

Another oral thrombin inhibitor for stroke prevention in atrial fibrillation?

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Atrial fibrillation (AF), the most common arrhythmia, is associated with a five-fold increase in the risk of stroke (1). Furthermore, cardio-embolic strokes in AF patients tend to be severe, and are often fatal or associated with serious morbidity. Vitamin K antagonists, such as warfarin, produce about a 64% reduction in the risk of stroke in AF patients (2), but have numerous limitations that curtail their uptake and diminish their effectiveness. These limitations include a slow onset of action, a variable dose requirement, reflecting common genetic polymorphisms that influence their metabolism, and an unpredictable anticoagulant response because of differences in dietary vitamin K intake and numerous drug-drug interactions, which increase or decrease the anticoagulant effect (3). With the anticoagulant response so variable, routine monitoring is necessary to ensure that the international normalised ratio (INR) is therapeutic because over-anticoagulation is associated with an increased risk of haemorrhage, whereas under-anticoagulation increases the risk of thrombosis. Such monitoring is inconvenient for patients and physicians and costly for the healthcare system. Because of the complexity of management, only about one-half of eligible patients with AF receive warfarin, and among those who receive such treatment, the INR is frequently outside of the therapeutic range (4). The large

unmet need caused by the limitations of warfarin has prompted the development of new oral anticoagulants with potential advantages over existing agents.

Ximelagatran, the first oral thrombin inhibitor, was effective for stroke prevention in patients with AF, but was withdrawn in 2006 because of potential hepatic toxicity (5). The effectiveness of ximelagatran prompted development of a second generation of oral thrombin inhibitors. The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial demonstrated the effectiveness of dabigatran etexilate, the first of this new generation, for stroke prevention in AF, endorsing thrombin as an appropriate target for new anticoagulants. Two doses of dabigatran etexilate were compared with warfarin in this trial; the higher dose regimen (150 mg twice-daily) was associated with significantly fewer intracranial bleeds and strokes compared with warfarin, whereas the lower dose (110 mg twice-daily) was associated with significantly less major bleeding than warfarin and similar efficacy (6).

AZD0837 is the second of the new generation of oral thrombin inhibitors. A follow-up of ximelagatran, AZD0837 is a pro-drug of AR-H067637, a selective and reversible inhibitor of free and fibrin-bound thrombin (7). Cytochrome P450 isoenzymes in the liver convert AZD0837 to AR-H069927, an intermediate that undergoes further metabolism to AR-H067637, the active form. In healthy individuals, AR-H067637 has a plasma half-life of 9–14 hours and the drug is cleared in the urine and faeces. An immediate-release preparation was the first formulation of AZD0837 evaluated in clinical trials; a more recent extended-release formulation enables once-daily dosing.

In this issue of *Thrombosis and Haemostasis*, Olsson et al. (8) report the results of a phase II, randomised, controlled, dose-finding study evaluating the safety and tol-

erability of the immediate-release formulation of AZD0837 in 250 patients with AF who had at least one risk factor for stroke. Patients were allocated to a three month course of AZD0837, at doses of 150 or 350 mg twice daily, or warfarin, dose-adjusted to achieve an INR of 2–3. There was blinding to AZD0837 dose, but the comparison with warfarin was open-label. More than 90% of patients included in the study had previously received warfarin and 60–71% of patients allocated to the warfarin arm had INR values within the target range between study day 12 and 90. Consistent with its anticoagulant effects, AZD0837 produced a dose-dependent prolongation of the activated partial thromboplastin time and thrombin clotting time and suppression of the endogenous thrombin potential. Reductions in the levels of D-dimer and prothrombin fragment 1.2 with AZD0837 were similar to those with warfarin.

Although rates of adverse events were similar with AZD0837 and warfarin, serious adverse events and adverse events leading to treatment discontinuation were more common in patients randomised to the higher-dose AZD0837 arm than they were in those assigned to lower-dose AZD0837 or to warfarin. Gastrointestinal complaints, such as nausea and diarrhea, were the most frequent adverse events leading to AZD0837 discontinuation. Arrhythmic or ischaemic cardiac events occurred in 7% of patients who received AZD0837 at a dose of 350 mg twice-daily compared with 1% of those given lower-dose AZD0837 and in none who received warfarin. Both doses of AZD0837 were associated with a 10% increase in serum creatinine, but creatinine levels returned to normal within days of stopping treatment. This phenomenon has been attributed to AZD0837-induced inhibition of the tubular secretion of creatinine (9). There were no strokes during the study and no differences in the rates of major bleeding

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amongst the three treatment groups. Minor bleeding was more frequent in patients assigned to higher dose AZD0837 than it was in those given lower dose AZD0837 or warfarin. Unlike ximelagatran, there was no signal for liver toxicity with AZD0837.

