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Anticoagulation for non-valvular atrial aibrillation – towards a new beginning with ximelagatran

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Abstract

Objectives: Ximelagatran is a novel oral direct thrombin inhibitor. It has favorable pharmacodynamic properties, with a broad therapeutic range without the need for anticoagulation monitoring. We aimed to discover whether ximelagatran offers a genuine future replacement to warfarin for patients in persistent atrial fibrillation (AF).

Materials and methods: We provide an evidence-based review of the relative merits and disadvantages of warfarin and aspirin. We subsequently present an overview of the evidence for the utility of ximelagatran in the treatment of AF.

Results: Adjusted dose warfarin is recommended over aspirin for patients in AF at high risk of future stroke. Some of this benefit is partially offset by the higher bleeding risks associated with warfarin therapy. The SPORTIF III and V studies have shown that ximelagatran is not inferior to warfarin in the prevention of all strokes in patients with AF (both persistent and paroxysmal). This benefit was partially offset by the finding of a significant elevation of liver transaminases (>3 × normal) in 6% of patients.

Conclusions: Current data would suggest that ximelagatran might represent a future alternative to warfarin. The lack of need for anticoagulant monitoring has been partially offset by a need for regular monitoring of liver function. Further data from randomized clinical trials is clearly needed.

Introduction

Atrial Fibrillation (AF) is the most common sustained tachyarrhythmia encountered in clinical practice [1], with an incidence that doubles with every decade after 55 years of age [2]. With an aging population and improved survival of patients with cardiac disease, its prevalence continues to rise and currently affects as many as 5% of persons ≥ 65 years old [3]. Consequently, AF has become a "new epidemic" of cardiovascular disease in Western society [4].

AF is not a benign problem. It is associated with a doubling of overall morbidity and mortality from cardiovascular disease [5] and it is the most common cause of embolic stroke [6]. Patients with non-rheumatic AF (NRAF) have a 5.6-fold greater risk for embolism, and those with AF of rheumatic valvular origin have a 17.6-fold greater risk, as compared to healthy control individuals [7]. This equates to an increased incidence of stroke approximating 5% per year for primary events and 12% per year for recurrent events [8,9].

Oral anticoagulant therapy has been shown to reduce the thromboembolic risk of AF. At 60 years post introduction, warfarin still remains the mainstay of oral anticoagulant treatment. Despite its demonstrated superior efficacy over aspirin for the prevention of stroke in AF, warfarin treatment is complicated by a magnitude of potential problems, which limit its use, with patients walking a tight rope between bleeding and clotting [2,9]. In this article we present an evidence-based overview of current knowledge about oral anticoagulation in atrial fibrillation.

We initially review the relative merits and disadvantages of warfarin and aspirin. This is followed by an up-to-date assessment of the new oral anticoagulant ximelagatran, which offers the potential to be a genuine and long-awaited replacement for warfarin therapy in patients with atrial fibrillation.

Evidence for warfarin and aspirin

Five randomized controlled clinical trials of warfarin (see Table 1 and Additional file: 1) versus control or placebo have demonstrated the effectiveness of antithrombotic therapy for the prevention of stroke in patients with NRAF [10-14]. Meta-analysis of these five primary prevention trials concluded that the relative risk of stroke was reduced by 68% (from 4.5% per year to 1.6% per year, 95% CI 50–79% $p < 0.001$), whereas the risk of major bleeding increased (from 1.0% to 1.3%) [15]. The European Atrial Fibrillation Trial compared warfarin, aspirin and placebo in patients with NRAF who had experienced a transient ischemic attack or stroke within the previous three months [16]. The risk of recurrence was 12% among placebo patients, dramatically higher than the 4.5% annual risk in the overall population of patients with NRAF. The relative risk reduction with warfarin was 66% ($p < 0.001$), virtually identical to that calculated in the five major randomized controlled trials, but the absolute reduction in strokes was much greater (80 per year per 1000 versus 31 per year per 1000) because of the high baseline stroke rate in this population [16].

The reduction in the risk of stroke afforded by aspirin, although less pronounced than that for adjusted-dose warfarin, is still significant. Meta-analysis of the six randomized trials of aspirin versus placebo (see Table 2 and Additional file: 2) has shown that aspirin significantly reduces the risk of stroke by 22% (95% CI 2%–38%), with no significant increase in the risk of major hemorrhage [10,11,16-21]. Aspirin leads to an absolute stroke risk reduction of 1.5% a year for primary prevention and 2.5% per year for secondary prevention (numbers needed to treat of 66 and 40, respectively).

Meta-analysis of five randomized trials comparing aspirin with warfarin for the primary prevention of stroke in NRAF (see Table 3 and Additional file: 3) showed that warfarin reduces the risk of stroke compared with aspirin by 36% (95% CI: 14%–52%) [10,16,21-24]. Low-intensity warfarin alone or in combination with aspirin is significantly less effective than adjusted-dose warfarin for this indication [25].

