Ximelagatran: A Novel Oral Direct Thrombin Inhibitor for Long-Term Anticoagulation

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The ideal anticoagulant agent would have a fixed oral dose without need for dose adjustment, a wider therapeutic window than that of warfarin, and acceptable bleeding risks without the need for routine coagulation monitoring. Ximelagatran is a new oral agent that, when converted to its active form, melagatran, directly inhibits thrombin, thus blocking its activity and modulating several of its key functions. For the prevention of venous thromboembolism after orthopedic surgery, treatment of venous thromboembolism, and prevention of stroke in patients with atrial fibrillation, clinical trials indicate that ximelagatran meets the criteria for a superior anticoagulant.
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Key words: Venous thromboembolism • Thrombin • Ximelagatran • Melagatran • Atrial fibrillation • Chronic anticoagulation

Ximelagatran is a novel oral direct thrombin inhibitor (DTI) that, when converted to its active form, melagatran, acts directly as an inhibitor of thrombin. DTIs specifically inhibit thrombin, thus blocking its activity and modulating several of its key functions. Their action is in contrast to heparin and its derivatives, which inhibit thrombin and other coagulation serine proteases via antithrombin, and to the warfarin-type drugs that interfere with the synthesis of the precursors of the coagulation serine proteases. To date, three

DTIs are approved for clinical use; however, they are all administered parenterally. Ximelagatran, administered orally, is the most promising and extensively evaluated drug in this category. This summary describes preclinical and clinical studies performed with this new compound to assess it in a variety of clinical applications.

Thrombin: A Key Therapeutic Target

The coagulation cascade is a complex system that yields several key therapeutic targets. The most frequently prescribed drugs for outpatient anticoagulation are the vitamin K antagonists (eg, warfarin) because they are the only orally administered anticoagulants currently available. Warfarin targets the vitamin K–dependent hydroxylation of several coagulant factors. These factors are manufactured in the liver, and their synthesis is influenced by oral intake of vitamin K. Warfarin, despite its proven anticoagulant efficacy, remains a therapeutic challenge given the need for frequent coagulation monitoring (via international normalized ratio [INR]) and dose adjustment. Results of numerous studies have indicated that even under the most ideal circumstances, the time in therapeutic range with warfarin is limited; hence, there is considerable risk for both bleeding and recurrent thrombotic events.[1] Ximelagatran is an oral agent that is bio-converted to its active form, melagatran, which has a direct inhibitory effect on thrombin (Figure 1). Preclinical and clinical trial work with ximelagatran has demonstrated promising results in the prophylaxis and treatment of venous thromboembolism (VTE) and, most recently, the prevention of stroke in atrial fibrillation.

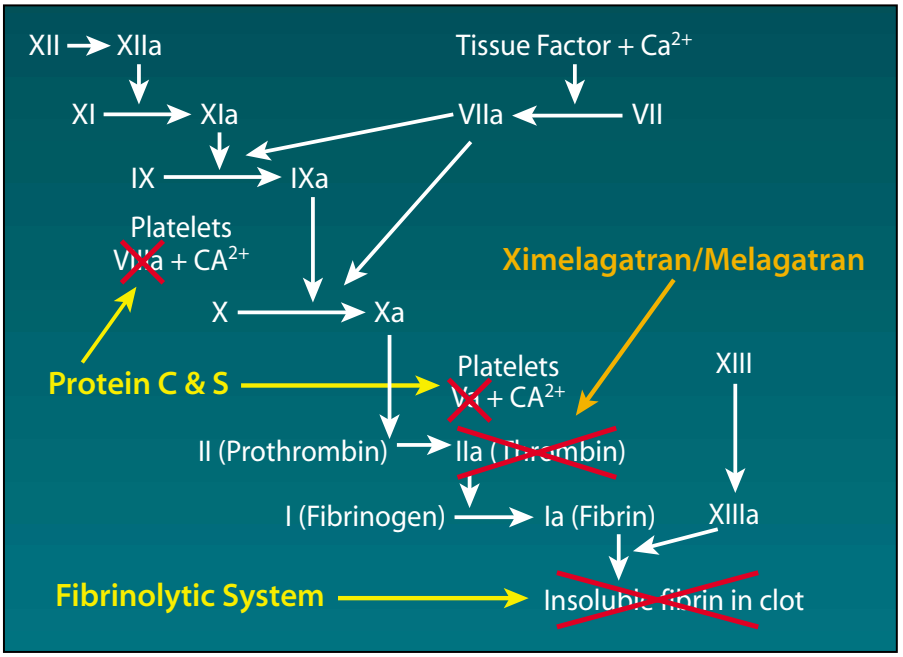

Figure 1. *Mechanisms of action of endogenous antithrombotics (proteins C, S, and the fibrinolytic system) in relation to the action of ximelagatran and its active derivative, melagatran, on the coagulation cascade.*

