Treatment of Venous Thromboembolism with the Oral Thrombin Inhibitor, Ximelagatran

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Abstract

Background: Venous thromboembolic diseases are treated initially with low molecular weight heparin followed by oral coumarins.

Objectives: To investigate an orally available direct thrombin inhibitor for the acute treatment of venous thromboembolism as well as for prophylaxis of recurrent events.

Methods: The direct thrombin inhibitor ximelagatran was compared with subcutaneous LMW heparins followed by oral warfarin in a double-blind randomized prospective multicenter trial in patients with acute VTE. A pharmacokinetic study was performed in the VTE patients. For assessing the prevention of recurrent VTE, double-blind prospective randomized studies were conducted as follows: a) ximelagatran compared to warfarin for 6 months, and b) prolonged anticoagulation of ximelagatran vs. placebo for 18 months after termination of 6 months coumarin therapy.

Results: Two dose-finding studies and the pharmacokinetic analysis of ximelagatran in acute VTE were completed. About 2,500 patients were randomized to investigate 2 x 36 mg ximelagatran versus 2 x 1 mg/kg body weight enoxaparin followed by warfarin. The study hypothesized that the efficacy was equal in both treatment regimens for recurrent VTE documented by objective methods. The second study, with 1,234 patients, aimed to demonstrate a reduced incidence of recurrent thromboembolic events documented by objective methods after 18 months of treatment with 2 x 24 mg ximelagatran daily compared to placebo.

Conclusion: These large-scale clinical trials will soon yield the results of the comparison between oral ximelagatran and subcutaneous LMW heparin for treatment of acute VTE, and of warfarin for prophylaxis of recurrent events for 6 months and for a prolonged prophylaxis for another 18 months.

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Treatment of acute venous thromboembolism is initially performed with subcutaneous low molecular weight heparin, which has been demonstrated to be more effective and as safe and convenient as intravenous activated partial thromboplastin time-adjusted unfractionated heparin [1]. LMW heparin is given once or twice daily at a body weight-adjusted dosage [2,3] or as a fixed, body weight-independent dose of 2 x 8,000 IU subcutaneously [4].

The disadvantages of LMW heparins for the treatment of thromboembolism include bleeding complications, heparin-induced thrombocytopenia, local hematomas, and allergic reactions [1]. Thus, new anti-thrombotic medications are currently being developed to improve the efficacy and safety of anticoagulants. Direct thrombin inhibitors, now available for oral administration, are currently the most promising drugs for this indication.

For the prevention of recurrent thromboembolic events vitamin K antagonists are given for a period of about 6 months [5]. The most widely used coumarins are warfarin, phenprocoumon, and phenindione. Major drawbacks of the oral anticoagulant treatment are severe and fatal bleeding complications as well as cutaneous allergic reactions, alopecia, or coumarin-induced skin necrosis. The anticoagulant effect has to be controlled by the prothrombin time, expressed as international normalized ratio. The INR should range between 2 and 3 [6]. After termination of oral anticoagulation, recurrent thromboembolic events have been reported for up to 24 months in as much as 25% of patients [7,8].

Direct thrombin inhibitors are peptides that reversibly bind to α-thrombin. A double prodrug has been developed to improve the current therapy with LMW heparins and coumarin. Ximelagatran is under investigation in several phase III clinical trials for the acute treatment of VTE and prophylaxis of recurrent events. Ximelagatran is converted to melagatran after oral intake through enzymatic cleavage by esterase and by hydrolysis. Pharmacokinetic studies have shown a rapid and reproducible absorption within 30–60 minutes after ingestion, which is independent of food intake, age, and renal function up to renal clearances as low as 20 ml/min [9].

The treatment concept of VTE encompasses both the acute and chronic phases of therapy. Named the THRIVE program – **thr**ombin **i**nhibition in **v**enous thrombo**e**mbolism – it uses the oral direct thrombin inhibitor ximelagatran.

