Ximelagatran: the future in anticoagulation practice?

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Abstract

Recent years have shown a diverse array of new antithrombotic drugs in development or appearing in clinical practice. Until now, warfarin has remained the anticoagulant drug of choice despite the numerous disadvantages associated with its use. Ximelagatran, an oral direct thrombin inhibitor (DTI), has now emerged as a serious contender to replace warfarin as standard anticoagulation. Its use in prophylaxis and treatment of venous thromboembolic disease is already well established and recent data also suggest the benefits of ximelagatran over warfarin in non-valvular atrial fibrillation, both in terms of safety and efficacy. This review will examine ximelagatran as a novel anticoagulant with its application in numerous clinical settings, such as venous thromboembolism and non-valvular atrial fibrillation, and how it may one day replace warfarin as the anticoagulant of choice.

Key words: anticoagulation, warfarin, ximelagatran, thromboembolism, atrial fibrillation.

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Introduction

Ximelagatran is an oral direct thrombin inhibitor, and is a novel and unique anticoagulant. Increasing evidence is emerging of its superiority to conventional methods of anticoagulation. Its role in prophylaxis against thromboembolism in the perioperative setting is now established. Current studies in progress aim to confirm its efficacy and superior safety profile in other areas where anticoagulation is necessary, such as atrial fibrillation and acute coronary syndromes.

This enormous potential for ximelagatran suggests that it may one day replace warfarin as the anticoagulant of choice, thereby considerably reducing the burden of anticoagulation clinics. In this review, we shall discuss the mechanism of action of ximelagatran, its pharmacodynamics and pharmacokinetics, as well as its current and future use in clinical practice.

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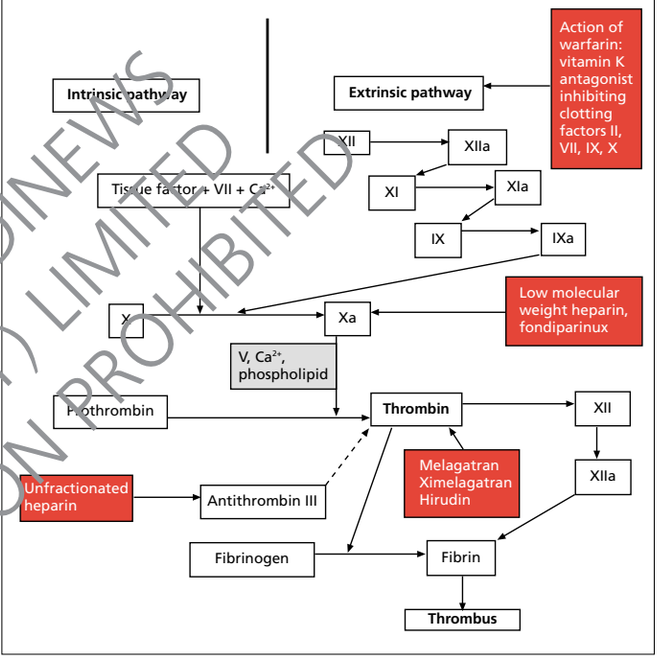
Figure 1. Summary of the clotting cascade and the mechanism of action of selected anticoagulants. The anticoagulants are shown in the shaded boxes and have inhibitory actions on the specified factors



Thrombosis and current anticoagulation practice

The formation of thrombus and its propagation in the general circulation is dependent on the three components of Virchow's Triad, namely abnormalities of the blood vessel wall, blood flow and blood clotting components. Thrombus formation is problematic in both arterial and venous circulations in a variety of pathological conditions; prevention of thrombus formation or its further propagation are central to anticoagulant therapy. Thrombin plays a key role in haemostasis and thrombosis, and is required for the generation of fibrin, which is an essential pre-requisite for thrombus formation. Thus, the prevention of thrombin generation, either directly or indirectly, is the aim of anticoagulation. The direct inhibition of thrombin generation prevents cleavage of fibrinogen to fibrin and blocks the final

stage of the coagulation system and consequent thrombus formation.

Current anticoagulation practice involves drugs that either inhibit thrombin directly or affect its generation by interacting with other clotting factors (figure 1). For example, low molecular weight heparin (LMWH) acts primarily by preferentially inhibiting factor Xa, whilst unfractionated heparin acts on antithrombin III. The primary action of warfarin is as an antagonist of vitamin K, inhibiting the production of clotting factors II, VII, IX and X. Nonetheless, the use of warfarin is fraught with well-recognised problems, namely slow onset of action, frequent coagulation monitoring, dose adjustments and multiple interactions with other agents.

