

PEER REVIEWED

Ximelagatran

A promising new oral anticoagulant

by Lee P. Skrupky and Karen Kopacek, RPh

Anticoagulation is a cornerstone of therapy in both treatment and prevention of various thromboembolic conditions. Two highly prevalent conditions in which thromboembolism may occur include atrial fibrillation and orthopedic surgery. An estimated 2.3 million people are diagnosed annually with atrial fibrillation (AF)¹ and approximately 450,000 persons receive a joint replacement each year.² Possible thromboembolic complications of these conditions include stroke, pulmonary embolism (PE), and deep vein thrombosis (DVT) — all serious consequences with potentially fatal outcomes. Antithrombotic therapy is therefore crucial in these conditions.

Current antithrombotic therapy to prevent venous thromboembolism (VTE) in orthopedic surgery³ and stroke in AF⁴ includes the use of low molecular weight heparin (LMWH) and warfarin. While these therapies significantly reduce the risk of clot formation, they have inherent risks and unique disadvantages. Warfarin requires frequent laboratory monitoring and dosage adjustments. It also has numerous drug, food, disease and lifestyle interactions. While LMWH requires less laboratory monitoring and has few drug interactions, the patient is required to administer subcutaneous injections once or twice daily.

Ximelagatran (Exanta™ - AstraZeneca), a new oral direct thrombin inhibitor, is being studied as an alternative to LMWH and warfarin and may play an important role in antithrombotic therapy. Ximelagatran offers the convenience of oral therapy and quick and reversible inhibition of clot formation. In addition, it does not require laboratory monitoring for efficacy. A review of ximelagatran's

properties and published clinical trials is provided on page 38.

PHARMACOLOGY

Ximelagatran is classified as a direct thrombin inhibitor. Other direct thrombin inhibitors currently available in the United States include hirudin or lepirudin (Refludan®), argatroban, and bivalirudin (Angiomax®). Compared with other drugs in this class that are administered by continuous infusion, ximelagatran will be the first oral agent.

Ximelagatran is a prodrug which is utilized to improve upon the poor oral bioavailability of melagatran, the active species.^{5,6,7} Melagatran reversibly binds to the arginine side pocket of the arginine site pocket of both free and clot-bound thrombin (Factor IIa), quickly leading to inactivation (Figure 1).^{5,8} Thrombin inhibition by melagatran occurs quickly. Ultimately, the conversion of fibrinogen (Factor I) to fibrin by thrombin (the final step of the coagulation process) is blocked (Figure 2). Melagatran can also inhibit thrombin generation.⁷

PHARMACOKINETICS

Ximelagatran is rapidly absorbed following oral administration and is converted in the body to the active species, melagatran.⁵ Oral bioavailability, as measured by melagatran concentrations, ranges between 18-25%.^{5,6,9,10} Peak concentrations (C_{max}) are attained ap-

proximately two to three hours (t_{max}) post dose.^{9,10,11} A linear relationship between ximelagatran dose and melagatran concentration exists¹² and absorption is not affected by food.^{5,6,13}

The primary route of elimination of melagatran is renal excretion (approximately 80%), and clearance of the drug correlates with creatinine clearance.^{12,13} The elimination half-life of melagatran ranges from three to five hours.^{9,10,11,14} In patients with severe renal impairment, clearance is reduced and the half-life is approximately doubled, prompting a recommendation for dosage reductions in these patients.^{17,18} The metabolic pathway for elimination is not well understood at this time;⁶ however, melagatran pharmacokinetics are not altered in persons with mild to moderate hepatic impairment.^{15,16} Ximelagatran pharmacokinetics are not influenced by the type of thromboembolic disease, ethnicity, obesity, gender or age.^{9,12,19,20,21}

FIGURE 1

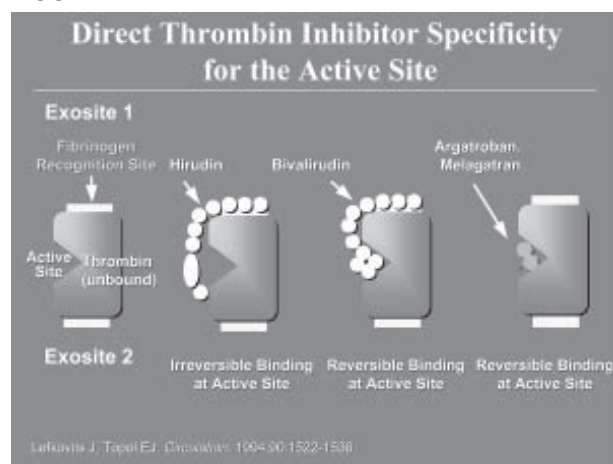
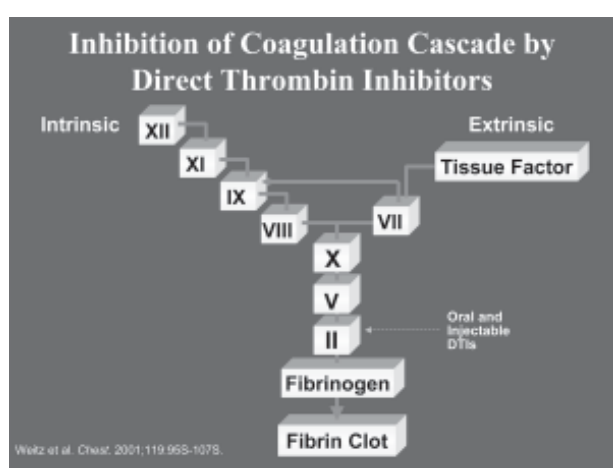


FIGURE 2



CLINICAL EFFICACY

Prevention of venous thromboembolism following orthopedic surgery

Several phase II and III trials have investigated the efficacy of ximelagatran in preventing VTE in patients undergoing total hip or knee replacement surgery. While the primary goal of earlier trials was dose-finding, more recent trials have compared the efficacy of ximelagatran to that of LMWH and warfarin.