Methods and Results

Treatment of acute VTE

The efficacy and safety of ximelagatran were compared in a dose-finding study with dalteparin/warfarin. Ximelagatran was given twice daily at doses of 24, 36, 48 or 60 mg orally over 4 weeks. Treatment was compared with 2 x 100 IU dalteparin subcutaneously per day, followed by warfarin with an INR target of 2–3. Diagnosis was confirmed by ascending phlebography and was repeated on day 28. The Marder score of day 28 compared to day 1 did not show differences within the treatment groups. Side effects of bleeding complications, recurrent thromboembolism, or mortality were not different between the treatment groups [10].

A second, larger clinical trial compared the same dose regimens of ximelagatran with dalteparin/warfarin for 4 weeks. The Marder

LMW = low molecular weight

VTE = venous thromboembolism

INR = international normalized ratio

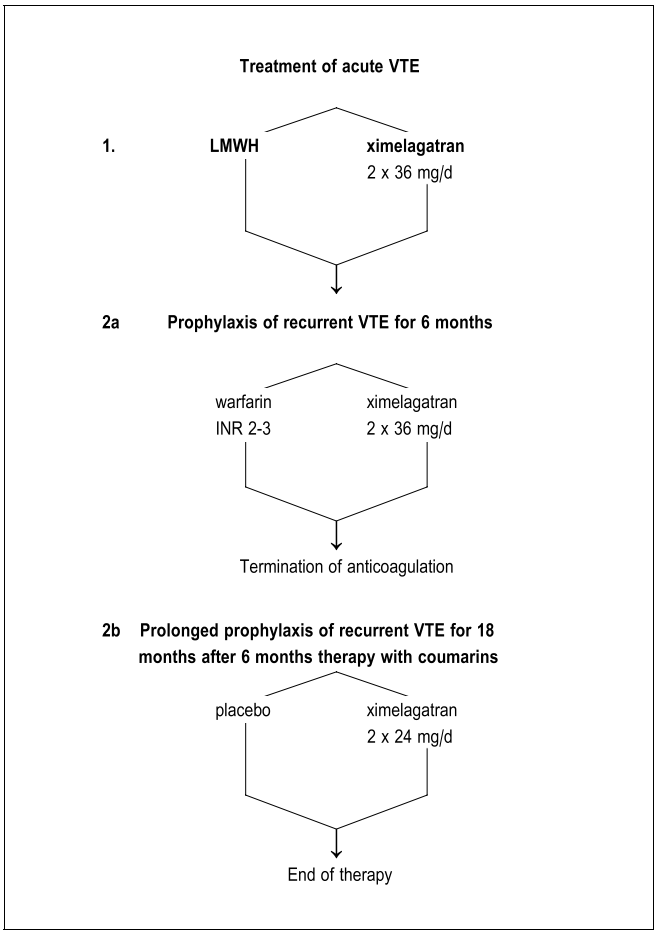

Figure 1. Clinical studies on ximelagatran to treat venous thromboembolism

score decreased by more than 5 points in 30–35% of patients in all treatment groups and by more than 5 points in 1–7% of patients without differences between the groups. Recurrent VTE, bleeding complications, or cessation of treatment due to any reason were similar in all treatment groups (65–73 patients per treatment group) [11].

Prophylaxis of recurrent VTE

For further studies, it was decided to investigate 2 x 36 mg ximelagatran for treatment of acute venous thromboembolism and for prevention of recurrent events over a period of 6 months in a double-blind, randomized, double-dummy prospective clinical trial. The control group was treated with 2 x 1 mg/kg body weight enoxaparin, followed by warfarin adjusted to an INR of 2–3. The study design of the THRIVE II and THRIVE V program will be combined for evaluation. The primary endpoint was the incidence of recurrent VTE after 6 months. Upon clinical suspicion of an occurrence, objective methods were used to demonstrate the diagnosis. The aim of the study was to evaluate the equivalent efficacy in both treatment groups. Secondary endpoints were incidence of mortality and severe bleeding complications. A total of 2,500 patients were incidence of included in the study. The post-study observation period was 2 weeks.