Current practice guidelines and evidence from further trials provide recommendations for adjusted-dose warfarin (international normalized ratio [INR], 2.0–3.0) for patients at high risk of future stroke [26-28]. Several published guidelines describe for physicians which AF patient groups are at high risk of stroke and which groups would gain relative benefit from warfarin therapy. The current recommendations of the American College of Chest Physicians are summarized. (see Table 4 and Additional file: 4) [8,29].

Problems with warfarin therapy

Despite the efficacy of warfarin therapy, there are several inherent problems related to its use. Warfarin exerts its pharmacokinetic effects by reducing the synthesis of vitamin K-dependent procoagulant factors II, VII, IX and X. Warfarin's dose response is influenced by numerous drug interactions (it is metabolized by the P450 enzyme complex), hepatic dysfunction, changes in the gut flora, and patient compliance and alcohol intake [30]. Warfarin has a very narrow therapeutic range, with marked variability in its dosage response that necessitates frequent venipuncture to maintain appropriate dosage [31]. Clinical trials have demonstrated that ischemic stroke is far more likely with an INR < 2.0, whereas an INR > 4.0 increases the risk of intracranial hemorrhage [32-34].

These concerns over warfarin use have resulted in considerable under-treatment of a large proportion of AF patients at risk, the very population that would most benefit from anticoagulant therapy [35-37]. Failure to prescribe anticoagulant agents to these patients is often due to physicians' perceiving the risk of major bleeding as unacceptably high because of the presence of such clinical risk factors as hypertension, falls, a history of gastrointestinal tract bleeding, worries about drug interactions and lack of assurance about compliance [38-43]. Unfortunately, attempts to reduce the potential risk of bleeding using a low- and fixed-dose of warfarin have been unsuccessful, being associated with a four-fold increased risk in stroke [43-45].

Ximelagatran

Ximelagatran (Astra Zeneca) is a novel oral direct thrombin inhibitor (oral DTI) that is rapidly converted to melagatran, its active form, following absorption [46]. Melagatran has been shown to be a potent, rapidly binding competitive inhibitor of human alpha-thrombin that

