The search for new anticoagulants: dabigatran etexilate

"*Dabigatran etexilate promises to not only decrease demands on hospital time and resources, but also provides us with an orally administered anticoagulant that can be prescribed safely on an out-patient basis.*"

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Thrombin is a key enzyme in the blood coagulation cascade and a major factor in the initiation and propagation of thrombosis. Thrombin inhibition therefore represents a therapeutic target for numerous thromboembolism-related disorders, such as venous thromboembolism (VTE) and arterial thrombosis [1]. Historically, antithrombotic therapy was mainly based on the orally-administered vitamin K antagonists (VKAs; e.g., warfarin), or on parenteral indirect thrombin inhibitors such as unfractionated heparin and low-molecular weight heparins via activation of antithrombin.

Despite high clinical effectiveness, these anticoagulants have important limitations. VKAs have a slow onset/offset of action, and a narrow therapeutic range requiring frequent anticoagulation monitoring and dosage adjustment, while heparins have only a parenteral formulation [2]. These disadvantages provide the impetus for the development of newer anticoagulants, the direct thrombin inhibitors (DTIs) and oral factor Xa inhibitors.

The DTIs inactivate thrombin directly by blocking its catalytic or fibrinogen-binding sites, or both [1]. Independence from co-factor levels (e.g., antithrombin III) makes their action more predictable, and their ability to inhibit both plasma and fibrin-bound thrombin predisposes to high anticoagulant activity [3]. The first member of the group, ximelagatran, revealed a number of attractive advantages over traditional VKAs, such as low interindividual variability, rapid onset of action and a predictable anticoagulant response, eliminating the requirement for routine anticoagulation monitoring [4]. Several large clinical trials on over 30,000 patients demonstrated that ximelagatran had an efficacy and risk of bleeding similar to the traditional anticoagulants [5]. However, ximelagatran was found to be associated with risks of hepatotoxicity [6], as well as a higher number of cardiovascular events after cessation of treatment, raising the possibility of a ximelagatran-induced rebound effect on the coagulation system [7]. As a result, ximelagatran was withdrawn from the market.

The next member of the oral DTI family, dabigatran etexilate, is a synthetic small benzamidine-based molecule that binds reversibly to the active site of the thrombin, thus inhibiting it [8]. Dabigatran benefits from its oral formulation and, in contrast to warfarin, dabigatran can be administered as a fixed dose with a rapid onset of action. Dabigatran provides a predictable and consistent anticoagulation effect without the need for coagulation monitoring. As it does not undergo hepatic metabolism, dabigatran has a relatively low potential for drug–drug interaction without significant drug–food interactions. In comparison with enoxaparin, dabigatran etexilate has a similar level of safety and efficacy, but its primary benefit is its convenience due to oral administration [9]. Therefore, dabigatran etexilate promises to not only decrease demands on hospital time and resources, but also provides us with an orally administered anticoagulant that can be prescribed safely on an out-patient basis.

The risk of liver damage as a side effect of dabigatran etexilate has been extensively investigated, but not observed until now. However, short-term exposure to ximelagatran also did not appear to increase the risk of liver toxicity, whereas its long-term administration led to a few cases of fatal hepatotoxicity. Therefore, further observations of long-term dabigatran safety are required. Dabigatran etexilate has, however, been approved in the EU for the primary prevention of VTE in patients with elective total hip- and knee-replacement surgery, and this decision was based on the evidence available from the different clinical studies on dabigatran [101].

Dabigatran for prophylaxis of venous thromboembolism

Dabigatran have been investigated for the prophylaxis of venous thromboembolism in various Phase II and III clinical trials.

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Nine oral doses of dabigatran were tested on 314 patients undergoing total hip replacement in The Boehringer Ingelheim Study in ThROmbosis (BISTRO I), with mandatory bilateral venography. No major bleeding events were observed and no patients developed symptomatic deep-vein thrombosis (DVT) during the 6–10 days treatment period [10].

In the large, multicenter, double-blind BISTRO II study, which enrolled 1973 patients undergoing either hip or knee replacement, patients were randomized to either 6–10 days of oral dabigatran etexilate or subcutaneous enoxaparin [11]. The primary efficacy outcome of the incidence of VTE (detected by bilateral venography or symptomatic events) during treatment was significantly lower in patients receiving dabigatran (150 mg or 225 mg twice daily, or 300 mg once daily) than enoxaparin. Major bleeding was significantly lower with 50 mg of dabigatran twice daily, but the rate of bleeding was elevated with higher doses of the drug, nearly reaching statistical significance (in comparison with enoxaparin) with the 300 mg once-daily dose of the drug.

In the Phase III multicenter, double-blind, randomized RE-MODEL trial, the efficacy of dabigatran etexilate in preventing VTE was compared with enoxaparin in 2076 patients undergoing elective knee-replacement surgery. No significant difference in total VTE occurrence and all-cause mortality between the treatments was found during 3 months follow-up [12]. Dabigatran was also demonstrated to be noninferior to enoxaparin at reducing the risk of thromboembolic disease in the RE-NOVATE trial of 3494 patients following hip-replacement surgery [13].