Prophylaxis of recurrent VTE after termination of 6 months oral anticoagulation

A prospective clinical trial was conducted in patients who received 6 months oral anticoagulation therapy after an initial deep vein thrombosis. In none of the patients was further anticoagulation indicated. Patients were randomized to receive 2 x 24 mg ximelagatran or placebo in a double-blind randomized manner in a multicenter, multinational prospective trial over a period of 18 months. The primary endpoint was the incidence of recurrent VTE, documented by objective methods. The hypothesis of the trial was a reduction in incidence of thromboembolic diseases with ximelagatran compared to placebo. Secondary endpoints were reduced incidence in mortality and combined events of current thromboembolism and mortality. The study group comprised 1,234 patients.

Pharmacokinetics of ximelagatran in VTE

Pharmacokinetic investigations were performed in 12 patients with hemodynamically stable pulmonary embolism using 2 x 48 mg ximelagatran orally for 10 days. Neither recurrent thromboembolism nor severe bleeding complications or other side effects occurred during the treatment period [12]. The pharmacokinetic and pharmacodynamic parameters of ximelagatran showed a two to threefold prolongation of APTT 2 hours after oral administration and a 1.5-fold prolongation 12 hours after oral administration. There was no accumulation of the APTT in patients over 10 days. The pharmacokinetic determination of ximelagatran showed an acceptable variability of plasma levels [13] ranging from 0.3 to 0.9 mol/L 2 hours after oral ingestion and 0.1–0.3 mol/L 12 hours after administration. No accumulation was demonstrated for the entire treatment period.

Discussion

Oral anticoagulation is the standard treatment for patients with a first event of proximal deep vein thrombosis and is given over 6 months [5]. However, once oral anticoagulation is discontinued recurrent venous thromboembolism may occur. A prolonged oral anticoagulation reduces the incidence of VTE or recurrent events but increases the rate of bleeding complications. Ximelagatran may improve the outcome in these patients due to an improved efficacy/safety ratio, a shorter half-life, and lack of interaction with the Cytochrom P 450 2C9-System [14].

Oral direct thrombin inhibitors may improve the treatment for venous thromboembolism; and with LMW heparin/vitamin K antagonist they can be used for acute treatment as well as to prevent recurrent events. The rationale for their use includes: direct inhibition of thrombin independent of antithrombin, oral absorption with low variability, shortened biologic half-life of about 4 hours, no binding to proteins other than thrombin, no interaction with Cytochrom P 450 2C9-System, no food interaction, a wide therapeutic range, and no need for monitoring.

In conclusion, the first dose-finding studies have demonstrated the efficacy of the oral direct thrombin inhibitor ximelagatran for

APTT = activated partial thromboplastin time

both the acute treatment of venous thromboembolism and prophylaxis of recurrent events compared to the two-drug regimen of low molecular weight heparin and warfarin.

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Even where sleep is concerned, too much is a bad thing

Homer's Odyssey (9th cent. BC)

Capsule

Strong bones via tailored hormones

Interest in alternative preventive strategies against bone loss has intensified in light of the recent announcement of risks associated with hormone replacement therapy. Previous cell culture studies showed that estrogen and androgen protect bone through a mechanism distinct from the DNA-mediated mechanism underlying their effects on reproductive organs. Kousteni et al. now show that a synthetic compound (estren) that mimics these "nongenotropic" effects can increase bone mass in estrogen- or androgen-deficient mice without adverse effects on reproductive organs.

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Capsule

Anopheles homing in on us

The G protein-coupled receptors (GPCRs) in *Anopheles gambiae* are of special interest because of their importance to the mosquito's life cycle and because odorant and gustatory receptors are likely to contribute to the extraordinary success of this mosquito as a human disease vector. Hill et al. present an initial survey of GPCRs found in the *A. gambiae* genome sequence and characterized 79 possible odorant receptors for tissue expression.

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