The Melagatran for Thrombin inhibition in Orthopaedic surgery (METHRO II) trial²² compared varying doses of melagatran followed by ximelagatran to dalteparin for VTE prevention after total hip or knee replacement. Patients were randomized to one of four twice-daily doses of subcutaneous (SQ) melagatran started immediately prior to surgery (1 mg, 1.5 mg, 2.25 mg, or 3 mg), followed with twice-daily doses of oral ximelagatran (8 mg, 12 mg, 18 mg, or 24 mg) or dalteparin 5000 IU SQ, once daily, started the evening before surgery. Prophylaxis was maintained for seven to 10 days until bilateral venography was performed. The primary endpoint was the combined rate of DVT and PE. A significant dose-dependent decrease in VTE rate was reported with increasing melagatran/ximelagatran dosage combinations. The rate of VTE was significantly lower with the highest dose of melagatran/ximelagatran compared to dalteparin therapy. Excessive bleeding was uncommon, but the number of patients with excessive bleeding was more frequent in those receiving ximelagatran 24 mg compared to all treatment groups. Anemia was the most common adverse event, but no significant differences in adverse events existed between the dalteparin and ximelagatran groups.²² There was a small and transient rise in alanine and aspartate transaminases in all treatment groups, and was most pronounced in those patients receiving dalteparin. Even in patients with enzyme levels exceeding three times the upper limit of normal (ULN), none of the patients had clinical symptoms of liver dysfunction, and enzyme activities returned to normal four to six weeks after surgery.

A phase III trial compared the efficacy and safety of ximelagatran and warfarin for VTE prophylaxis following total knee

arthroplasty.²³ Patients were randomized to receive seven to 12 days of treatment with ximelagatran 24 mg twice daily started on the morning after surgery or warfarin (adjusted-dose, targeted to international normalized ratio [INR] 2.5) started on the evening after surgery. Primary endpoints were the incidence of asymptomatic and symptomatic DVT or PE and bleeding. No statistically significant differences were found in the incidence of VTE and major or minor bleeding between the ximelagatran versus warfarin groups.²³ This study did not monitor alanine or aspartate transaminases, so no information is available on either drug's effect on liver enzyme activity. The authors concluded that fixed-dose ximelagatran started the morning after total knee arthroplasty is well tolerated and is as effective as adjusted-dose warfarin for VTE prophylaxis.

The members of the EXULT A (Exanta Used to Lessen Thrombosis A) study group conducted a study of similar design to determine whether higher dose ximelagatran was superior to warfarin in patients undergoing total knee replacement.²⁴ This study differed in that the primary endpoints were the combination of VTE and death from all causes and the incidence of bleeding. Patients were randomized to 7-12 days of ximelagatran 24 mg or 36 mg twice daily started the morning after surgery or warfarin (adjusted-dose, targeted to INR 2.5) started the evening after surgery. A significantly lower rate of VTE and death was noted in the ximelagatran 36 mg group compared to the warfarin group, which was not demonstrated with the ximelagatran 24 mg dose. There were no significant differences between treatment groups with respect to bleeding.²⁴ Unlike the earlier study comparing ximelagatran to warfarin, this trial monitored alanine aminotransferase in all study patients. Enzyme concentrations greater than three times the ULN occurred in a similar number of patients receiving ximelagatran and warfarin. Based on these positive results, the EXULT A study group concluded that ximelagatran 36 mg should be considered as an alternative to warfarin.

In summary, the phase II METHRO trial found a dose-response relationship between increasing ximelagatran/mela-

gatan doses and decreasing rates of VTE and demonstrated the superiority of ximelagatran 24 mg to dalteparin in VTE prophylaxis. Two larger phase III trials compared fixed-dose ximelagatran with adjusted-dose warfarin. While both studies reported comparable efficacy rates for ximelagatran 24 mg and warfarin, the second study demonstrated the superiority of ximelagatran 36 mg in reducing the rate of VTE and all cause mortality compared to warfarin. Bleeding rates for ximelagatran in all three studies were similar to those reported for warfarin and dalteparin. The authors of both phase III trials concurred that ximelagatran is an attractive alternative to other available antithrombotic agents since it does not require laboratory monitoring for efficacy. Refer to Table 1 for detailed trial results investigating the prophylactic use of ximelagatran VTE following orthopedic surgery.

Prevention of stroke and systemic embolism in atrial fibrillation

The Stroke Prevention by Oral Thrombin Inhibitor in atrial Fibrillation (SPORTIF II) trial²⁵ was a dose-guiding study that examined the dosing, tolerability, and safety of oral ximelagatran in chronic non-valvular atrial fibrillation (NVAF) patients. Patients were assigned to receive one of three fixed-doses of ximelagatran (20 mg, 40 mg, or 60 mg) twice daily, without routine monitoring for efficacy, or adjusted-dose warfarin that was managed and monitored according to normal routines, targeting an INR of 2 to 3. Unfortunately, this small, short-term study was not powered to allow for statistical comparisons between the treatment groups. A total of 254 patients received the study drug during the 12-week period, during which time four neurologic events occurred. One nonfatal ischemic stroke and one transient ischemic attack (TIA) occurred in the ximelagatran 60 mg group and two TIAs occurred in the warfarin group. The incidence of major bleeding was low, with only one event occurring in the warfarin group. Minor bleeding was also rare and occurred in four, five, seven, and six patients receiving ximelagatran 20 mg, 40 mg, 60 mg, and warfarin, respectively. Eight patients receiving ximelagatran experienced an in-