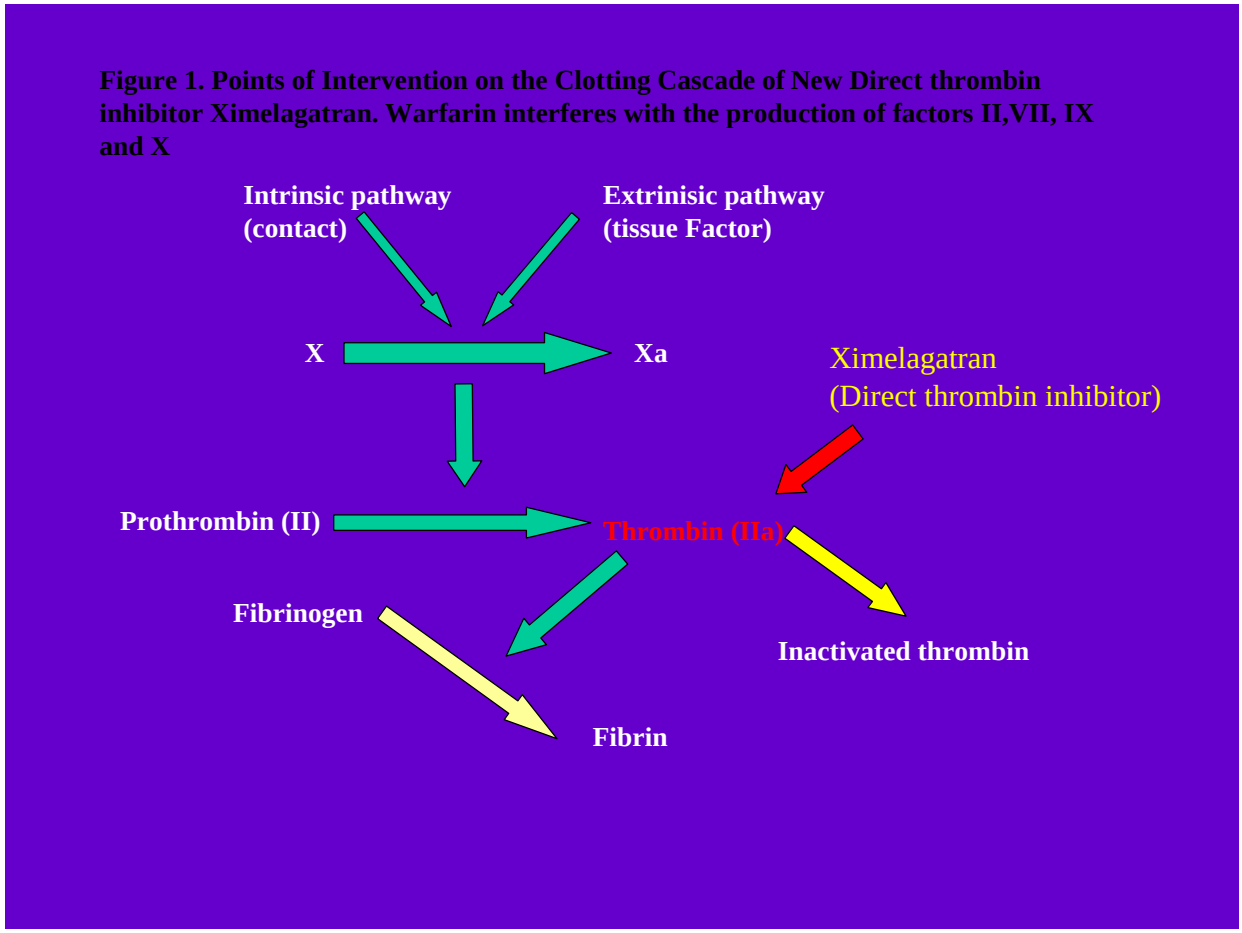

Figure 1

inhibits both thrombin activity and thrombin generation (see Figure 1) [47]. Melagatran has a broad therapeutic interval that enables it to be administered safely across a wide range of doses with no increased risk of bleeding. Although melagatran has all the pharmacodynamic properties required of a new antithrombotic agent, it unfortunately exhibits low oral bioavailability, which is further reduced by the concomitant intake of food. This limitation precluded its development as an oral agent, but it did propel the development of its precursor, ximelagatran, which is 170 times more lipophilic than melagatran and remains uncharged at intestinal pH. Ximelagatran is therefore much better than melagatran at penetrating the gastrointestinal barrier and, as a consequence, has sufficient bioavailability (20%) for oral administration with low between-subject variation [47,48].

The absorption and bioconversion of ximelagatran to melagatran is rapid. The maximum plasma concentration of melagatran is achieved 2–3 hours after oral ximelagatran administration, with a mean half-life elimination of three hours. Its pharmacokinetic profile is predictable and stable over time [49,50], and is unaffected by patient body weight, age, sex, or ethnic origin [50-52]. With a metabolism that is independent of the hepatic P450 system, ximelagatran exhibits low potential for drug interactions and has no known food interactions [49,50,53,54], making coagulation monitoring and dose adjustments unnecessary [50-52]. Recent data, however, suggest that in patients with severe renal impairment, a reduction in dose and/or an increase in the administration interval would be appropriate [55]. At present there is no reversal agent to counteract drug-related hemorrhage.

Additional advantages of direct thrombin inhibitors include a targeted specificity for thrombin, the ability to inactivate clot-bound thrombin, and an absence of plasma protein and platelet interactions, which can lead to complications such as heparin-induced thrombocytopenia.

The SPORTIF studies

SPORTIF II was a 12-week, randomized, parallel group, dose-guiding study in non-valvular AF (NVAF) patients with at least one additional risk factor for stroke [56]. The primary endpoint was the number of thromboembolic events and bleedings. Three groups received ximelagatran (n = 187) at 20, 40, or 60 mg twice daily, given in a double-blind fashion, without routine coagulation monitoring. In a fourth group, warfarin (n = 67) was managed and monitored according to normal routines, aiming for an INR of 2.0 to 3.0. All three doses of ximelagatran compared favorably with warfarin, without the need for dose adjustment or coagulation monitoring.

The SPORTIF III and V are phase III trials designed with the primary objective of establishing the non-inferiority of ximelagatran relative to warfarin for the prevention of all strokes (ischemic and hemorrhagic) and systemic embolic events in patients with AF (persistent and paroxysmal) who have one or more additional risk factors for stroke [57]. To be included, patients were required to have persistent or paroxysmal non-valvular AF verified by at least two ECG recordings, one of which was made within two weeks of randomization. Secondary endpoints were death, acute myocardial infarction, major and minor bleeding, and discontinuation of treatment. SPORTIF III was conducted over 259 European sites as an open-label study, with blinded endpoint assessment. SPORTIF V was a double-blind study involving 409 North American sites. In both studies, patients were randomized to either a fixed 36 mg, twice-daily dose of ximelagatran or to warfarin (INR 2.0–3.0, monitoring interval ≤ 4 weeks) [56].

The two trials were well matched, with a mean patient age of 70 years (69% males). Seventy-two percent of patients had > 1 risk factor for thromboembolism.

