Ximelagatran Compared with Heparin and Warfarin in the Primary Treatment of Deep Vein Thrombosis and/or Pulmonary Embolism

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A. Study Purpose and Rationale

This study proposes to examine the efficacy and safety of Ximelagatran (AstraZeneca), an experimental orally administered anticoagulant in the primary treatment of pulmonary emobolism or deep vein thrombosis. Traditional treatment of these conditions, also collectively referred to as venous thromboembolism (VTE) require an initial 5-7 days of hospitalization with daily monitoring of serum aPTT while receiving a continuous unfractionated heparin infusion, followed by 6-months of warfarin therapy requiring frequent outpatient blood draws for dosage adjustment to maintain a therapeutic INR. Given an estimated incidence of 1 of 1000 patients per year, studying more easily administered therapies can result in increased convenience and a cost-benefit for the medical establishment. Ximelagatran is a direct thrombin inhibitor with predictable and reproducible pharmokinetic properties and a broad therapeutic window which obviates the need for chronic monitoring of serum markers of anticoagulation. In addition it is not metabolized by the P450 liver enzymes and therefore does not interfere with the metabolism of drugs commonly used in clinical practice. Studies comparing Ximelagatran with warfarin or placebo in the prevention of deep vein thrombosis after knee surgery or secondary prevention of VTE, respectively have shown it to be a well tolerated and safe alternative to warfarin therapy for these indications. This study proposes to establish ximelagatran as a safe, efficacious, more convenient, and potentially cost-saving alternative in the primary treatment of VTE.

B. Study Design and Statistical Analysis

This will be a randomized, double blind, placebo-controlled, parallel group study with a standard therapy arm involving unfractionated heparin transitioned to warfarin and the experimental therapy arm using the study drug. The standard therapy arm will also receive a placebo pill twice daily instead of the study drug. The study drug arm will receive ximelagtran 24 mg twice daily and initially receive continuous saline infusion instead of heparin and then a placebo pill instead of warfarin. All laboratory measurements will be sent to a central study center where medication adjustments will be made for both treatment arms and placebo arms according to standardized protocols. Using an estimated rate of recurrence of VTE of 2% in the standard therapy group, detecting an absolute difference of 2.5% with an alpha error of 0.05 and a power of 90% will require 1134 patients in each arm of the study. Adding an estimated loss to follow-up during the study of 10% brings the total number of patients to 1250 per arm and 2500 for the entire study. The patients will be randomized to each arm using a computer randomization. At the conclusion of the study period the rate of recurrence in each arm of the study will be calculated as a relative risk and rejection or acceptance of the null hypothesis will be determined using the Chi-square test using intention-to-treat principles.

C. Study Procedure

All patients with an objectively documented VTE will have baseline standard laboratory analysis of their CBC, chemistries, and coagulation profiles at the start of the study. All patients have a full diagnostic evaluation for both pulmonary embolism and deep vein thrombosis documented. Diagnostic criteria for deep-vein thrombosis include either a noncompressible segment on compression ultrasonography or an intraluminal filling defect on venography of the lower extremities. Diagnostic

criteria for pulmonary emoblism include an intraluminal filling defect on spiral computed tomography (CT)or pulmonary angiography, a high-probability ventilation-perfusion lung scan, or a nondiagnostic lung scan with documentation of deep-vein thrombosis.

All patients will initially be hospitalized for 5-7 days while on continuous infusion of actual or placebo anticoagulant and all of them will have their aPTT levels checked every six hours until in the therapeutic range and daily subsequently. On hospital day one patients will also be started on placebo or ximelagatran twice daily. Patients will be started on warfarin as soon as possible, but no later than three days after enrollment into the trial. Starting on hospital day three patients will have their INR checked daily until it is in the therapeutic range. Patients will subsequently have their coagulation profiles checked every other day for the first week, then bi-weekly for the 1st month and monthly for the remaining six months.

Patients will be instructed on the symptoms of recurrent VTE be asked to report the study center ER or clinic if any of the symptoms arise. In addition, followup visits to screen for symptoms of physical findings of VTE will be scheduled at bi-monthly intervals throughout the study period. All recurrences will be evaluated and subject to the same diagnostic criteria outlined above. In addition, patients will have CBC and chemistry analysis at bi-monthly intervals and will be screened for any potential side effects of therapy with a focus on bleeding. Major bleeding is defined as a drop in hemoglobin by >2, a need for transfusion of 2 or more units of packed red cells, bleeding into a vital structure such as retroperitoneal or intracranial, or any bleeding that requires cessation of therapy. All other bleeding will be considered minor.

