The Role of Oral Direct Thrombin Inhibitors in Cardiovascular Disease

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On April 10, 2004, a panel of experts gathered to discuss the use of anticoagulation therapy in various cardiac disorders. This supplement summarizes, in a series of articles by the participants, the salient issues that were covered. We have the pleasure of chairing this superb educational endeavor.

Atrial fibrillation (AF) is recognized as the most commonly sustained arrhythmia in adults, one that increases in incidence and prevalence with advancing age.[1] The most serious, frequent, and predictable complication of AF is embolic stroke.[1] For decades, a cornerstone of preventive therapy in AF has been long-term anticoagulation with warfarin. This supplement presents the rationale, supportive data, and clinical trial evidence for a new class of chronic anticoagulants called oral direct thrombin inhibitors.[2] The first of these agents available to clinicians and tested in randomized trials is ximelagatran, which is a prodrug for the active metabolite melagatran.[2] The authors of this supplement have provided cutting edge information with respect to thrombosis and its management that we hope will be valuable to the readership of *Reviews in Cardiovascular Medicine*.

Dr. Kereiakes presents a detailed, clear, and understandable overview of the

coagulation cascade and the pathophysiology of clot formation. As noted, thrombin is the lynchpin of coagulation, with multiple and varied interactions. Warfarin, the only currently available oral anticoagulant, acts on Vitamin K-dependent clotting factors and has many well-known disadvantages, not the least of which is slow time to onset and offset. The indirect thrombin inhibitors heparin or low-molecular-weight heparin are administered intravenously or subcutaneously. Ximelagatran is given twice daily, does not have the myriad drug-drug and food modifying effects of action associated with warfarin, and has proven efficacy against both venous and arterial thrombus formation. Liver enzyme elevations, which typically resolve spontaneously or after drug cessation, occur in 6% to 10% of patients. Rare cases of liver failure have been reported.

Dr. Reiffel begins his article with the assumption that ximelagatran receives USFDA approval, presenting clinicians with a plethora of new treatment options for their patients. Who will be candidates for ximelagatran? In whom should it be avoided or its use more carefully monitored? If used, how does the physician transfer from warfarin to ximelagatran, or the reverse? Dr. Reiffel applies his considerable clinical experience to these issues. Data from the Stroke Prevention by Oral Thrombin Inhibition in Atrial Fibrillation (SPORTIF) trials support ximelagatran use in patients with AF who are at high risk for stroke. Unfortunately, its use in the setting of cardioversion is not well defined and will require prospective trial data for confirmation. Dr. Reiffel proposes various methods to switch from warfarin to ximelagatran, ranging from administration of Vitamin K to a gradual crossover of drugs, depending on the clinical scenario.

Dr. Lepor reviews clinical and economic implications of ximelagatran use. Multiple randomized clinical trials have demonstrated a major stroke reduction in high-risk AF patients prescribed warfarin, and its use for this purpose is codified in several published guidelines. Yet, nearly 50% of such patients are not taking this agent, by either physician or patient choice. The published reasons for this are multifactorial, but an overriding problem is the difficulty of managing warfarin's anticoagulation status. The socioeconomic implications of stroke prevention are enormous, with substantial costs to patients, their families, and society in general. More widespread anticoagulation of high-risk AF patients, for example, using ximelagatran, will likely go far in lessening this burden.

Dr. Waldo discusses in detail stroke prevention trials in AF and the need for anticoagulation in high-risk patients. He reminds us of a major finding from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, that anticoagulation should not be discontinued in patients with stroke risk who appear to be in sinus rhythm during antiarrhythmic drug therapy. Asymptomatic episodes of AF are common and could lead to a thromboembolic event in the absence of appropriate anticoagulation. The design and results of SPORTIF III and V, which compared fixed dose ximelagatran (36 mg twice daily) with adjusted dose warfarin (INR 2-3) in AF patients with risk factors for stroke, are also reviewed. Both drugs effectively reduced stroke and ximelagatran was not inferior to warfarin.

The supplement issue ends with a review of antithrombotic strategies in acute coronary syndromes (ACS) by Drs. Granger and Weaver. Instability and rupture of a coronary artery plaque initiates ACS and thrombin is key to thrombus generation in ACS. Antithrombotic therapies include aspirin, glycoprotein IIb/IIIa receptor antagonists, clopidogrel, heparin, and the recently investigated direct thrombin inhibitor ximelagatran. In the Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Recent and Myocardial Damage (ESTEEM) study, ximelagatran was studied in patients following myocardial infarction, and was significantly more effective than placebo in reducing the primary combined endpoint of death, severe recurrent ischemia, and myocardial infarction. Major bleeding with ximelagatran was 1.8% compared with 0.9% for placebo, not significantly different. As noted in other trials, some patients developed reversible liver enzyme abnormalities. ■

References

1. Prystowsky EN. Management of atrial fibrillation: therapeutic options and clinical decisions. *Am J Cardiol*. 2000;85(10A):3D-11D.
2. McCullough PA, Dorrell KA, Sandberg KR, Yerkey MW. Ximelagatran: a novel oral direct thrombin inhibitor for long-term anticoagulation. *Rev Cardiovasc Med*. 2004;5(2):99-103.