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IM - REVIEW

New direct thrombin inhibitors

Alessandro Squizzato · Francesco Dentali · Luigi Steidl · Walter Ageno

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Abstract Direct thrombin inhibitors (DTIs) are a class of anticoagulants that bind selectively to thrombin and block its interaction with its substrates. Dabigatran etexilate and AZD0837, the new generation of DTIs, are now under intense development, and are potentially of great interest for internists. Dabigatran etexilate is a potent, non-peptidic small molecule that specifically and reversibly inhibits both free and clot-bound thrombin by binding to the active site of thrombin molecule. It has been already licensed in the European Union and in Canada for the prevention of VTE in patients undergoing hip- and knee-replacement surgery. Ongoing trials are evaluating its efficacy and safety for the treatment of deep venous thrombosis and pulmonary embolism, primary and secondary prevention of VTE, prevention of systemic embolism in patients with non-valvular atrial fibrillation, and prevention of cardiac events in patients with acute coronary syndromes. AZD0837 is the prodrug of ARH06737, a potent, competitive, reversible inhibitor of free and fibrin-bound thrombin. At present, only limited, preclinical, phase I and phase II clinical data have been presented. The drug has now entered a phase III clinical program in the population of patients with atrial fibrillation. Their properties and the oral administration render these compounds, theoretically, more convenient than both vitamin K antagonist and low molecular weight heparins. However, only reports from clinical practice patterns over the next months and years will tell us how and when to use the new DTIs.

Keywords Anticoagulants · Thrombin inhibitors · Dabigatran · Venous thromboembolism · Atrial fibrillation

A. Squizzato · F. Dentali · L. Steidl · W. Ageno
Department of Clinical Medicine,
University of Insubria, Varese, Italy

A. Squizzato (✉)
U.O. Medicina I, Ospedale di Circolo,
Viale Borri 57, 21100 Varese, Italy
e-mail: alexsquizzo@libero.it

Introduction

Over the last five decades, there has been little progress in the development of oral anticoagulants, with the choices being limited to the vitamin K antagonists. The situation is rapidly changing with the development of orally active small molecules that directly target thrombin or activated factor X (FXa). Direct thrombin inhibitors (DTIs) are a class of anticoagulants that bind selectively to thrombin and block its interaction with its substrates [1]. Older DTIs are administered parenterally and are currently approved in specific settings, such as the treatment of heparin-induced thrombocytopenia for recombinant hirudin and argatroban, the treatment of patients undergoing percutaneous coronary interventions for bivalirudin, and the prophylaxis against venous thromboembolism in patients undergoing hip-replacement surgery for desirudin [1]. Newer DTIs have the advantages to be administered orally. Ximelagatran was the first of this new generation. Unfortunately, after that initial studies led to its temporary licensing in Europe for thromboprophylaxis in patients undergoing major orthopedic surgery, the drug was withdrawn from the world market in 2006 because of potential idiosyncratic severe (even lethal) hepatic toxicity [2]. Ximelagatran did, however, have many desirable properties and demonstrated that an oral anticoagulant specifically targeting thrombin without routine monitoring could be effective in preventing tromboembolic complications in patients with atrial

fibrillation or venous thromboembolism, with a bleeding risk profile similar to that of the vitamin K antagonists. Dabigatran etexilate and AZD0837 are now under development, and are thus potentially of great interest for internists [3].

Aim of the present narrative review is to focus on published data of new oral DTIs, in particular dabigatran etexilate, as it has been already licensed for the prevention of venous thromboembolism (VTE) in major orthopedic surgery [4]. Mechanism of action will be initially briefly described.