Newer anticoagulants have been recently introduced, with their application mainly in the field of perioperative prophylaxis against thromboembolic disease. For example, hirudin is a direct thrombin inhibitor shown to have a superior anticoagulant effect to enoxaparin that can be used in patients with heparin-induced thrombocytopenia, although it requires twice-daily administration.[1] Fondiparinux is a new synthetic pentasaccharide which acts through specific inhibition of factor Xa, preventing thrombin generation, but is again limited in its application due to the need for subcutaneous administration.[2]

With the exception of warfarin, the use of other anticoagulants (except perhaps intravenous unfractionated heparin) in the field of clinical cardiology is limited to prophylaxis of thromboembolic disease in immobile in-patients, with very little evidence for their safety and efficacy in areas such as atrial fibrillation or valvular disease. The shortcomings of warfarin have led to a race for the development of an orally administered agent that is as efficacious as LMWH, that has multiple indications with high benefit-risk ratios, is safe in terms of haemorrhagic complications, and that has a rapid onset of action and predictable pharmacodynamics/pharmacokinetics and therefore does not require regular monitoring of clotting parameters and dosage adjustment (table 1).

Table 1. Features of an improved anticoagulant – does ximelagatran fit the requirements?

- Multiple indications with high benefit-risk ratios
- Infrequent dosing schedule, preferable oral administration
- Rapid onset of action
- Predictable pharmacodynamics/pharmacokinetics
- Low risk of toxic side effects
- Effective antidote available
- Cost-effective

Ximelagatran – the solution?

Ximelagatran is a novel, orally administered, direct thrombin inhibitor. It belongs to a novel class of anticoagulants known as direct thrombin inhibitors (DTI). The development of DTIs began with the isolation of hirudin from the medicinal leech (*Hirudo medicinalis*). Drugs in this class include lepirudin (a recombinant hirudin), bivalirudin (a semisynthetic DTI), argatroban (a small synthetic arginine analogue that inhibits thrombin's active site by ionic binding), desirudin (a recombinant desulfato hirudin) and the dipeptide melagatran (a reversible DTI).[3]

In contrast to all heparin products, which act indirectly via antithrombin (AT) to inhibit both thrombin and factor Xa, DTIs bind to thrombin specifically and inhibit its catalytic activity without involvement of AT. Smaller DTIs offer the advantage of inhibition of both free and bound thrombin. Thus, DTIs may provide more effective inhibition of thrombus progression than agents such as unfractionated heparin and LMWH that inhibit free thrombin only.[3]

The rapid absorption and conversion of ximelagatran to its active form, melagatran ensures rapid onset of action. Following parenteral administration of melagatran, bioavailability is complete and variability is low, while the reverse is true after oral administration, i.e. bioavailability is low and variability is high.[4] Melagatran specifically acts as a potent and competitive inhibitor of α-thrombin.[5,6] Furthermore, the competitive binding of melagatran is not only restricted to clot-bound thrombin but also acts on free circulating thrombin.[7] Melagatran does not accumulate in body compartments and is mainly excreted, unmetabolised, via the renal route, suggesting that plasma concentrations are mainly influenced by renal function and weight.[8] There are no known drug or food interactions, which is yet another preferable characteristic to warfarin.[9] In the proposed therapeutic plasma concentration range, melagatran induces modest prolongations of the activated partial thromboplastin time (APTT, an indicator of the intrinsic coagulation pathway), as performed in human plasma *in vitro* and *ex vivo*.

In a study on healthy volunteers, ximelagatran has been shown to inhibit thrombin generation and platelet activation. Its activity is concentration-dependent. Furthermore, direct thrombin inhibition by melagatran has been shown to be superior for the inhibition of platelet activation compared to the indirect antithrombin-mediated inhibition of thrombin by enoxaparin.[10] It has been suggested that this superior effect of ximelagatran on platelets may be due to reduced occupancy of platelet thrombin receptors by catalytically active thrombin and/or smaller molecular size, allowing for easier access to clot-bound thrombin.[11]

Ximelagatran in thromboembolic disease

Early clinical trial work involving ximelagatran has been directed at patients who are at risk of venous thromboembolism, mainly in the field of orthopaedic surgery. Table 2 summarises some of the clinical studies with ximelagatran.

