Ximelagatran for stroke prevention in atrial fibrillation

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Evaluation of: Olsson SB. 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 nonvalvular atrial fibrillation (SPORTIF III): randomized controlled trial. *Lancet* 362,1691–1698 (2003).

For decades, warfarin has been the gold standard anticoagulant that is recommended in patients with atrial fibrillation for the prevention of stroke and systemic embolic events. However, warfarin therapy has several disadvantages; including significant risks of bleeding, a narrow therapeutic margin necessitating frequent monitoring and interactions with numerous drugs and foods. These limitations created a need for safer, more convenient alternative anticoagulants for stroke prevention. Ximelagatran (Exanta™, Astrazeneca) is a novel, oral direct thrombin inhibitor that inhibits the final step in the coagulation process, namely, the conversion of fibrinogen to insoluble fibrin by thrombin. It has a rapid onset of action, a relatively wide therapeutic margin and a low potential for food and drug interactions. In addition, it can be administered in a fixed dosage, which obviates the need for anticoagulation monitoring, thus simplifying treatment and improving compliance. The Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) program has been investigating the safety and efficacy of ximelagatran for the prevention of stroke in patients with AF. This report discusses the implications of the recently published Phase III trial, SPORTIF III, which evaluated the efficacy and safety of ximelagatran as compared with warfarin in high-risk patients with AF.

Keywords:
anticoagulation, atrial fibrillation, cerebrovascular disease, direct thrombin inhibitors, stroke prevention, trials, warfarin, ximelagatran

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice that affects cardiovascular morbidity and mortality and generates significant healthcare costs. It is also the strongest independent risk factor for stroke and systemic embolic events. The incidence of stroke is increased fivefold in patients with AF to approximately 5% per year for primary events and 12% per year for recurrent events, compared with patients without AF. Management of AF has therefore been subject to extensive research to determine the optimal therapies for this important and common arrhythmia. This article discusses the implications of the Stroke Prevention by Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III study [1], which has recently been published and is considered one of the landmark trials in cardiovascular pharmacotherapy.

It has been well established from recent studies in AF that anticoagulation constitutes an important therapy in patients with AF for the prevention of thromboembolic stroke [2]. For decades, warfarin has been the gold standard anticoagulant that is recommended for such an indication. However, warfarin therapy carries a risk of major hemorrhage of approximately 1.2% per year, it also has a narrow therapeutic margin necessitating frequent coagulation monitoring to ensure appropriate dosing and possesses significant interactions with numerous drugs and foods.

These limitations result in under treatment of a considerable proportion of the AF population at risk and create a need for safer, more convenient alternatives to warfarin for stroke prevention. Research and development of several alternative agents targeting different points of the coagulation pathway is underway but the most promising of these has been the direct thrombin inhibitors.

Thrombin is the central enzyme in hemostasis. It is formed from prothrombin, via Factor Xa, and its major activity is in the final step of coagulation where it cleaves fibrinopeptides from fibrinogen to produce fibrin. The procoagulant effects of thrombin can be blocked by inactivating the enzyme itself or by preventing its generation. Three direct thrombin inhibitors have already been approved and are in clinical use: hirudin (Refludan®, Aventis), bivalirudin (Agiomax™, The Medicines Company) and Argatroban® (Texas Biotechnology Corporation).

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Each of these is administered intravenously and each has been used in unstable coronary syndromes and for the prevention of postoperative venous thromboembolism.

Ximelagatran (Exanta™, AstraZeneca) is a novel, oral direct thrombin inhibitor that inhibits the final step in the coagulation process – the conversion of fibrinogen to insoluble fibrin by thrombin. Ximelagatran is converted to its active metabolite, melagatran, after oral administration. Ximelagatran has stable pharmacokinetics independent of the hepatic P450 enzyme system and has no known clinically significant food or drug interactions. It is rapidly absorbed from the gut and converted to its active form, melagatran, the maximum concentration of which is attained 1.6–1.9 h after administration. Melagatran is not metabolized or bound to plasma proteins and its clearance is predominantly via the kidneys, with a half-life of 4–5 h, Ximelagatran compared favorably with both low-molecular-weight heparin and adjusted-dose warfarin for prevention of venous thromboembolism, and with warfarin for treatment of established deep vein thrombosis [3].