A recent phase II study by Lip and colleagues compared four different doses of the extended-release formulation of AZD0839 (150, 300, or 450 mg once-daily or 200 mg twice-daily) with warfarin in 955 patients with AF. Rates of adverse events were similar across all treatment groups, but AZD0837 was associated with a dose-dependent increase in adverse events, most of which were gastrointestinal, which prompted study drug discontinuation (9). There were no differences in the rates of stroke amongst the treatment groups, but rates of bleeding were lower with the 150 and 300 mg once-daily doses of AZD0837 than with warfarin, and these doses were not associated with an excess of serious adverse events. There was no evidence of an excess in cardiac events with extended-release AZD0837 nor was there any signal for hepatic toxicity.

What are the implications of these results for the future development of AZD0837? The phase II studies reported by Olsson and Lip confirm that AZD0837 inhibits coagulation in a dose-dependent fashion, but also demonstrate that the drug is associated with

a dose-independent increase in gastrointestinal side-effects that necessitated treatment discontinuation in some patients. Although an excess of cardiac events was noted with the highest dose of the immediate-release formulation of AZD0837, there was no apparent cardiac signal with lower doses of the extended-release formulation. This is an important issue because dabigatran etexilate was associated with an excess of myocardial infarction compared with warfarin, equivalent to two additional events per 1,000 patients treated (6). The increase in the risk of myocardial infarction with dabigatran etexilate is small and these events are unlikely to be of major clinical significance because cardiovascular mortality was lower with dabigatran etexilate than with warfarin. Although there is no obvious biological mechanism for the increase in myocardial infarction, the results with dabigatran etexilate and AZD0837 raise the question as to whether this is a class effect with oral thrombin inhibitors. More information is needed, and the results of ongoing trials with oral factor Xa inhibitors will inform us as to whether excess myocardial infarction is unique to thrombin inhibitors. Nonetheless, the potential for cardiac events and the gastrointestinal side effects with higher dose regimens should not discourage further development of AZD0837. Despite higher rates of dyspepsia and an increased

risk of myocardial infarction, dabigatran etexilate exhibited clinically important advantages over warfarin for stroke prevention in AF patients (6) and AZD0837 may have similar benefits.

Do we need another new oral anticoagulant for stroke prevention in AF? The RE-LY trial has established dabigatran etexilate as the new standard of care for stroke prevention in AF and it will be challenging to achieve further improvements in efficacy and safety. Rivaroxaban, apixaban and edoxaban are in advanced stages of development for stroke prevention in AF with results expected in 2010 and 2011 (► Table 1). Does AZD0837 offer practical or safety advantages over dabigatran etexilate and these other new oral anticoagulants? The phase II studies do not clearly identify any safety advantages of AZD0837 over warfarin, but the extended-release formulation offers a more convenient once-daily administration compared with dabigatran etexilate, which must be given twice-daily. The anticoagulant effects of AZD0837 are more consistent over a 24-hour period than are those of once-daily rivaroxaban or edoxaban, which have half-lives closer to 12 hours. Whether this will endow AZD0837 with an efficacy advantage is unknown. Building on the results of the phase II studies, a large phase III warfarin-con-

Characteristic	AZD0837	Dabigatran etexilate	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	Thrombin	Factor Xa	Factor Xa	Factor Xa
Prodrug	Yes	Yes	No	No	No
Bioavailability (%)	22–55	6	80	60	50
Dosing	Fixed, once daily	Fixed, twice daily	Fixed, once daily	Fixed, twice daily	Fixed, once daily
Half life (hours)	9 – 14 *	12–14	7 – 11	12	9 – 11
Renal clearance (%)	66	80	66†	25	35
Routine coagulation monitoring	No	No	No	No	No
Drug interactions	Potent inhibitors of CYP3A4‡	Potent inhibitors of P-gp	Potent inhibitors of CYP3A4 and P-gp‡	Potent inhibitors of CYP3A4‡	Potent inhibitors of CYP3A4 and P-gp‡
Phase III trials	ASSURE§	RE-LY¶	ROCKET-AF	ARISTOTLE AVERROES	ENGAGE

CYP, cytochrome P-450; P-gp, P-glycoprotein. *Reflects the half-life of the active metabolite; the extended release formulation achieves a longer effective half-life. †Of drug cleared by the kidneys, one half is unchanged drug, while inactive metabolites constitute the remainder. ‡Potent inhibitors of both CYP3A4 and P-glycoprotein include azole antifungals (e.g. ketoconazole, itraconazole, voriconazole, and posaconazole) and protease inhibitors, such as ritonavir. Potent inhibitors of CYP3A4 include azole antifungals, macrolide antibiotics (e.g. clarithromycin) and protease inhibitors (e.g. atazanavir). §Trial planned, but not yet randomizing patients. ¶Trial has been completed (6).

Table 1: Comparison of the pharmacological features of new oral anticoagulants in phase III evaluation for stroke prevention in patients with atrial fibrillation.

trolled trial is required to determine the efficacy, safety and convenience of AZD0837 for stroke prevention in AF.

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