TABLE 1. VTE PREVENTION FOLLOWING ORTHOPEDIC SURGERY TRIAL RESULTS

Reference	Study Design	Study Population	Primary Endpoint	Results
METHRO II ²²	<p>Randomized, placebo-controlled, double-dummy, dose-response phase II trial conducted in 59 centers located in 13 European countries.</p> <p>Total of 1876 patients were randomized from September 1998 to June 1999 to one of four doses of SC melagatran followed by oral ximelagatran (1495) or dalteparin (381) prophylaxis.</p> <p>1270 underwent total hip replacement 606 total knee replacement</p> <p>First melagatran dose given immediately before surgery, second injection given 7-11 hour post-op, followed by twice daily injections until oral ximelagatran could be started (within 1-3 days).</p> <p>1 mg melagatran/8 mg ximelagatran (364) 1.5 mg melagatran/12 mg ximelagatran (377) 2.25 mg melagatran/18 mg ximelagatran (375) 3 mg melagatran/24 mg ximelagatran (379)</p> <p>Dalteparin 5000 IU once daily initiated the evening before surgery and continued until evening before venography.</p> <p>Prophylaxis continued until bilateral venography performed 7-10 days after surgery to assess for DVT.</p> <p>Antithrombotics, thrombolytics, antiplatelets, and NSAIDs discontinued 7 days prior to surgery and held during study drug administration.</p> <p>Elastic compression stockings allowed but not pneumatic compression devices.</p> <p>Study sponsored by AstraZeneca.</p>	<p>Men and women scheduled for elective total hip or knee replacement, between ages of 18-85 years, and weighing 50-110 kg were recruited.</p> <p>Patients with history of VTE, suspected post-thrombotic state, immobility prior to surgery, history of stroke or bleeding (intracranial, intraocular, or gastrointestinal) in last 12 months, major surgery in last 12 weeks, cancer, uncontrolled hypertension (BP >200/100 mmHg), renal impairment (Scr >150 μmol/L) or failure, liver disease, anemia, thrombocytopenia, drug addiction, known allergy to LMWH, iodine, or contrast media, or women of child-bearing potential were excluded.</p>	<p>Combined rate of thromboembolic events (DVT/PE).</p>	<p>Total of 1477 patients were included in primary endpoint analysis; venography not performed in 182 patients and 221 were not evaluable.</p> <p>Total of 382 patients developed VTE during the study (25.9%); 213/998 total hip replacement patients (21.3%) and 169/479 knee replacement patients (35.5%).</p> <p>Significant dose-dependent decrease in VTE rates seen with increasing doses of melagatran/ximelagatran (37.8, 24.1, 23.7, and 15.1%, respectively; p=0.0001).</p> <p>Overall frequency of VTE in melagatran 3 mg/ximelagatran 24 mg group was significantly lower than dalteparin group (15.1 vs. 28.2%, p=0.0001). In total hip patients, rate of VTE was 11.9% with melagatran 3 mg/ximelagatran 24 mg vs 25.5% with dalteparin (p=0.0005). In knee replacement patients, VTE rate was 22% with melagatran 3 mg/ximelagatran 24 mg vs 33.7% with dalteparin (p=0.08, NS). No significant differences in VTE frequency noted between other melagatran/ximelagatran groups and dalteparin.</p> <p>No significant difference in total frequency of adverse events (31.7-41.5%) occurred between treatment groups during treatment or follow-up. Most commonly reported adverse event was anemia.</p> <p>Rates of excessive bleeding ranged from 1.1- 5% in melagatran/ximelagatran groups vs 2.4% in dalteparin group (NS). Number of patients with excessive bleeding was higher in melagatran 3 mg/ximelagatran 24 mg group compared to all other groups (NS).</p> <p>Small and transient rise in alanine and aspartate transaminases noted in all treatment groups, but most pronounced in dalteparin group. Increases in alanine transaminase >3x ULN occurred 10.8% in dalteparin group vs. 3.8% in melagatran/ximelagatran groups. No differences in enzyme levels noted between treatment groups 4-6 weeks after surgery.</p>
Francis et al. ²³	<p>Randomized, placebo-controlled, double-blind, parallel-group phase III trial conducted in 74 centers in the US and Canada.</p> <p>Total of 680 patients were randomized from March to September 2000 to receive either ximelagatran (348) or warfarin (332) prophylaxis for 7-12 days.</p> <p>Ximelagatran 24 mg twice daily initiated the morning after surgery (at least 12 hours post-op) while warfarin initiated the day of surgery after adequate hemostasis with dose adjusted to target INR 2.5.</p> <p>Efficacy was evaluated by unilateral venography, conducted within 12 hours of final antithrombotic dose and performed on leg or legs that had undergone surgery, and clinical evaluation between weeks 4-8.</p> <p>Antithrombotic, thrombolytic, or antiplatelet drugs discontinued within 7 days of surgery and held during study drug administration.</p> <p>Study sponsored by AstraZeneca.</p>	<p>Men and women scheduled for elective total knee arthroplasty, older than 18 years of age, and weighing 40-125 kg were recruited</p> <p>Women had to be surgically sterile, post-menopausal for at least 2 years, or using reliable contraception to be eligible.</p> <p>Patients with immobilization for more than 3 days prior to surgery, history of major surgery, ischemic stroke, or MI within 30 days, history of bleeding (intracranial, retro-peritoneal, intraocular, and GI) within 90 days, uncontrolled hypertension, cancer, liver disease, thrombocytopenia, drug or alcohol abuse within 6 months, allergy to contrast media or iodine, contra-indication to warfarin, or severe renal impairment (CrCL <30 mL/min) were excluded.</p>	<p>Incidence of proximal or distal DVT or PE</p>	<p>Total of 537 patients included in primary endpoint analysis (276 in ximelagatran group, 261 in warfarin group); 69 patients did not have evaluable venograms.</p> <p>Treatment duration was 8.1 ± 2.1 days for ximelagatran group vs 7.7 ± 2.3 days for warfarin group (NS).</p> <p>Total of 110 patients developed VTE during the study; 53 (19.2%) in ximelagatran group compared to 67 (25.7%) in warfarin group (p=0.07, NS).</p> <p>Approximately one-third of warfarin patients had INR values between 1.8-3 at day 3; one-half had INR values in this range at venography. No trend was noted toward higher VTE rate when INR was sub-therapeutic.</p> <p>Most commonly reported adverse effect was wound bleeding (7% in ximelagatran group vs 5.5% in warfarin group; p=0.2). Overall bleeding rates between treatment groups were similar for major bleeding (1.7 vs 0.9%, respectively; p=0.2, NS) and minor bleeding (7.8 vs 6.4%, respectively; p=0.2, NS).</p> <p>Changes in serum alanine or aspartate transaminase concentrations were not reported.</p>
EXULT A Study Group ²⁴	<p>Randomized, placebo-controlled, double-blind, parallel-group trial</p> <p>Total of 2301 patients recruited from 116 centers in the U.S., Canada, Israel, Mexico, and Brazil were randomized to receive twice-daily ximelagatran 24 mg (775), twice-daily ximelagatran 36 mg (762), or warfarin (764) prophylaxis for 7-12 days.</p> <p>Ximelagatran initiated the morning after surgery (at least 12 hours post-op) while warfarin initiated the evening of surgery with dose adjusted to target INR 2.5 and continued until venography performed 7-12 days later.</p> <p>Antithrombotic, thrombolytic, or antiplatelet drugs discontinued within 7 days of surgery and held during study drug administration.</p> <p>Study sponsored by AstraZeneca</p>	<p>Men and women (without childbearing potential) scheduled for total knee replacement and weighing 40-136 kg were recruited.</p> <p>Patients using pneumatic leg compression, with immobilization for more than 3 days prior to surgery, history of major surgery, stroke, MI within 30 days, history of bleeding (intracranial, retro-peritoneal, intraocular, or GI) within 90 days, uncontrolled hypertension, cancer, alanine or aspartate aminotransferase level >2x ULN, thrombocytopenia, drug or alcohol abuse within 6 months, allergy to contrast media or iodine, contraindication to warfarin, or impaired renal function (CrCL <30 mL/min) were excluded.</p>	<p>Incidence of total DVT, PE, and death from all causes</p>	<p>Total of 1851 patients included in primary endpoint analysis (629 in ximelagatran 36 mg group, 614 in ximelagatran 24 mg group, and 608 in warfarin group); 434 patients did not have evaluable venography and 16 did not receive treatment.</p> <p>Total number of patients who developed VTE or died from any cause was 449 patients; 128 receiving ximelagatran 36 mg, 153 receiving ximelagatran 24 mg, and 168 receiving warfarin. Incidence of VTE or death was significantly lower for ximelagatran 36 mg group compared to warfarin group (20.3 vs. 27.6%; p=0.003) and similar between the ximelagatran 24 mg and warfarin groups (24.9 vs 27.6%, p=0.28, NS).</p> <p>Bleeding events during treatment was similar between treatment groups for major bleeding (ximelagatran groups 0.8% vs warfarin group 0.7%; NS) and any bleeding (ximelagatran 36 mg 5.3%, ximelagatran 24 mg 4.8%, and warfarin 4.5%; NS).</p> <p>Alanine aminotransferase concentrations were elevated > 3x UNL in 10 ximelagatran patients vs 12 warfarin patients.</p>