The SPORTIF program has been investigating the safety and efficacy of ximelagatran for the prevention of stroke in patients with AF. A Phase II study, SPORTIF II [4] and its extension trial, SPORTIF IV, demonstrated the safety and efficacy of ximelagatran compared with warfarin in patients with nonvalvular AF. The program also included two long-term. Phase III clinical trials of the safety and efficacy of ximelagatran compared with warfarin in patients with AF at high risk of ischemic stroke; SPORTIF III and SPORTIF V. The two trials were conducted independently but their designs were similar in order to facilitate pooling of their results when completed. This report describes the SPORTIF III trial, which has been published recently in the *Lancet* [1].

Methods & results

SPORTIF III was a multicenter, open-label, parallel-group trial comparing oral ximelagatran with adjusted-dose warfarin for the prevention of stroke and systemic embolism in high-risk patients with AF. Treatment was administered n an open-label basis at 259 sites in 23 countries in Europe, Australia, New Zealand and Asia, with blinded end-point event assessment. A group of 3410 patients with persistent or paroxysmal AF and one or more stroke risk factors (previous stroke, hypertension, or congestive heart failure [CHF]) were randomized to open-label warfarin (target international normalized ratio [INR] = 2.0–3.0, n = 1703) or ximelagatran 36 mg twice daily (n = 1704). Exclusion criteria included mitral stenosis and valvular heart surgery, recent cerebrovascular accident (CVA), bleeding risk, planned cardioversion or surgery, liver or renal disease (calculated creatinine clearance < 30 ml/min) and treatment with a platelet inhibitor other than aspirin at 100 mg/day or less within 10 days. Randomization was balanced for use of aspirin and a history of CVA or transient ischemic attack (TIA). Primary end point was stroke (ischemic and hemorrhagic) or systemic embolism adjudicated by masked event assessment. Secondary end points were bleeding, treatment discontinuation and single and combination events including acute myocardial infarction (AMI). The study was designed to have 90% power, a minimum of 12 months of follow-up per patient and an aggregate of 80 primary events. The main outcomes were assessed by local study affiliated neurologists or stroke specialists, masked to treatment. The authors compiled data on all but ten patients who never took the study drug.

The mean age was 70 years, 70% were men, 20% were on aspirin, 21% had onset less than 1 year, 8% had paroxysmal AF and two or more stroke risk factors were present in 70%. Mean INR of the warfarin arm was 2.5 across all measurements during the duration of the study.

Slightly more patients taking warfarin (86%) completed the study compared with 82% taking ximelagatran. Over a mean of 17.4 ± 4.1 months, 96 patients had a primary event, 56 on warfarin and 40 on ximelagatran. The event rate by intention to treat was 2.3% per year with warfarin and 1.6% with ximelagatran (0.7% absolute and 29% relative risk reduction [RRR] p = 0.10). All-cause mortality was 3.2% in each group. The INR was below 2.0 in 25% of warfarin-treated patients at the time of an ischemic CVA or TIA, or systemic embolus. There was no difference in intracranial hemorrhage (0.2% with ximelagatran vs. 0.4% with warfarin, p = nonsignificant [NS]) or major bleed (1.3% with ximelagatran vs. 1.8% with warfarin, p = NS), however combined minor and major hemorrhages were lower with ximelagatran than with warfarin (29.8 vs. 25.8% per year; RRR 14%, p = 0.007). CHF occurred in 2.9 versus 3.9% (p = 0.063) and AMI in 1.1 versus 0.6% (p = 0.068) for ximelagatran versus warfarin, respectively. Raised serum alanine aminotransferase (ALT) above three times the upper limit of normal occurred more frequently in the ximelagatran

arm (6.5 vs. 0.7%, $p < 0.001$) with most of this occurring in the first 6 months. The ALT values dropped in patients who either stopped the drug or who remained on it.