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Preclinical Experience With Ximelagatran

The active form of ximelagatran is melagatran, which inhibits thrombin. For purposes of this report, ximelagatran will be used to indicate the actions of both the active and inactive drug. Ximelagatran was developed to overcome the low and variable oral absorption of melagatran. Ximelagatran is rapidly absorbed and has a bioavailability of 20% after single and repeated dosing.[2] It has been administered in single doses up to 98 mg in humans.[2] Melagatran is cleared primarily via the kidneys (80%). Direct thrombin inhibition with ximelagatran blocks the formation of fibrin without a quantitative effect on the prothrombin time or partial thromboplastin time. Despite no useful clinical measure of its anticoagulant effect, the activated clotting time and the activated partial thromboplastin time are the best measures for a crude downstream indicator of thrombosis. Because of thrombin's role in a positive feedback loop promoting generation of more thrombin, inhibition of this step not only inhibits thrombin activity but also thrombin generation. By melagatran acting independently of antithrombin III, it is able to inhibit fibrin-bound thrombin. Ximelagatran has a rapid onset of action (showing its anticoagulant effect within one hour after oral administration) as compared with warfarin. In an arterial hemostasis model in the rat, ximelagatran has

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been shown to have a slope of 1.2 for its dose-response curve, suggesting a therapeutic window wider than that of warfarin.[3] In venous thrombosis models in the rat, ximelagatran reduced thrombus weight to a degree similar to that of low molecular weight heparins, suggesting that it may have therapeutic potential for the treatment of deep venous thrombosis.[4,5]

In the dose-ranging study METHRO II, the highest dosing scheme of melagatran, 3 mg subcutaneously followed by oral ximelagatran 24 mg twice daily, was found to be superior to the low molecular weight heparin dalteparin administered subcutaneously at 5000 U/d after total hip or knee replacement.

VTE Prophylaxis After Orthopedic Surgery

In Europe, a series of clinical trials known as METHRO (Melagatran for Thrombin Inhibition in Orthopedic Surgery) were conducted using subcutaneously administered melagatran followed by oral ximelagatran given twice daily. In the dose-ranging study METHRO II, the highest dosing scheme of melagatran, 3 mg subcutaneously followed by oral ximelagatran 24 mg twice daily, was found to be superior to the low molecular weight heparin dalteparin administered subcutaneously at 5000 U/d after total hip or knee replacement.[6] The frequency of radiographically proven lower-extremity VTE was significantly lower with melagatran/ximelagatran than with dalteparin (15.1% vs 28.2%, $P < .0001$). In METHRO III, the same melagatran/ximelagatran approach was compared with 40 mg/d subcutaneous enoxaparin in 2788 patients undergoing total hip or knee replacement.[7] The primary efficacy end point was VTE (deep vein thrombosis detected by mandatory venography, pulmonary embolism, or unexplained death). VTE occurred in 31.0% and 27.3% of the ximelagatran and enoxaparin groups, respectively ($P = .053$).

In a North American head-to-head trial of ximelagatran versus warfarin after total knee arthroplasty, those patients randomized to oral ximelagatran 24 mg twice daily starting on the day after surgery had a lower incidence of VTE compared with those on warfarin starting in the evening of the day of surgery (19.2% vs 25.7%, respectively, $P = 0.070$).[8] In this trial, major bleeding occurred in 1.7% of the ximelagatran group and 0.9% of the warfarin group ($P > .05$). In a confirmatory double-blind trial, the Exanta Used to Lessen Thrombosis A (EXULT A) trial, 1851 patients were randomized to ximelagatran 24 mg or 36 mg versus adjusted-dose warfarin for 7–12 days after total knee replacement.[9] The primary end point of total VTE or death occurred in 20.3%, 24.9%, and 27.6% of the patients receiving 36 mg ximelagatran, 24 mg ximelagatran, and adjusted-dose warfarin to a target INR of 2.5, respectively ($P = .003$ and $P = .28$ for ximelagatran comparisons to warfarin).

During the 18 months of study, VTE recurred in 12.6% of placebo-treated patients as compared with 2.8% of ximelagatran-treated patients (P < .0001), without any differences in major or overall bleeding events.