D. Study Drugs

Unfractionated heparin and warfarin are both approved standard therapy for VTE. Ximelagatran is an investigational orally administered thrombin inhibitor. Recent phase III trials for secondary prevention of VTE and prevention of DVT/PE after knee surgery both safely used a dosage of 24 mg twice daily. A transient and self-limited liver transaminase elevation was seen in 6.4% of patients during the first four months of therapy with ximelagatran. Bleeding rates secondary too all three drugs in this study have been equivalently reported in previous trials as 1-4%.

E. Medical Device

This study will not require the use of investigational devices. All device use including ultrasound, Cat Scan, V/Q scanning and angiography equipment will follow standard clinical algorithms previously described elsewhere.

F. Study Questionnaires

This study will not involve the use of questionnaires.

G. Study Subjects

All patients greater than 18 years of age are eligible for inclusion if they have an objectively confirmed deep vein thrombosis of the leg or pulmonary embolism requiring antithrombotic therapy. Patients are considered ineligible for the study if they receive therapeutic doses of anticoagulation with heparin or oral anticoagulants for greater than 24 hours; if they require thrombolysis, embolectomy, or a vena cava filter; if anticoagulation is contraindicated for any reason, i.e. bleeding diathesis or thrombocytopenia (platelets <100,000); if they have a creatinine clearance less than 30 ml/hr; if they have clinically significant liver disease or persistent elevations of their transaminases greater than 3 times normal. In addition patients will be excluded if they are pregnant or lactating and if they have a serious illness with an expected survival of less than 6 months.

H. Recruitment of Subjects

A nurse practitioner will screen for all potentially eligible patients presenting to the emergency rooms of each study facility. If a patient is identified, they will be eligible for the study only if his/her physician can be contacted to discuss eligibility for the study and the physician grants permission to approach the patient. If no primary physician is identified by the patient the patient will be considered eligible for the study.

I. Confidentiality of Study Data

All study subjects date will be kept under a unique code identifier and will be accessible only to the principle investigators on the trial.

J. Potential Conflict of Interest

Investigators involved in this trial do not have any affiliation with AstraZeneca or its affiliate companies.

K. Location of the Study

This will be a multicenter trial. Centers will be allowed to participate once they have obtained IRB approval at their home institutions. At CPMC this trial will be based at the clinical offices of the investigators within the department of medicine.

L. Potential Risks

The study drug, ximelagatran may not be as effective as the standard therapy leading to an increased risk of recurrent deep vein thrombosis or pulmonary embolism compared to the patients in the heparin/warfarin arm of the study. This may lead to an increased risk of worsening of the patients' condition or even death. Anticoagulation carries a 2-4% risk of major bleeding during the course of the study period. An approximate 6% risk of elevated transaminases has been associated with the use of ximelagatran in prior trials, but this lab abnormality is of unclear significance. In addition, there may be other adverse outcomes associated with the use of ximelagatran that have not been previously reported.

M. Potential Benefit

Patients may or may not benefit from participation in this study. There is a benefit to society from knowing the safety and efficacy of an additional therapeutic option for VTE. Patients will also receive treatment for their condition at no cost.

N. Alternative Therapies

The alternative to the study drug is the standard therapy which will be the control arm of this study. After the completion of the trial period of 6 months patients will have the option of continuing on long-term low dose warfarin or conventional dose warfarin as per the PREVENT or ELATE trials, respectively.

O. Compensation to Subjects

Subjects will be compensated for any cost they incur as a direct result of the study. These include travel, hospital, clinic visits, and any necessary testing throughout the duration of the trial. Otherwise the subjects participation is considered voluntary.

P. Minors as Research Subjects

Minors will be excluded from the study

Q. Radiation or Radioactive Substances

Patients will not be exposed to radiation in addition to what is required as a result of standard clinical procedures. Patients may be exposed to standard Cat Scan techniques which result in an average of 110 mrem per test and ventilation/perfusion scanning which result in an average of 10-15 mrem per test..