Venous thromboembolism

The METHRO (Melagatran for THRombin inhibition in Orthopaedic surgery) trials were the first to provide good evidence for the use of combinations of melagatran and ximelagatran. The METHRO I study[12] was a pilot study comparing sub-

Table 2. Key clinical studies involving ximelagatran

Trial	Study area	Trial details	Key findings
METHRO I	Prophylaxis of VTE in orthopaedic surgery	Pilot dose-ranging study comparing subcutaneous melagatran and oral ximelagatran with dalteparin in patients undergoing hip/knee replacements	Ximelagatran/melagatran combination as effective as dalteparin group in preventing VTE, with no significant difference in bleeding rates
METHRO II	Prophylaxis of VTE in orthopaedic surgery	Randomised, controlled, double-dummy, dose-response, multi-centre trial comparing ximelagatran/melagatran combination against dalteparin	Highest dose of ximelagatran/melagatran more effective at prevention of VTE, with no difference in bleeding rates
THRIVE III	Treatment of established VTE	Patients with known VTE randomised to either ximelagatran or placebo after six months' warfarin treatment	Ximelagatran group had fewer recurrences of VTE and composite of recurrent VTE and all-cause mortality reduced
SPORTIF II	Prophylaxis of thromboembolism in NVAF	Dose-guiding study comparing three doses of ximelagatran to dose-adjusted warfarin in NVAF	Limited data on thromboembolism due to short duration of trial (12 weeks) but no significant difference in bleeding rates
SPORTIF III	Prophylaxis of thromboembolism in NVAF	Randomised open-label study comparing fixed-dose ximelagatran with dose-adjusted warfarin for prevention of thromboembolism in NVAF	Ximelagatran group had fewer strokes and systemic embolisms. Combined minor and major haemorrhages rate lower in ximelagatran group
SPORTIF V	Prophylaxis of thromboembolism in NVAF	Randomised double-blinded study comparing fixed-dose ximelagatran with dose-adjusted warfarin for prevention of thromboembolism in NVAF	Ximelagatran shown to be non-inferior to warfarin for prevention of strokes and systemic embolic events

Key: VTE = venous thromboembolism; NVAF = non-valvular atrial fibrillation

cutaneous melagatran followed by oral ximelagatran with dalteparin in patients undergoing hip or knee surgery. Patients were randomised to receive either dalteparin 5,000 IU subcutaneously (sc) once daily or sc melagatran (1, 2 or 4 mg twice daily) for two days before surgery, followed by oral ximelagatran (6, 12 or 24 mg twice daily) for 6–9 days. The melagatran/ximelagatran combination was shown to be as effective as dalteparin in preventing thromboembolism, with no significant difference in the incidence of haemorrhagic complications.

This was followed by the METHRO II study,[13] a large randomised, double-dummy, dose-response, multi-centre trial investigating three different dosing regimens of melagatran and ximelagatran against dalteparin in patients undergoing either total hip or knee replacement. Of 1,900 patients, 1,495 were assigned to four dose categories of sc melagatran from just before surgery (1.00 mg, 1.50 mg, 2.25 mg or 3.00 mg twice daily), followed from the day afer surgery by oral ximelagatran (8 mg, 12 mg, 18 mg or 24 mg twice daily). Three hundred and eighty one patients were assigned subcutaneous dalteparin 5,000 IU once daily before surgery. The essential findings of this study were that the highest dose of melagatran/ximelagatran was associated with a significantly lower rate of venous thromboembolism compared to dalteparin, with a strong inverse relationship between venous thromboembolism and the dose of melagatran/ximelagatran. In addition, the risk of bleeding was not significantly greater in the group taking the highest dose of melagatran/ximelagatran than in the dalteparin group, demonstrating the safety of this agent compared to standard unfractionated heparin. However, a dose-response relationship was demonstrated in terms of risk of bleeding between the highest and lowest doses of melagatran/ximelagatran.