Mechanism of action

Thrombin has a central role in the clotting process: it converts soluble fibrinogen to fibrin; activates factors V, VIII and XI, which generates more thrombin; stimulates platelets; and, by activating factor XIII, favors the formation of cross-linked bonds among the fibrin molecules, stabilizing the clot [1]. Thrombin-inhibiting drugs can block the action of thrombin by binding to three domains: the active site or catalytic site and two exosites [1]. Dabigatran etexilate, similarly to argatroban and melagatran, is an univalent DTI that binds exclusively to the active site of thrombin with the advantage, in comparison with heparins, to inactivate fibrin-bound thrombin. Moreover, dabigatran etexilate is a reversible DTI, like argatroban, bivalirudin, and melagatran, that dissociates relatively quickly from thrombin, leaving a small amount of free, enzymatically active thrombin available for control of hemostasis. Reversible binding may contribute towards safer and more predictable anticoagulant treatment compared to irreversible binding, as reported for hirudin, the first of this class of drugs [5].

Dabigatran etexilate

Dabigatran etexilate (Pradaxa®, BIBR 1048), developed by Boehringer-Ingelheim, is the prodrug of dabigatran (BIBR 953), a potent, non-peptidic small molecule that specifically and reversibly inhibits both free and clot-bound thrombin by binding to the active site of thrombin molecule [6]. It has been already licensed in the European Union and in Canada for the prevention of VTE in patients undergoing hip- and knee-replacement surgery [5]. Ongoing trials are evaluating its efficacy and safety for the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE), primary and secondary prevention of VTE, prevention of systemic embolism in patients with non-valvular atrial fibrillation (AF), and prevention of cardiac events in patients with acute coronary syndromes (ACS) [3].

Pharmacodynamic and pharmacokinetic properties

Dabigatran etexilate is absorbed from the GI tract with a bioavailability of 5–6% [2, 7]. Absorption requires an acid microenvironment and is reduced by acid suppression therapy [7]. Dabigatran etexilate is rapidly absorbed, except in the immediate postoperative period, when absorption is delayed. Once absorbed, dabigatran etexilate is rapidly converted by esterases into its active metabolite, dabigatran (BIBR 953). The onset of its anticoagulant activity is rapid, with plasma levels of dabigatran peak at 2 h. Half-life ranges between 12 and 17 h [2]. Dabigatran produces a predictable anticoagulant effect, requires no coagulation monitoring and can be given once daily (od). Dabigatran etexilate prolongs the activated partial thromboplastin time, but its effect is not dose-linear and it is not suitable for a precise quantification of the anticoagulant effect. At least 80% of dabigatran is excreted unchanged via the kidneys; therefore, the drug is contraindicated in patients with severe renal failure, with a creatinine clearance less than 30 ml/min [2] (Table 1). There were no clinically important pharmacokinetic interactions with digoxin (a P-glycoprotein substrate), or drugs that are substrates and/or inhibitors of hepatic cytochrome P450 enzymes [8]. No significant interaction was demonstrated with atorvastatin that is a substrate for liver CYP3A4 and substrate/inhibitor of P-glycoprotein, an efflux transporter [9]. Conversely, co-administration of amiodarone, another potent P-glycoprotein inhibitor, is associated with an increased concentration of dabigatran etexilate of about 60% [3]. Pantoprazol reduces dabigatran bioavailability more than 20% [3]. Whether this is clinically relevant is not clear. No additive effects on platelet aggregation were observed when dabigatran etexilate was administered with aspirin or diclofenac [3].

Antidote

Currently, no specific antidote is available for DTIs. At therapeutically relevant doses, either recombinant factor

Table 1 Main pharmacological characteristics of dabigatran etexilate

Dabigatran etexilate
Oral prodrug, converted to dabigatran, a potent reversible DTI
Inhibits both clot-bound and free thrombin
Fast onset and offset of action
Absolute bioavailability ~6.5%
Predictable and reproducible PK/PD
Half life 12–17 h
Renal excretion 80%
No monitoring

DTI Direct thrombin inhibitor, *PK/PD* pharmacokinetic/pharmacodinamic

VIIa or activated prothrombin complex concentrates can reverse the prolonged bleeding time in rats treated with high doses of dabigatran [3, 10], but clinical evaluation of this approach to support the use of these agents has not been performed [3]. The use of fresh frozen plasma use is suggested in the official summary of product characteristics based on an empirical rationale. However, the content of thrombin in fresh frozen plasma is relatively low and probably quite a number of units are needed.