TABLE 2. STROKE PREVENTION IN ATRIAL FIBRILLATION STUDIES

Reference	Study Design	Study Population	Primary Endpoint	Results
SPORTIF II ²⁵	<p>Randomized, parallel-group, dose-guiding trial conducted in 37 centers in 11 countries in Europe and the U.S.</p> <p>257 patients were randomized to receive ximelagatran 20 mg, 40 mg, or 60 mg twice daily or open-labeled warfarin, dose adjusted to targeted INR of 2-3 according to local clinical practice.</p> <p>Nonsteroidal anti-inflammatory drugs or fibrinolytic agents were prohibited within 7 days of enrollment.</p> <p>Aspirin therapy was not recommended, but doses ≤160mg/day could be used at investigator's discretion.</p>	<p>Patients ≥18 years of age with chronic NVAF verified by 2 or more ECGs within the previous year and 1 defined risk factor for stroke were recruited.</p> <p>Risk factors included: HTN, age ≥65 years, previous stroke or TIA, previous systemic embolism, LVEF ≤40% or symptomatic CHF within 3 months, diabetes mellitus, or coronary artery disease.</p> <p>Patients with history of stroke or systemic embolism within 2 years, conditions associated with increased bleeding risk, NVAF secondary to reversible disorders, presence of mechanical heart valves, MI, CABG or PTCA within 3 months, BP >180/100 mmHg, liver insufficiency, contraindications to warfarin, anemia, thrombocytopenia, or renal impairment (CrCL <40 mL/min) were excluded.</p>	None	<p>Total 254 patients received treatment (59 ximelagatran 60 mg, 62 ximelagatran 40 mg, 66 ximelagatran 20 mg, and 67 warfarin).</p> <p>Sixty-one percent of patients were male with a mean age of 69.5 years.</p> <p>One nonfatal ischemic stroke and one transient ischemic attack (TIA) occurred in the ximelagatran group and two TIAs occurred in the warfarin group.</p> <p>Only one major bleed occurred in a patient receiving warfarin therapy. Minor bleeds were rare and occurred in 4, 5, 7, and 6 patients receiving ximelagatran 20 mg, 40 mg, 60 mg, and warfarin, respectively.</p> <p>Adverse events were reported in 90 ximelagatran-treated patients (48.1%) and 34 warfarin-treated patients (50.7%).</p> <p>Eight patients had transient increases in S-ALAT levels >3x ULN after 4-8 weeks of ximelagatran treatment. Levels normalized during continued treatment in 5 patients and after drug withdrawal in 3 patients. All patients remained asymptomatic.</p>
SPORTIF III ²⁶	<p>Randomized, open-label, parallel-group trial conducted in 259 centers in 23 countries in Europe, Asia, and Australia.</p> <p>Total of 3410 patients from August 2000 to September 2001 were randomized to receive either ximelagatran 36 mg twice daily or warfarin, dose adjusted titrated to targeted INR of 2-3 according to local clinical practice.</p> <p>Mean duration of follow-up was 17.4 months or 4941 patient-years of exposure.</p> <p>Concomitant daily aspirin therapy (dose <100 mg) allowed. Other antithrombotic drugs were prohibited.</p> <p>Study sponsored by AstraZeneca</p>	<p>Similar inclusion and exclusion criteria as SPORTIF II except renal impairment was defined as CrCL <30 mL/min, and patients with active liver disease or persistent elevation of liver enzymes >2x UNL or women of child-bearing potential, pregnant, or lactating were excluded.</p>	Stroke (ischemic or hemorrhagic) or systemic embolic events	<p>Total of 3407 patients were randomized (1704 to ximelagatran, 1703 to warfarin) and 2842 completed the study.</p> <p>Primary events occurred in 56 warfarin patients during 2440 patient-years at risk (yearly rate 2.3%) compared to 40 ximelagatran patients during 2446 patient-years (yearly rate 1.6%) (p=0.10; Absolute Risk Reduction = 0.7%).</p> <p>Major bleeding rates were similar for ximelagatran and warfarin (1.3% vs 1.8%, respectively; p=0.2281). Combined rate of major and minor bleeding was significantly lower for ximelagatran vs warfarin group (25.8% vs. 29.8%, respectively; p=0.0065)</p> <p>Significantly larger number of ximelagatran patients used aspirin for at least half of the study period compared to the warfarin group (13% vs. 10%, respectively; p=0.01).</p> <p>Alanine aminotransferase levels >3x ULN occurred in 14 (1%) warfarin patients vs 107(6%) ximelagatran patients (p<0.0001). Elevations >5x ULN occurred in 57 patients assigned to ximelagatran (3.4%).</p>