SPORTIF III

The SPORTIF III trial (see Table 5 and Additional file: 5) included 3,410 patients (mean follow up 17.4 months) [58]. The INR values fell within the intended therapeutic range for the entire duration of exposure in 66% of the study population, and values were within the extended range of 1.8 to 3.2 more than 80% of the time, a rate much better than in most published reports or experienced in clinical practice. By intention-to-treat analysis, there was no difference in the primary endpoint (rates of stroke or systemic embolic events) between warfarin (56: 2.3%/yr) and ximelagatran (40: 1.6%/yr). However primary events in on-treatment analysis were significantly lower in the ximelagatran (29, 1.3%/yr) versus warfarin-treated patients (52, 2.2%/yr; RRR 43%, p = 0.018). The combined rate of major and minor bleeding events was found to be significantly lower for ximelagatran than for warfarin (475 vs 554 events; p = 0.007). There was no significant difference in all-cause mortality between the ximelagatran (78: 3.2%) and warfarin groups (79: 3.2%), despite the lack of coagulation monitoring and fixed-dose regimen with ximelagatran. There was a "net clinical benefit" (combined rate of primary events, major bleeding, and death with each treatment) in favor of ximelagatran treatment (6.1%/year with warfarin and 4.6%/year with ximelagatran, RRR 25%, p = 0.022).

There was no difference in the overall rate of adverse events between patients randomized to warfarin (1,452, 85%) and those assigned to ximelagatran (1,472, 87% p = 0.228). The serum concentration of alanine aminotransferase rose >3 × the upper limit of normal in 14 (1%) patients in the warfarin group and 107 (6%) in the ximelagatran group (p < 0.0001, see table 5 and Additional file: 5). Of the 107 patients in the ximelagatran group, 48 discontinued the study drug prematurely (42 of 48 returned to normal), and 59 continued treatment with raised serum concentrations of alanine aminotransferase. Fifty-five of these returned to normal, three returned to less than twice the upper limit of normal, and one in whom the amount of alanine aminotransferase was greater than twice the upper limit of normal before the study remained at this value.

SPORTIF V

The SPORTIF V trial (see Table 5 and Additional file: 5) included 3,922 patients with NVAF. Study results have been presented but not yet published [59]. Anticoagulation with warfarin was meticulously monitored. The INR remained within the target range 68% of the time and within an extended INR range of 1.8–3.2 eighty-three percent of the time, where no dose adjustment would be deemed necessary. The difference in primary event rates by intention-to-treat analysis fell within the non-inferiority parameters, with an absolute difference of 0.45% per year between groups (p = 0.13). By on-treatment analysis, the absolute difference was +0.55% per year (95% CI -0.06%–1.16%, p = 0.089) for ximelagatran vs warfarin.

The rates of intracerebral hemorrhage and major bleeding were low and were not significantly different between groups, with a trend for major bleeding that favored ximelagatran. When all bleeding was considered, there was a statistically significantly lower rate of major and minor bleeding with ximelagatran compared with warfarin. Elevations of serum transaminase enzymes in the

ximelagatran group reached beyond three times the upper limit of normal in 6% of ximelagatran patients, compared with 0.8% in the warfarin group (table 5 and Additional file: 5).

Summary of SPORTIF III and V

SPORTIF III and V are complementary studies that together represent the largest combined randomized trial of anticoagulation in AF to date. The data confirm the non-inferiority of ximelagatran as compared to warfarin for the prevention of embolic events in AF. In the combined studies, a total of 91 patients with events were seen for ximelagatran compared with 93 for warfarin (1.6 percent/yr vs. 1.6 per percent/yr), supporting the efficacy of ximelagatran in the prevention of strokes and thromboembolic events in patients with atrial fibrillation. Ximelagatran is also associated with less combined major and minor bleeding than warfarin.

However, optimism is tempered by the need for monitoring of liver function, probably monthly, for at least the first six months of treatment [59]. This rise in serum transaminase typically occurred within two and six months after initiation of treatment and then normalized, whether or not treatment was continued.

Will ximelagatran replace warfarin?

Recent data demonstrating the efficacy of ximelagatran for the treatment and prevention of venous thromboembolism as well as for administration after myocardial infarction should give the drug a wide clinical platform [60-66]. However, improved convenience is likely to come at a significant financial cost. Added to this limitation is encouraging recent mortality data about warfarin [67], and the increasing trend toward the use of anticoagulation clinics and home patient monitoring [68,69]. This will clearly reduce both the cost and inconvenience of warfain use, while furthering improved anticoagulation control.

There is no doubt that ximelagatran offers an exciting alternative to warfarin. Nonetheless, we do feel that it is still too early to say whether or not it will represent a viable future replacement. We await longer-term data, which are likely to become available after the launch of this product onto the market within the next two years.

Competing interests

The authors connected with this publication have no competing interests to declare. We have no affiliation with Astra Zeneca.

Additional material

Additional file 1

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