VTE prevention in orthopedic surgery

Three phase III randomised controlled trials (RCTs) for VTE prevention in orthopedic surgery have been published: RE-MODEL, RE-NOVATE, and RE-MOBILIZE [11–13] (Table 2). All trials were designed to show non-inferiority of dabigatran as compared to the comparator, enoxaparin. Two doses of dabigatran, 150 and 220 mg, were tested in each study because data from a dose-ranging study suggest that the optimum total daily dose for effective and safe prevention of venous thromboembolism in total hip- or knee-replacement surgery is between 100 and 300 mg [2].

In the RE-MODEL trial, 2,076 patients undergoing knee arthroplasty were randomized to receive either dabigatran etexilate (at doses of 150 or 220 mg qd, starting with half of the dose given 1–4 h after surgery) or enoxaparin at the European dose regimen (given subcutaneously od at a dose of 40 mg, starting 12 h prior to surgery) [2, 11], all administered for a median of 8 days. Patients were followed for 12–14 weeks. The primary end point, the composite of total VTE events (symptomatic or venographic deep vein thrombosis and/or symptomatic pulmonary embolism), and all-cause mortality, during treatment 6–10 days, occurred in 40.5 and 36.4% of patients given 150 and 220 mg of dabigatran etexilate, respectively, and in 37.7% of those randomized to enoxaparin. Major bleeding occurred in 1.3, 1.5, and 1.3% of those given 150 mg dabigatran etexilate, 220 mg dabigatran etexilate and enoxaparin, respectively, while rates of major bleeding plus clinically relevant, non-major bleeding were 7.1, 7.4, and 6.6%, respectively. None of these differences was statistically significant. Levels of alanine aminotransferase >3 times the upper limit of normal were observed in 3.7 and 2.8% of patients receiving 150 and 220 mg of dabigatran etexilate, respectively, compared with 4.0% of those given enoxaparin [2, 11]. The RE-NOVATE trial randomized 3,494 patients undergoing hip-replacement surgery to oral dabigatran etexilate (either 150 or 220 mg qd, starting with half of the dose given 1–4 h after surgery)

Table 2 Phase III studies of dabigatran exetilate in orthopedic surgery

Study	Type of surgery	Comparator	Number of patients	Time to 1st administration of dabigatran (h post-surgery)	Treatment duration (days)
Part I					
RE-NOVATE	THR	Enoxaparin 40 mg od, starting evening before surgery	3,494	1–4	28–35
RE-MOBILIZE	TKR	Enoxaparin 30 mg bid, starting 12–24 h post-surgery	2,615	6–12	6–10
RE-MODEL	TKR	Enoxaparin 40 mg od, starting evening before surgery	2,010	1–4	6–10

	Enoxaparin	Dabigatran (150 mg)	Dabigatran (220 mg)
Part II			
DVT, PE and all-cause mortality (%)			
RE-NOVATE	6.7	8.6	6.0
		$p < 0.0001$*	$p < 0.0001$*
RE-MOBILIZE	25.3	33.7	31.1
		$p = 0.0009$†	$p = 0.02$†
RE-MODEL	37.7	40.5	36.4
		$p = 0.0005$*	$p = 0.0345$*
Major bleeding (%)			
RE-NOVATE	1.6	1.3	2.0
RE-MOBILIZE	1.4	0.6	0.6
RE-MODEL	1.3	1.3	1.5

DVT (venographic and symptomatic) deep venous thrombosis, *PE* pulmonary embolism