Other trials involving melagatran/ximelagatran in thromboembolic disease following orthopaedic surgery are consistent with the findings of the METHRO trials, demonstrating this novel anticoagulant's superiority in preventing thromboembolism with a comparable safety profile.[14] The THRIVE III trial illustrates this, for example. THRIVE III was an international, multi-centre, double-blind, placebo-controlled study examining the effects of long-term secondary prevention of venous thromboembolism in patients who had received standard anticoagulation treatment for six months. One thousand two hundred and thirty three patients with venous thromboembolism who had undergone six months of anticoagulant therapy were randomised to secondary prevention with ximelagatran 24 mg orally, twice daily, or placebo for 18 months. The risk of subsequent recurrence after the standard six months' treatment of established venous thromboembolic disease is considerable (approximately 6% per year), and further extension of treatment with warfarin in standard venous thromboembolic disease is associated with a considerable risk of major haemorrhage of about 3%. In THRIVE III, subjects were randomised to receive fixed-dose ximelagatran or placebo for a further 18 months without monitoring of coagulation. Venous thromboembolism was significantly lower in the patients assigned to

ximelagatran compared to placebo (hazard ratio=0.16; p<0.0001). This was associated with a low incidence of haemorrhage, demonstrating that fixed-dose ximelagatran was safe, effective and well tolerated after a period of standard anticoagulation for venous thromboembolism.[15]

Atrial fibrillation

Atrial fibrillation (AF) is the commonest arrhythmia encountered in clinical practice and is the strongest independent risk factor for stroke.[16] The benefits of oral warfarin treatment in reducing the risk of stroke in patients with non-valvular atrial fibrillation (NVAF) have been well established. A meta-analysis of five studies showed that anticoagulation with warfarin produced a 62% relative risk reduction for stroke compared with placebo.[17] Furthermore, this benefit has been demonstrated for both primary and secondary prevention.[18]

The Stroke Prevention by ORal Thrombin Inhibitor in atrial Fibrillation (SPORTIF II) trial[19] was a prospective, multi-centre, randomised, parallel-group, dose-guiding study comparing three separate fixed doses of 20, 40 or 60 mg twice-daily ximelagatran compared to dose-adjusted warfarin (aiming for an international normalised ratio [INR] of 2.0 to 3.0) performed at 37 centres in 11 countries in Europe and the US. The study was conducted over 12 weeks and so an accurate assessment of embolic complications in each patient group was not possible. The main aim of the study was to determine the tolerability and safety of three fixed oral doses of ximelagatran compared to warfarin. There were no significant differences in clinical or thromboembolic events between the groups but, as suggested, interpretation of these findings in a short term study are limited. In terms of bleeding, there was no significant difference between ximelagatran and warfarin in this 12 week period, suggesting a comparable safety profile for both drugs.

Another study, SPORTIF III, determined whether ximelagatran could offer similar protection against stroke compared to warfarin, in a randomised, open-label treatment allocation study in 23 countries. This study compared a fixed dose of 36 mg twice daily of ximelagatran with dose-adjusted warfarin (aiming for INR 2.0–3.0) in patients with NVAF and at least one additional risk factor for stroke including previous stroke, hypertension or heart failure. The primary end points were all strokes (both ischaemic or haemorrhagic) and systemic embolic events, based on intention to treat. Preliminary results presented at last year's American College of Cardiology 52nd Annual Scientific Session (Chicago, US, 30th March–2nd April 2003) were very encouraging. In moderate to high-risk patients with NVAF, ximelagatran was non-inferior to warfarin (using intention-to-treat analysis) and reached statistical superiority (using on-treatment analyses) to warfarin in preventing stroke and systemic embolic events.[20]

The main results of SPORTIF III were published last year in the *Lancet*.[21] The study population consisted of 3,407 patients with NVAF, with a history of stroke or TIA in 24%, hypertension in 72% and left ventricular dysfunction in 34%. By the end of September 2002, a total of 4,941 patient-years at-risk had accumulated, giving a mean duration of follow-up of 17.4 months (SD 4.1). The primary event rate was 2.3% in the warfarin group (56 patients) and 1.6% in the ximelagatran group (40 patients). The absolute risk reduction was 0.7% per year (95% CI -0.1 to 1.4) and the relative risk reduction was 29% (95% CI -6.5 to 52).

Haemorrhagic stroke occurred in nine patients in the warfarin group and four in the ximelagatran group (p=0.266). Major bleeding occurred in 1.8% of the patients in the warfarin group and 1.3% of the patients in the ximelagatran group (p=0.228). When major and minor bleeding were combined for analysis, significantly more bleeding was reported in patients randomised to warfarin (n=547; 29.8% per year) than in those randomised to ximelagatran (n=478; 25.8% per year), giving a relative risk reduction of 14% (p=0.0065).