crease in S-alanine aminotransferase (S-ALAT) above three times the ULN. All eight patients were asymptomatic and the S-ALAT concentrations normalized with continued treatment or drug withdrawal.

As a result of the 12-week SPORTIF II trial, the long-term SPORTIF III trial²⁶ was conducted to compare the safety and efficacy of extended ximelagatran therapy with warfarin in patients with NVAF at risk for ischemic stroke. In this study, 3407 patients with NVAF and one or more risk factors for stroke were randomized to receive either ximelagatran 36 mg twice daily or warfarin (adjusted-dose, targeted to INR 2-3). Concomitant low-dose aspirin therapy was permitted during the study in doses up to 100 mg daily. The mean duration of follow-up was 17.4 months. The primary endpoint of ischemic or hemorrhagic stroke or systemic embolism was not significantly different between the ximelagatran versus warfarin treatment groups. While major bleeding rates were similar for ximelagatran and

warfarin, the combined rate of major and minor bleeding was significantly lower for the ximelagatran group.²⁶ Serum alanine aminotransferase concentrations greater than three times ULN occurred more frequently in the ximelagatran group than warfarin. Rises took place two to six months after initiation of treatment and returned towards baseline either spontaneously or after discontinuation of treatment. While this trial demonstrated the efficacy of ximelagatran prophylaxis in high-risk patients, important criticisms include the trial's open-label design and the significantly larger number of patients in the ximelagatran group who used aspirin for at least half of the study period.

To summarize, two studies have investigated the use of ximelagatran in patients with atrial fibrillation, although only one of these trials was designed for statistical comparisons. The results of SPORTIF III suggest that ximelagatran is as efficacious as warfarin in preventing stroke in NVAF patients. The results of SPORTIF

V, a large phase III trial similar in design to SPORTIF III, are eagerly awaited. As opposed to the open-label design of SPORTIF III, SPORTIF V is double-blinded and will provide additional information regarding the comparison of ximelagatran and warfarin in this patient population. Refer to Table 2 for a detailed summary of the SPORTIF trials.

Secondary prophylaxis after myocardial infarction

The efficacy and safety of the oral direct thrombin inhibitor in patients with recent myocardial damage (ESTEEM) trial²⁷ is the only one to date that has investigated the use of ximelagatran as secondary prophylaxis after myocardial infarction. This phase II, double-blinded, dose-guiding study recruited patients who had recent ST-segment elevation (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI) along with at least one of the following risk factors: age ≥65 years, diabetes mellitus, previous MI, known multivessel coronary disease, previous is-

chemic stroke, peripheral arterial disease, symptomatic congestive heart failure or ejection fraction <40%, or history of hypertension. Major exclusion criteria included percutaneous coronary intervention performed in the last four months or planned within 60 days, recent stroke, conditions known to increase bleeding risk, thrombocytopenia, need for treatment with other oral antithrombotic agents, blood pressure >180/100 mmHg, renal dysfunction (creatinine clearance <30 ml/min), known liver disease, or liver enzyme concentrations >2x ULN. A total of 1883 patients were randomized from January 2001 to September 2002 from 191 centers in 18 countries to receive one of four ximelagatran doses (24 mg, 36 mg, 48 mg, or 60 mg) twice daily or placebo. All patients received aspirin 160 mg once daily for cardioprotection. The primary efficacy outcome was the dose-response relationship of ximelagatran combined with aspirin therapy in comparison with placebo (aspirin alone) for the combined endpoint of all-cause mortality, non-fatal MI, and severe recurrent ischemia. After six months of treatment, the risk of the composite endpoint was significantly lower in the ximelagatran combined with aspirin groups compared to aspirin alone (placebo) (12.7% vs. 16.3%, respectively; $p=0.036$). No indication of a dose-response relationship was observed between the four ximelagatran treatment groups. Total bleeding (major and minor) was more frequent in patients receiving ximelagatran plus aspirin than in those on aspirin alone (22% vs. 13%, HR 1.76, 95% CI 1.38-2.25), and increased in a dose-related manner. Major bleeding events were low and occurred in 1.8% of patients treated with ximelagatran and 0.9% of patients receiving placebo (Hazard Ratio 1.97, 95% CI 0.8-4.84). The number of patients with alanine transaminase concentrations more than 3x ULN was significantly higher in the ximelagatran groups than the placebo group ($p<0.0001$). The raised concentrations were detected at two to six months of treatment, peaked after 60-120 days, and returned to normal within 60-90 days regardless of whether treatment continued. On account of the lack of a dose-response relationship, the authors concluded that 24 mg twice-daily

ximelagatran achieved maximum efficacy with an acceptable safety profile.²⁷ Large-scale trials are needed to provide more definitive evidence of the efficacy and safety of ximelagatran as secondary prophylaxis after MI.