* Non-inferior to enoxaparin

† Inferior to enoxaparin

or subcutaneous enoxaparin at the European dose regimen (40 mg qd, starting 12 h prior to surgery) for an average of 33 days [2, 12]. Patients were followed for 12–14 weeks. The primary efficacy end point, a composite of total venous thromboembolic events (venographic or symptomatic deep vein thrombosis or symptomatic pulmonary embolism) and all-cause mortality during treatment 28–35 days, occurred in 8.6 and 6.0% of patients given dabigatran etexilate 150 or 220 mg, respectively, and in 6.7% of those treated with enoxaparin. Major bleeding occurred in 1.3 and 2.0% of patients treated with dabigatran etexilate 150 and 220 mg, respectively, and in 1.6% of those given enoxaparin. None of these differences was statistically significant [2, 12]. Finally, in the North American RE-MOBILIZE trial, 2,615 patients undergoing knee-replacement surgery were randomized to oral dabigatran etexilate (either 150 or 220 mg od, starting with a half dose given 8–12 h after surgery) or subcutaneous enoxaparin at the American dose regimen (30 mg bid starting 12–24 h after surgery) for 12–15 days [2, 13]. The primary efficacy end point, a composite of total VTE events (symptomatic or venographic deep vein thrombosis and/or symptomatic pulmonary embolism), and all-cause mortality, during treatment 12–15 days, occurred in 33.7 and 31.1% of patients treated with dabigatran 150 or 220 mg, respectively and in 25.3% of those given enoxaparin. Major bleeding occurred in 0.6% of patients treated with either dose of dabigatran and in 1.4% of those given enoxaparin. This was the only study in which dabigatran resulted significantly less effective than enoxaparin. This difference may reflect the higher dose of the enoxaparin regimen used as a comparator and/or the delayed start of dabigatran etexilate [2, 13].

A meta-analysis compared the efficacy and safety data for the recommended dose of dabigatran etexilate, 220 mg od, with enoxaparin. Analyses were performed combining RE-MODEL and RE-NOVATE, which compared dabigatran etexilate with enoxaparin 40 mg od, and also including RE-MOBILIZE, which compared dabigatran etexilate with enoxaparin 30 mg twice [14]. No significant differences were detected between dabigatran etexilate and enoxaparin in any of the end points analyzed. Relative risks for the composite end-point total VTE and all-cause mortality were 0.95 [95% confidence intervals 0.82–1.10] and 1.05 [0.87–1.26] in the two and three trial analyses, respectively. A subsequent meta-analysis of RE-MODEL and RE-NOVATE studies supported only the conclusions of the individual trials that dabigatran etexilate is non-inferior to enoxaparin 40 mg od, with a similar safety profile [14]. However, in all statistical analyses heterogeneity among the trials could not be ruled out.

Non-valvular atrial fibrillation

A phase II trial in 502 patients with atrial fibrillation compared a 3-month course of treatment with 3 different doses of dabigatran etexilate (50, 150 or 300 mg bid) or with warfarin (with doses adjusted to achieve a target international normalised ratio (INR) of 2.0–3.0) [2, 15]. Using a factorial design, patients also were randomized to aspirin (81 or 325 mg daily) or to placebo. Recruitment into the high dose dabigatran etexilate plus aspirin arm was stopped early because of 4 gastrointestinal bleeds in 63 patients. Addition of aspirin in the other groups did not appear to increase the risk of bleeding. In the low dose dabigatran etexilate arm, 2 of 105 patients suffered a thromboembolic event. Building on these data, 361 of the 432 patients randomized to dabigatran etexilate continued open-label treatment at doses of 50, 100 or 300 mg bid, or 150 or 300 mg qd for at least 16 months. The two lowest doses of dabigatran etexilate (50 bid or 150 qd) were discontinued early because of annual stroke rates of 8.4 and 8.1%, respectively. The annual stroke rate with the 300 mg qd dose was 9.5%, whereas rates were lower with the other doses. The cumulative frequency of elevations in alanine aminotransferase of $>3 \times$ the upper limit of normal was 2% in patients receiving dabigatran etexilate for at least 12 months compared with 1% in those given warfarin. Based on these data, the recently completed phase III RELY trial has compared dabigatran etexilate doses of 110 or 150 mg bid with dose-adjusted warfarin for stroke prevention in 18,000 patients with nonvalvular atrial fibrillation and at least 1 risk factor for stroke [16]. A total of 18,113 patients were included in the study. The primary outcome is stroke (including hemorrhagic stroke) or systemic embolism. Safety outcomes include bleeding, liver function abnormalities, and other adverse events. The trial was expected to accrue a minimum of 450 events with a minimum 1-year follow-up. The results of the study will be presented later this year. Dabigatran etexilate is also currently undergoing phase III evaluation in the RECOVERY, REMEDY, and RESONATE studies, for both the acute treatment and the secondary prevention of VTE.