However, the primary end point of a composite of total VTE (including proximal DVT, distal DVT, pulmonary embolism and all-cause mortality) was not achieved in the RE-MOBILIZE noninferiority trial in 2615 patients following knee replacement surgery. Obtained results were probably associated with increased incidence of asymptomatic distal DVT detected by venography at the end of therapy, as major VTE occurrence was similar across all treatment groups [14].

An ongoing study, the RE-NOVATE study, comparing 220 mg of dabigatran with enoxaparin (40 mg once daily) for an extended treatment period of 28–35 days in patients undergoing hip-replacement surgery, is expected to shed further light on the effectiveness and safety of dabigatran [102].

After evaluating the clinical trial data available, the UK National Institute for Health and Clinical Excellence (NICE) has recommended dabigatran etexilate as a possible treatment option for the primary prevention of venous thromboembolic events in adults undergoing elective total hip- or elective total knee-replacement surgery throughout the National Health Service (NHS) of England and Wales.

Stroke prophylaxis in atrial fibrillation & venous thromboembolism treatment

Dabigatran is being investigated for stroke prophylaxis in atrial fibrillation and the treatment of venous thromboembolism in various Phase II and III clinical trials.

A randomized, dose-guiding Phase II trial (PETRO) revealed that 12-week administration of dabigatran in combination with aspirin in 502 patients with atrial fibrillation had a similar safety and antithrombotic efficacy as that of warfarin [15]. In the Phase III, randomized, double-blind RE-LY trial, two doses of dabigatran are compared with standard warfarin therapy for stroke prevention in 18,000 patients with atrial fibrillation. This study has completed enrolment and results are expected in early 2009 [103].

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Further Phase III trials are being conducted as part of the RE-VOLUTION program, and include two randomized, double-blind trials to assess dabigatran etexilate in comparison with warfarin. In one trial (RE-MEDY), dabigatran etexilate is to be administered for 18 months to 2000 patients with VTE to assess its efficacy in secondary prevention of VTE [104]. The RE-COVER trial is designed to determine utility of the drug for the treatment of patients with VTE [105].

Opinions & future perspective

Although several promising new anticoagulants are being evaluated, those anticoagulants that can overcome the side effects and disadvantages of warfarin are the ones evoking the greatest interest. The lessons learnt from ximelagatran, whilst learnt the hard way by the developers of this drug, indicate that thrombin is a prospective target for future strategies. The concepts of fixed dosing with no need for continuous monitoring of the coagulation profile grant this group of drugs a clear advantage over existing anticoagulants such

as warfarin. While the skeptics may argue that warfarin is considerably cheaper than the newer anticoagulants, one has to bear in mind the cost of continuous monitoring while conducting any analysis of warfarin's cost–effectiveness.

Similarly, it can even be argued that had it not been for its hepatotoxicity, ximelagatran would perhaps have been licensed for both short-term and long-term indications. Although long-term data are limited, transaminase elevations have not been a concern with dabigatran thus far. Therefore, accumulated data holds further promise for a bright future for dabigatran.

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Based on the action of DTIs, bleeding events may be inevitable when relatively high concentrations are administered. In contrast, synthetic direct inhibitors of factor Xa that are currently in development, such as rivaroxaban (Bayer AG [Leverkusen, Germany]/Ortho-McNeil Pharmaceutical Inc. [NJ, USA]; Phase III trials), apixaban (Bristol-Myers Squibb Co. [NY, USA]/Pfizer Inc. [NY, USA]; Phase III trials), otamixaban (Sanofi-Aventis [Paris, France]; Phase II trials), and DU-176b (Daiichi Sankyo Co. Ltd. [Tokyo, Japan]; Phase II trials) have been reported to have low risk of bleeding side effects. This may be at least partly explained by the fact that they do not inhibit the activity of residual thrombin in blood circulation, which may initiate platelet activation for hemostasis, whereas DTIs such as dabigatran are shown to inhibit platelet aggregation [16]. Therefore, the administration of DTIs might be associated with a greater risk of bleeding episodes in the treatment of thrombosis, when compared with direct factor Xa inhibitors. In addition, rivaroxaban is being investigated as a once-daily dose preparation in the ROCKET-AF study, while dabigatran etexilate has to be taken twice daily, which can potentially lead to patient compliance issues.

Whilst the development of newer anticoagulants is driven by the need for greater efficacy, and the hope for easier treatment monitoring, it is also important to remember that the novel drugs must also be safer than the existing ones. All new drugs will have to be thoroughly assessed for each separate indication before their clinical potential can be fully utilized. Even then, we will not know which is really the best until we conduct head-to-head trials comparing them against each other, which will again take many years.

Financial & competing interests disclosure

GL has received funding for research, educational symposia, advisory boards, consultancy and lecturing from different manufacturers of drugs used for the treatment of thrombosis, including Boehringer Ingelheim, who manufacture dabigatran. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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