Discussion & significance

This SPORTIF III study is the first landmark trial in 50 years to provide an effective oral anticoagulant that is noninferior to the gold standard anticoagulant, warfarin. It established that in high-risk patients with AF, treatment with the novel oral direct thrombin inhibitor, ximelagatran, was noninferior with regards to stroke and systemic embolic events compared with warfarin therapy. Usually, the strength of evidence is less with a noninferiority trial as all kinds of clinical trial assumptions are made. There are assumptions inherent in noninferiority trials, so the data are always a little tentative and the evidence is not as strong as a superiority trial, however, the clinical situations for the SPORTIF III trial appear to be very similar to real-life use of warfarin, except perhaps that warfarin control might be poorer in real life, which would bias the trial in favor of the control, not ximelagatran. Therefore, the trial appears to have reasonable strength. In addition, although this trial was an open-label study which could provide a basis for bias, the main outcomes were assessed by investigators masked to treatment allocation and the outcome end points used are of the 'hard end points', thus minimizing any possible bias. Moreover, the recently presented SPORTIF V trial [5] which was a double-blind trial of ximelagatran versus warfarin in a similar patient population of AF, also showed similar, noninferior primary end-point results.

The main area of some concern in the SPORTIF III trial was the ALT elevation that was noted in some patients treated with ximelagatran. A subgroup of 107 patients (6.5%) receiving ximelagatran developed elevation of ALT that was more than three times the upper limit of normal; 59 of these patients remained on the drug and 48 discontinued. In all cases the ALT levels returned to normal over time. The significance of these alterations in ALT, which appear transient or reversible, remains uncertain. Certainly, monitoring of liver function for a short period is less onerous than life-long monitoring of the INR, as is required with warfarin. Moreover, there still remains a need to determine the long-term safety of exposure to ximelagatran, particularly regarding liver function.

Since patients with calculated creatinine clearance less than 30 ml/min were not eligible to participate, additional studies will be needed to assess the safety and efficacy of ximelagatran treatment in patients with impaired renal function.

Thus, the disadvantages of ximelagatran are the need for twice-daily administration, excess occurrence of adverse hepatic effects in 6.5% of patients (thus potentially requiring monitoring of liver function for up to 6 months after treatment initiation) and the need to estimate creatinine clearance, as ximelagatran is primarily eliminated by the kidneys.

Nonetheless, the advantages of ximelagatran are; that it has a rapid onset and offset of action, a predictable pharmacokinetic profile (uninfluenced by the patients age, sex, weight, ethnicity, or food intake) and therefore it is not necessary to adjust the dose or monitor anticoagulation activity. Furthermore, ximelagatran has a wider therapeutic margin than warfarin and a low potential for food and drug interactions.

Importantly, the cost effectiveness of ximelagatran needs to be established and compared with that of warfarin. Although the cost of ximelagatran when it becomes available will likely be more than warfarin, the savings in the costs of follow-up, including blood tests for coagulation monitoring and doctor visits, will likely balance the absolute increase in price. This remains to be examined by further studies after ximelagatran becomes commercially available.

Expert opinion & conclusion

The SPORTIF III trial met its objectives in establishing the efficacy and safety of the novel oral direct thrombin inhibitor ximelagatran in high-risk patients with AF. The main area of safety concern is that ximelagatran appears to require monitoring of hepatic function during the early months of therapy, although the significance of the alterations in ALT, which appear transient or reversible, remain uncertain. Additionally, the cost issues of this new drug remain to be established when it becomes commercially available.

Nonetheless, this study provided, for the first time in decades, a new effective oral anticoagulant that will remain an alternative to warfarin even if it does not replace it. Further research is awaited to evaluate the role of this promising new agent in other disease states in which anticoagulation is necessary, such as in patients with prosthetic heart valves.

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