Licensed indication

Dabigatran etexilate is currently licensed for the prevention of VTE in knee- and hip-replacement surgery. The recommended dose is 220 mg od [4]. The first dose should be administered between 1 and 4 h post-operatively at a half dose (110 mg). In patients with moderate renal insufficiency (creatinine clearence between 30 and 50 ml/min) and in the elderly (aged 75 or more), the recommended dose is 150 mg od (first dose, 75 mg) [4]. A dose reduction is also recommended for patients on amiodarone treatment.

AZD0837

AZD0837, developed by AstraZeneca, is the prodrug of ARH06737, a potent, competitive, reversible inhibitor of free and fibrin-bound thrombin [3]. It is a follow-up compound of ximelagatran, which is seemingly devoid of associated liver toxicity [3]. At present, only limited, preclinical, phase I and phase IIa clinical data have been presented, but have not been published. A phase IIb trial evaluating AZD0837 [17]. 955 AF patients with ≥1 additional risk factor for stroke were randomised to receive one of four doses of AZD0837 (150, 300 or 450 mg od or 200 mg twice daily, blinded treatment) or VKA (titrated for INR 2–3, open treatment) for 3–9 months [17]. Total bleeding events were similar or less in all AZD0837 groups (5.3–14.1%, mean exposure 138–145 days) compared with VKA (14.5% mean exposure: 160 days). Clinically relevant bleeding events (i.e., major + clinically relevant minor) in the whole cohort and the VKA-naïve sub-group were numerically less common in the AZD0837 150 and 300 mg od groups versus the AZD0837 450 mg od and 200 mg bid and VKA group. A similar frequency of serum alanine aminotransferase (ALT) >3 × the upper limit of normal was seen with AZD0837 compared to VKA (2.3 vs. 1.6%, respectively) [17]. The drug has now entered a phase III clinical program for the same indication [3].

The mean absolute bioavailability of this compound is in the range of 22–25%. An extended-release formulation has been developed, giving the possibility of using od dosing without significant peak-trough variability. The administration of AZD0837 to healthy male volunteers has demonstrated an increase in activated partial thromboplastin time and thrombin time of 1.6 and 7-fold, respectively, relative to baseline [3]. An interaction has been shown with the strong CYP3A4 inhibitor ketoconazole, but none with the weak inhibitor grapefruit juice [18]. No interaction was reported with digoxin [3].

Conclusions

After decades with only one class of oral anticoagulants—i.e., the vitamin K antagonists—the situation is rapidly changing with the development of DTI and FXa inhibitors. The two agents in the most advanced stages of development are dabigatran etexilate and rivaroxaban, which inhibit thrombin and FXa, respectively. Both are approved in the Europe and Canada for thromboprophylaxis in patients undergoing elective hip- or knee-replacement surgery. Other agents in earlier stages of development include several FXa inhibitors (apixaban, edoxaban, LY 517717, YM 150, betrixaban, eribaxaban [PD 0348292] and TAK 442) and one thrombin inhibitor (AZD0837) [2, 3]. With predictable anticoagulant responses and low potential for drug-drug interactions, these new agents can be given in fixed doses without coagulation monitoring. These properties and the oral administration render these compounds more convenient than both VKAs and low molecular weight heparins. Indeed, the favorable results of clinical trials support their potential to change current practice and management of patients requiring prophylaxis or treatment of both venous and arterial thrombosis. However, only reports from daily clinical practice over the next months and years will tell us if and when these changes will occur. A correct use of the new compounds and the correct management of particular conditions will be necessary to maintain a favorable balance between risks and benefits. In the meantime, both vitamin K antagonists and parenteral anticoagulant drugs will certainly maintain an important role, in particular in some patients categories such as patients with mechanical heart valves, in children (no available studies), patients with severe renal insufficiency, and in pregnant women. Finally, the possibility to monitor the effects of these new oral agents in case laboratory monitoring becomes necessary and the therapeutic management of bleeding complications appear now as major challenges for the near future.

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