

"Even when pharmacological VTE prophylaxis was provided for the duration of hospitalization, the median length of hospital stay was just 3 days in this study, which falls short of the 6-14 days of VTE prophylaxis provided in clinical trials in medical at-risk patients," Dr. Amin and his associates wrote.

A total of 2,854 patients (29.5%) first received prophylaxis on the last day or next-to-last day of their hospital stay.

In the 30 days following hospital discharge, 98.2% of the medical patients analyzed received no further pharmacologic VTE prophylaxis. Among the 174 medical discharges who did receive outpatient pharmacologic prophylaxis, most received warfarin alone, followed by enoxaparin plus warfarin. Patients with heart failure had the highest level of outpatient prophylaxis within 30 days after discharge (4.8%), and infectious disease patients had the lowest level (1.1%).

For the study, inpatient data from the Premier's Perspective database were cross-matched at the individual patient level with Ingenix LabRx outpatient data from the i3 database (January 2005–December 2007). Patients at least 40 years old and at risk of VTE according to the 2004 American College of Chest Physicians guidelines were included if they had cancer (without surgery), heart failure, severe lung disease, or infectious disease. The data, which came from hospitals in diverse geographic areas, "may not be representative of the U.S. population as a whole," the researchers noted.

The study excluded patients with contraindications to pharmacologic VTE prophylaxis and those without health plan eligibility in the 3 months before and the 6 months after hospitalization.

The authors disclosed receiving editorial support from Sanofi-Aventis U.S. in the preparation of the poster, but noted that they were fully responsible for all content and editorial decisions. Coauthor Jay Lin, Ph.D., is an employee of Sanofi-Aventis, and coauthor Amy Ryan is an employee of Premier Inc. ■

MY TAKE

VTE Prophylaxis Still Inconsistent

Over the last 2 decades, the medical community has repeatedly demonstrated the lack of uniform VTE prophylaxis for medical patients at risk. This analysis is contemporary and suggests that the push for VTE prevention by the National Quality Forum, the Agency for Healthcare Research and Quality, and the Leapfrog Group has not been that successful in changing practice. It will be interesting to see if the new Joint Commission core measures on VTE prevention lead to improvements.

This study also highlights the inadequate duration of VTE prophylaxis. Research shows that 6-14 days of prophylaxis is effective, yet patients today aren't hospitalized long enough to receive treatment of this duration. Achieving better outpatient prophylaxis is a major challenge, and some of the new anticoagulants soon to be available may help in this regard.

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