Treatment of acute DVT and secondary prophylaxis of VTE

The role of ximelagatran in the treatment of acute DVT was investigated in the Thrombin Inhibitor in Venous Thromboembolism (THRIVE) I trial.²⁸ THRIVE I was a dose-guiding study conducted from October 1998 to February 2000 in 41 centers in Sweden, Norway, Germany, and the Czech Republic. Three hundred fifty patients with acute DVT (83% proximal, 17% distal) were randomized to receive one of four double-blinded doses of ximelagatran (24 mg, 36 mg, 48 mg, or 60 mg) twice daily or open-label dalteparin (200 IU/kg SQ daily, maximum dose 18,000 IU) and adjusted-dose warfarin (titrated to target INR of 2-3). Treatment with unfractionated heparin or LWMH was permitted for a maximum of 24 hours prior to the first dose of study drug. The exclusion criteria used in this trial were similar to all other ximelagatran trials. Given that this was the first study involving outpatient administration of ximelagatran and the ethical considerations of a dose-guiding study in this area, the investigators limited the treatment duration to 14 days. After 14 days of study drug treatment, the patients continued treatment for another 14 days with standard therapy. As a result of the short treatment duration, the clinical endpoint of treatment failure rather than VTE recurrence was evaluated. Paired venograms were measured at baseline and at two weeks to assess the progression or regression of thrombus size and to obtain a Marder score (calculated volume of deep vein segments, max score = 40). A total of 295 patients had evaluable venograms (84%). Thrombus regression occurred in 69% of patients treated with either ximelagatran or dalteparin-warfarin (NS). Marder scores were similar between all groups. Thrombus progression occurred in 8% and 3% of patients treated with ximelagatran and dalteparin-warfarin, respectively (NS). No dose-response relationship was observed between the four ximelagatran treatment

groups. Only two patients receiving ximelagatran and two receiving dalteparin-warfarin discontinued the study due to bleeding. Occult gastrointestinal bleeding, microscopic hematuria, and total incidence of bleeding were similar between groups.²⁸ Mean alanine aminotransferase levels at the end of the study period were 25.8-29.7 IU/L in the ximelagatran groups and 53.2 IU/L in the dalteparin-warfarin group. While the THRIVE I study suggests a possible role for ximelagatran in the treatment of DVT, larger-scale long-term studies are required to assess clinical endpoints.

To assess the efficacy of ximelagatran for secondary prevention of VTE, the THRIVE III trial²⁹ compared the efficacy of ximelagatran prophylaxis to placebo in patients who had received six months of anticoagulation for DVT or PE. A total of 1233 patients were randomized between November 1999 and October 2000 at 142 centers in 18 countries to either ximelagatran 24 mg (617 patients) or placebo (616) twice daily for 18 months. The exclusion criteria used did not differ from other previous ximelagatran trials. Bilateral ultrasonography of the legs and perfusion lung scans were performed at baseline to assess the presence of VTE, as well as in response to symptoms for the duration of the study. The primary endpoint of symptomatic recurrent VTE was reported in 12 patients receiving ximelagatran versus 71 patients taking placebo (2.8% vs. 12.6%, respectively; $p<0.001$). Secondary endpoints included overall mortality, bleeding and ALT levels. Death from any cause occurred in six and seven patients in the ximelagatran and placebo groups, respectively. Major bleeding rates were low and similar for both groups (1.1% and 1.3%, respectively). Elevations in ALT greater than 3x ULN were noted in a higher percentage of patients treated with ximelagatran (6.4% vs. 1.2%, respectively; $p<0.001$). These levels returned to normal whether therapy was continued or discontinued in all but four patients; two with known hepatitis and two asymptomatic patients with levels at 1.6 and 1.8 times the upper limit of normal at the last observation in the study period.²⁹ The THRIVE III Investigators concluded that treatment with ximelagatran for an additional 18 months

after initial six month treatment for VTE was safe and effective at preventing recurrences.

INDICATIONS

AstraZeneca announced the submission of a New Drug Approval (NDA) to the Food and Drug Administration (FDA) for its oral direct thrombin inhibitor, ximelagatran (Exanta™), in December of 2003. The indications being sought include prevention of venous thromboembolism (VTE) in patients undergoing knee replacement surgery; prevention of stroke and systemic embolism associated with atrial fibrillation; and long-term secondary prevention of VTE following standard treatment for an episode of acute VTE. Exanta™ has already received approval in France for the prevention of VTE in major orthopedic surgery.

CONTRAINDICATIONS, WARNINGS, PRECAUTIONS

It is unclear at this time what contraindications, warnings, and precautions ximelagatran will have or if they will be similar to those of current antithrombotic therapies. One observation of concern that has been reported in multiple studies with ximelagatran²²⁻²⁹ is an increase in alanine aminotransferase (ALT) to above 3x ULN. This elevation in liver enzyme concentration generally occurs in the first four months for therapy²⁹ and regresses back to normal with drug discontinuation or further observation. No serious sequelae (e.g. liver failure) have been observed to date. Ximelagatran should not be used in patients with creatinine clearance <30 mL/min pending further study in this population.