Treatment of VTE

For the active treatment of VTE, there is an analogous series of trials with ximelagatran called THRIVE (Oral Direct Thrombin Inhibitor Ximelagatran for Venous Thromboembolism). Because idiopathic VTE is a chronic disease, a long-term, secondary VTE prevention trial in 1233 patients compared oral ximelagatran 24 mg twice daily with placebo (THRIVE III). During the 18 months of study, VTE recurred in 12.6% of placebo-treated patients as compared with 2.8% of ximelagatran-treated patients ($P < .0001$), without any differences in major or overall bleeding events.[10] We await the published results of active treatment trials for initial and recurrent idiopathic VTE comparing ximelagatran with currently used therapies, including low molecular weight heparins and warfarin.

Stroke Prevention in Patients With Atrial Fibrillation

SPORTIF (Stroke Prevention Using Oral Thrombin Inhibitors in Atrial Fibrillation) is a series of trials testing ximelagatran in patients with atrial fibrillation.[11] In the SPORTIF series, a total of 7320 patients with nonvalvular atrial fibrillation plus risk factors for stroke were randomized to adjusted-dose warfarin with a target INR between 2.0 and 3.0 or to fixed-dose oral ximelagatran 36 mg twice daily.

During the SPORTIF II study, a 12-week parallel-group dose-finding study, doses of oral ximelagatran to 60 mg twice daily were well tolerated in patients with nonvalvular atrial fibrillation.[12] In this population, there were no strokes during the 12 weeks

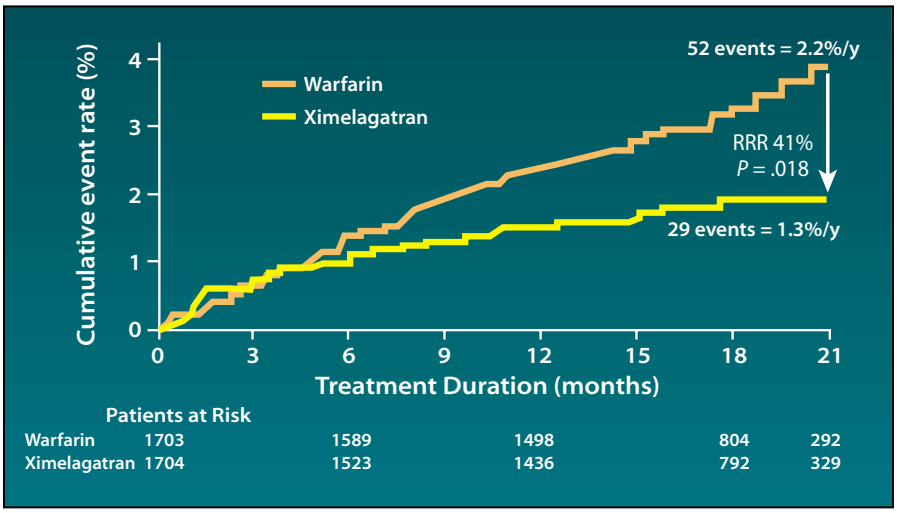


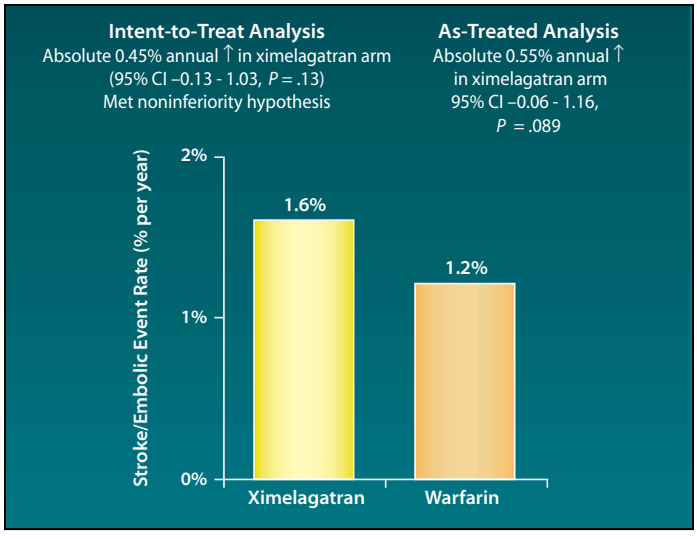
Figure 2. *Primary results of the SPORTIF III Trial in patients with atrial fibrillation. Adapted from Halperin.[13] RRR, relative risk reduction.* www.medreviews.com

of study, and the bleeding rates (major and minor) with ximelagatran were low and similar to those observed for well-controlled, dose-adjusted warfarin. During the course of treatment, of the 187 subjects who received ximelagatran, 8 (4.3%) had a transient increase in S-alanine aminotransferase (ALT) level more than three times the upper limit of normal. In these 8 patients, 5 had normalization of ALT with continued treatment, and three had ALT levels return to normal after ximelagatran was discontinued.