SPORTIF V was identical in many respects to SPORTIF III: it was a randomised study comparing dose-adjusted warfarin with fixed-dose ximelagatran in patients with NVAF and risk factors for stroke. However, SPORTIF V was a double-blind study and treatment allocation was double-dummy, with computerised algorithms to generate sham INR data. Data from this study were presented at the American Heart Association meeting in Orlando, Florida, US, in November 2003.[22]

SPORTIF V enrolled 3,922 patients at 409 sites in North America. All patients had NVAF with at least one additional risk factor for stroke, including previous stroke, previous systemic embolism, hypertension, age 75 years or older, and a history of congestive heart failure. The protocol stipulated a minimum drug exposure of 12 months per patient and an aggregate follow-up of 4,000 patient-years. The patients received either 36 mg ximelagatran twice daily, as a fixed dose, or dose-adjusted warfarin with a target INR of 2.0–3.0.

The primary end point (any stroke or systemic embolic event) occurred in 51 patients (1.6% per year) in the ximelagatran group compared with 37 patients (1.2% per year) in the warfarin group. This difference is not statistically significant (p=0.13). Rates of major bleeding were very similar between the two patient groups: they occurred in 2.4% per year of the ximelagatran group and 3.1% per year of the warfarin group (p=0.16). However, rates of minor and major bleeding combined were significantly lower in patients treated with ximelagatran (37% per year) than in patients treated with warfarin (47% per year) (p<0.001).

Serum levels of alanine aminotransferase rose to greater than three times the upper limit of normal in 6% of patients receiving ximelagatran, compared with 0.8% of patients receiving warfarin (p<0.001). There was also a rise in serum bilirubin to twice the upper limit of normal in 0.4% of ximelagatran patients. These changes occurred during the first six months of treatment and generally returned to normal whether or not treatment was continued.

Post-MI

Risk of ischaemia and myocardial infarction (MI) is high in the months following an acute coronary syndrome. ESTEEM

Key messages

- Ximelagatran is a safe, rapidly acting oral direct thrombin inhibitor with no known drug/food interactions and no requirement to monitor anticoagulant intensity or dosage
- Ximelagatran is becoming established as a good anticoagulant in the prevention and treatment of venous thromboembolism and non-valvular atrial fibrillation
- There is great potential for ximelagatran to replace warfarin as the anticoagulant of choice

(Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Recent Myocardial Damage) was a placebo-controlled, double-blind, multi-centre study that assessed 1,883 patients who had a recent ST-elevation or non-ST elevation myocardial infarction.[23]

Within 14 days of the index event, participants were randomised to oral ximelagatran 24 mg, 36 mg, 48 mg or 60 mg twice daily or to placebo for six months. All patients received acetylsalicylic acid 160 mg once daily. The primary efficacy outcome was the occurrence of all-cause mortality, non-fatal MI and severe recurrent ischaemia during six months of treatment with ximelagatran or placebo.

Oral ximelagatran significantly reduced the risk for the primary end point compared with placebo, with no indication of a dose-response between the different doses given. At six months, the estimated cumulative risk of the primary end point was 12.7% (range 12.1–13.7%) for the combined ximelagatran groups, compared with 16.3% in the placebo group: this gives a hazard ratio of 0.76 (95% CI 0.59–0.98) and a p value of 0.036.

Major bleeding events were rare: they occurred in 1.8% of the combined ximelagatran group and 0.9% of the placebo group (95% CI 0.80–4.84, hazard ratio 1.97).

Adverse effects

The most obvious adverse effect with ximelagatran is bleeding; in all the aforementioned trials there was no significant difference between ximelagatran and standard anticoagulation. Transient and asymptomatic elevation of liver enzymes has been reported with a small proportion of patients.[24] The mechanism of action responsible is not understood, although a similar finding has been reported with unfractionated and LMWH.[20] This phenomenon has been reported in the SPORTIF III and SPORTIF V studies, with the elevation of liver enzymes again reported as being transient and affecting only a minority of trial patients.

Summary

Ximelagatran has been established as an efficacious, safe and convenient anticoagulant. Published and ongoing trials have shown promising results with regards to safety, tolerability and efficacy compared to warfarin in prevention of venous thromboembolic disease and NVAF. Positive results in these studies may pave the way for further trials involving patients with heart failure at risk of thromboembolism, prosthetic valves and treatment of established venous thromboembolic disease. Given the superiority of ximelagatran over dalteparin in venous thromboembolism, there is also potential for trials involving ximelagatran/melagatran in the treatment of acute coronary syndromes. In time, the considerable burden placed on anticoagulation clinics may be significantly reduced.

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