ADVERSE REACTIONS

As with other antithrombotic treatments, bleeding is the main adverse effect to be monitored. Reported rates of major and minor bleeding during ximelagatran therapy have been found to be similar to those for warfarin^{23,24} and dalteparin.^{22,28} The incidence of bleeding was higher when ximelagatran therapy was combined with aspirin in the ESTEEM trial²⁷ and the potential risk with other antiplatelet, antithrombotic, and NSAIDs should be anticipated.

DRUG INTERACTIONS

Ximelagatran does not appear to have any interactions with the cytochrome P-450 system. Drugs metabolized by CYP2C19, CYP3A4, and CYP2C9 have been studied to support this finding.^{30,31}

MONITORING

Studies have found ximelagatran to produce predictable and reproducible pharmacokinetic and pharmacodynamic properties. No clinically significant interactions with the cytochrome P-450 system or food have been observed. Metabolism appears to be unaffected by age, sex, body weight, or ethnic origin. As a result of these properties, no laboratory monitoring for efficacy or serum drug concentrations are required during therapy.

DOSING

Phase II dose-guiding studies utilized ximelagatran dosages ranging from 12 mg to 60 mg twice daily. Larger phase III trials have further investigated ximelagatran doses of 24 mg and 36 mg in the prevention of VTE following knee-replacement and 36 mg for the prevention of VTE or systemic embolism among patients with atrial fibrillation. While a dose-dependent relationship was observed in the METHRO II trial, other dose-guiding studies have not repeated this finding. Based on current published data, the dosing of ximelagatran would likely be 24 mg or 36 mg administered orally twice daily depending on the drug's indication for use (VTE prevention in orthopedic patients or stroke prevention in atrial fibrillation patients, respectively).

CONCLUSION

Ximelagatran is a direct thrombin inhibitor under investigation as a unique oral antithrombotic agent that requires no laboratory monitoring for efficacy. Ximelagatran has been studied most extensively in the area of DVT prevention in patients undergoing hip or knee replacement, and the results of two phase III trials suggest that ximelagatran may be at least as efficacious as warfarin. In the phase III SPORTIF III trial investigating the use of ximelagatran for the prevention of stroke in NVAF patients, the drug was found to be equal in efficacy to war-

farin. The results of SPORTIF V will provide further valuable information regarding the use of ximelagatran for stroke prevention in this patient population. Initial studies have also been performed to investigate the use of ximelagatran in the treatment and secondary prophylaxis of DVT and secondary prophylaxis after MI. Preliminary results show positive benefits with ximelagatran therapy but further studies are needed in these areas before changes in treatment recommendations are made.

Importantly, trials with ximelagatran have found rates of major and minor bleeding similar to the gold standards for these conditions, namely LMWH and warfarin. Increases in ALT to levels 3x ULN or greater have been reported in several studies. This warrants frequent monitoring of liver function tests with the use of this medication. Since the drug is eliminated primarily by the kidneys, published trials to date have excluded patients with renal dysfunction, so use of ximelagatran in these patients will likely prompt a dosage reduction or avoidance of therapy.

Several important questions remain unanswered at this time regarding the potential role of ximelagatran. *How would this medication fit into (or change) the existing treatment guidelines for antithrombotic therapy and how would we select the patients that would benefit most from this drug?* While outcomes have been positive in the areas of VTE and stroke prevention in orthopedic surgery and NVAF, respectively, the populations studied may not allow for generalization to a large number of patients with comorbidities. *Is a lack of required monitoring for efficacy necessarily a good thing?* While frequent clinic visits present challenges for certain patients due to transportation or lifestyle conflicts, they provide an excellent opportunity for routine follow up, promotion of adherence, and patient collaboration with a health care professional to reach a tangible goal. Will patients currently followed by anticoagulation clinics require and benefit from periodic follow-up for disease and drug monitoring if taking ximelagatran? *What will the total cost of therapy be?* Despite the lack of laboratory monitoring for efficacy, monitoring for toxicity (liver function tests) during ximelagatran therapy is a possibility that

would add additional treatment costs. Also, the cost of ximelagatran must be compared to warfarin, which is available as a generic and is inexpensive compared to branded drugs. Thus, the answers to many important questions regarding the future role of ximelagatran are yet to be worked out and will be important in determining how best to utilize this novel drug. ●

Lee Skrupky is a 4th year PharmD student at the UW School of Pharmacy. Karen Kopacek is a clinical assistant professor at the UW School of Pharmacy.