Promising results of SPORTIF III, an open-label trial in 23 countries that enrolled 3407 patients, were presented at the annual meeting of the American College of Cardiology in March 2003.[13] The incidence of stroke and embolic events and of bleeding were lower with ximelagatran than with warfarin. The primary end point was all strokes (ischemic or hemorrhagic) and systemic embolic events. In an intention-to-treat analysis, there were 56 events in 21 months of treatment (for a 2.3% event rate per year) in the warfarin group and 40 events (or a 1.6% event rate per year) in the ximelagatran group. In an analysis of patients who continued on therapy throughout the trial, the annualized rates were 2.2% and 1.3% for the warfarin and ximelagatran groups, respectively, $P = .018$ (Figure 2). The rate of major and minor bleeding was 29.5% in the warfarin group and 25.5% in the ximelagatran group ($P = .007$). Transient hepatic enzyme elevations occurred in 6.5% of subjects assigned to ximelagatran.

The SPORTIF V trial was presented at the 2003 Scientific Sessions of the American Heart Association (Figure 3).[14] This double-blind trial randomized 3922 patients with atrial fibrillation and risk factors for stroke to ximelagatran 36 mg orally twice daily versus adjusted warfarin with a target INR of 2-3. The primary end point of all-cause stroke occurred at an annual rate of 1.6% and 1.2% of the ximelagatran and warfarin groups, respectively, $P = .13$ (95% CI for hazard ratio 0.13–1.03). Very importantly, this result met the end point for noninferiority on the intent-to-treat analysis and just missed noninferiority with the on-treatment analysis (95% CI 0.06–1.16, crossing the upper bound). Rates of major bleeding were low and are similar in the treatment groups. Again, elevation in hepatic transaminase levels occurred in 6.0% of those who received ximelagatran, with no serious cases of liver injury reported. The overall conclusions from SPORTIF III and V are that ximelagatran was at least as efficacious as warfarin for stroke prevention. With consideration to the rapid onset of action, low interindividual variability, and predictable dose response, xime-

Figure 3. *Primary results of the SPORTIF V trial in patients with atrial fibrillation Adapted from Halperin.[14]*



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lagatran may be a superior choice for patients in the future.

Commentary

The ideal anticoagulant drug may be thought of as one that has a fixed oral dose without need for dose adjustment, a wider therapeutic window than that of warfarin, and acceptable bleeding risks without the need for routine coagulation monitoring. It should also have demonstrated efficacy in large-scale randomized trials. For the applications of VTE prophylaxis after orthopedic surgery, treatment of VTE, and stroke prevention in atrial fibrillation, it appears that ximelagatran meets these criteria. We look forward to future studies in the primary treatment of acute coronary syndromes, intracardiac shunting, valvular heart disease, and hypercoagulable states. Ximelagatran has the potential to offer a major advance in anticoagulant therapy, but some issues remain unresolved, including its use (dose and dosing interval) in patients with impaired renal function. In addition, the management of asymptomatic increases in hepatic enzyme levels with ximelagatran will need further evaluation and fuller understanding. ■

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Main Points

- Ximelagatran is a novel oral direct thrombin inhibitor (DTI) that, when converted to its active form, melagatran, acts directly as an inhibitor of thrombin. DTIs specifically inhibit thrombin, thus blocking its activity and modulating several of its key functions.
- Preclinical and clinical trial work with ximelagatran has demonstrated promising results in the prophylaxis and treatment of venous thromboembolism (VTE) and, most recently, the prevention of stroke in atrial fibrillation.
- Ximelagatran has a rapid onset of action (showing its anticoagulant effect within one hour after oral administration) as compared with warfarin.
- In a North American head-to-head trial of ximelagatran versus warfarin after total knee arthroplasty, those patients randomized to oral ximelagatran 24 mg twice daily starting on the day after surgery had a lower incidence of VTE compared with those on warfarin starting in the evening of the day of surgery.
- During the 18 months of the THRIVE study, VTE recurred in 12.6% of placebo-treated patients as compared with 2.8% of ximelagatran-treated patients, without any differences in major or overall bleeding events.
- The overall conclusions from SPORTIF III and V are that ximelagatran was at least as efficacious as warfarin for stroke prevention. With consideration to the rapid onset of action, low interindividual variability, and predictable dose response, ximelagatran may be a superior choice for patients in the future.