REFERENCES

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults. *JAMA* 2001; 285:2370-2375.
2. American Dental Association, American Academy of Orthopaedic Surgeons. Advisory statement: antibiotic prophylaxis for dental patients with total joint replacements. ADA/AAOS; 2003 Available at: <http://www.aaos.org/wordhtml/papers/advistmt/1014.htm>. Accessed 4/27/04.
3. Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. *Chest* 2001; 119:132S-175S.
4. Albers GW, Dalen JE, Laupacis A, et al. Antithrombotic therapy in atrial fibrillation. *Chest* 2001; 119:194S-206S.
5. Gustafsson D, Nyström J-E, Carlsson S, et al. The direct thrombin inhibitor melagatran and its oral prodrug H 376/95: intestinal absorption properties, biochemical and pharmacodynamic effects. *Thrombosis Res* 2001; 101:171-181.
6. Hauptmann J. Pharmacokinetics of an emerging new class of anticoagulant/antithrombotic drugs: a review of small-molecule thrombin inhibitors. *Eur J Clin Pharmacol* 2002; 57:751-758.
7. Sarich TC, Eriksson UG, Mattsson C, et al. Inhibition of thrombin generation by the oral direct thrombin inhibitor ximelagatran in shed blood from healthy male subjects. *Thromb Haemost* 2002; 87:300-305.
8. Lebrazi J, Elalamy I, Samama MM. The in vitro effects of melagatran on clot bound thrombin. *Haemostasis* 2000; 30(Suppl 1):54.
9. Eriksson UG, Wollbratt M, Wolzt M, et al. Comparison of the pharmacokinetics of ximelagatran, an oral direct thrombin inhibitor, in patients with nonvalvular atrial fibrillation and elderly healthy subjects [abstract]. *Clin Pharmacol Ther* 2002; 71(2):P95.
10. Eriksson BI, Arfwidsson AC, Frison L, et al. A dose-ranging study of the oral direct thrombin inhibitor, ximelagatran, and its subcutaneous form, melagatran, compared with dalteparin in the prophylaxis of thromboembolism after hip or knee replacement: METHRO I. *Thromb Haemost* 2002; 87:231-237.
11. Wahlander K, Lapidus L, Olsson CG, et al. THRIVE IV: an open-label, pilot study of the treatment of pulmonary embolism with the oral direct thrombin inhibitor ximelagatran [abstract]. *Blood* 2001; 98(11):abstract 1130.
12. Cullberg M, Eriksson H, Eriksson UG, et al. Pharmacokinetics of melagatran after oral dosing with ximelagatran, a direct thrombin inhibitor, in patients with acute venous thromboembolism (VTE) [abstract]. *Clin Pharmacol Ther* 2002; 71(2):P61.
13. Johansson LC, Frison L, Logren U, et al. Influence of age on the pharmacokinetics and pharmacodynamics of ximelagatran, an oral direct thrombin inhibitor. *Clin Pharmacokinet* 2003; 42:381-392.
14. Grind M, Hamrén B, Bååthe S, et al. Pharmacokinetics of the oral direct thrombin inhibitor ximelagatran in patients with nonvalvular atrial fibrillation receiving long-term treatment: a population analysis by nonlinear mixed effect modeling [abstract]. *Clin Pharmacol Ther* 2002; 71(2):P31.
15. Eriksson UG, Eriksson-Lepkowska M, Ohlsson L, et al. Mild-to-moderate liver impairment has no influence on the pharmacokinetics of ximelagatran, an oral direct thrombin inhibitor [abstract]. *Clin Pharmacol Ther* 2002; 71(2):P99.
16. Eriksson UG, Eriksson-Lepkowska M, Ohlsson L, et al. The pharmacokinetics and pharmacodynamics of ximelagatran in patients with mild-to-moderate impairment of liver function [abstract]. *Blood* 2001; 98(11):abstract 184.
17. Johansson S, Eriksson UG, Samuelsson O, et al. The influence of severe renal impairment on the pharmacokinetics of oral ximelagatran and subcutaneous melagatran [abstract]. *Clin Pharmacol Ther* 2002; 71(2):P96.
18. Eriksson UG, Samuelsson O, Attman PO, et al. The pharmacokinetics and pharmacodynamics of oral ximelagatran and subcutaneous melagatran in patients with severe renal impairment [abstract]. *Blood* 2001; 98(11):abstract 1127.
19. Sarich TC, Peters GR, Wollbratt M, et al. No influence of obesity on the pharmacokinetics and pharmacodynamics of melagatran, the active form of the oral direct thrombin inhibitor, ximelagatran. *Clin Pharmacokinet* 2003; 42:485-492.
20. Johansson LC, Frison L, Lofgren U, et al. Influence of age on the pharmacokinetics and pharmacodynamics of ximelagatran, an oral direct thrombin inhibitor. *Clin Pharmacokinet* 2003; 42:381-392.
21. Johansson LC, Andersson M, Fager G, et al. No influence of ethnic origin on the pharmacokinetics and pharmacodynamics of melagatran, following oral administration of ximelagatran, a novel, oral direct thrombin inhibitor, to healthy male volunteers. *Clin Pharmacokinet* 2003; 42:475-484.
22. Eriksson BI, Bergqvist D, Kålebo P, et al. Ximelagatran and melagatran compared with dalteparin for prevention of venous thromboembolism after total hip or knee replacement: the METHRO II randomised trial. *Lancet* 2002; 360:1441-1447.
23. Francis CW, Davidson BL, Berkowitz SD, et al. Ximelagatran versus warfarin for the prevention of venous thromboembolism after total knee arthroplasty. *Ann Intern Med* 2002; 137:648-655.
24. Francis CW, Berkowitz SD, Comp PC, et al. for the EXULT A Study Group. Comparison of ximelagatran with warfarin for the prevention of venous thromboembolism after total knee replacement. *N Engl J Med* 2003; 349:1703-1712.
25. Petersen P, Grind M, Adler J, for the SPORTIF II Investigators. Ximelagatran versus warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. *J Am Coll Cardiol* 2003; 41:1445-1451.
26. Executive Steering Committee on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomized controlled trial. *Lancet* 2003; 362:789-797.
27. Wallentin L, Wilcox RG, Weaver WD, et al., for the ESTEEM Investigators. Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomized controlled trial. *Lancet* 2003; 362:1691-1698.
28. Eriksson H, Wahlander K, Gustafsson D, et al., for the THRIVE investigators. A randomized, controlled, dose-guiding study of the oral direct thrombin inhibitor ximelagatran compared with standard therapy for the treatment of acute deep vein thrombosis: THRIVE I. *J Thromb Haemost* 2003; 1:41-47.
29. Schulman S, Wahlander K, Lundstrom T, et al., for the THRIVE III Investigators. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. *N Engl J Med* 2003; 349:1713-1721.
30. Johansson S, Eriksson-Lepkowska M, Thuresson A, et al. Ximelagatran, an oral direct thrombin inhibitor, has no effect on the pharmacokinetics of P450-metabolized drugs [abstract]. *Clin Pharmacol Ther* 2002; 71(2):P65.
31. Eriksson-Lepkowska M, Thuresson A, Johansson S, et al. The effect of the oral direct thrombin inhibitor ximelagatran on the pharmacokinetics of P450-metabolized drugs, in healthy male volunteers [abstract]. *Blood* 2001; 98(11):abstract 3987.