New Oral Anticoagulants: A Brief Review

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ABSTRACT

This manuscript represents a brief review of the current oral anticoagulants that have come on the scene over the past decade and that are now in various stages of development through the process of phase II and III clinical trials. A brief review of the oral thrombin and direct factor Xa inhibitors is presented to apprise the practicing clinician of the status of these new agents. Efficacy and safety issues are mentioned as they relate to each agent and the need for alternative agents to replace the vitamin K antagonists for long-term anticoagulation therapy. Although none of the agents discussed in the review have been approved for clinical use, data accumulated thus far from the clinical studies have provided some degree of encouragement and optimism for their future approval.

INTRODUCTION

Over the past decade a host of new oral anticoagulants has emerged in an attempt to replace the warfarin derivatives that have served as the mainstay of oral anticoagulation for both primary and secondary prevention of thromboembolic disease. Since its discovery more than half a century ago (approved for clinical use in 1954), warfarin has become one of the most frequently prescribed drugs worldwide. However, over the decades of use, clinicians have come to recognize its narrow therapeutic window and the serious adverse effects associated with its administration (Figure 1). Frequent monitoring and dose adjustment to maintain the desired anticoagulation level have also provided a compelling need for replacement. Additionally, recent studies addressing the variability of response to warfarin administration have discovered frequent genetic polymorphisms that may account for the dose response differences in individuals. These genetic variants involve primarily the CYP2C9 gene located on chromosome 10 (C 10q) and the vitamin K epoxide reductase complex 1 (VKORC1) gene (Figure 2). As a result, genetic profiling of individuals has provided important, more predictable dose response data to warfarin administration for both induction and maintenance anticoagulation therapy that may reduce the adverse events associated with its administration. Providing the genetic status of each individual prior to initiating anticoagulation therapy to determine the risk, benefit, and cost of this quest will require a large, multi-institutional cooperative study.

These factors have stimulated a mounting tide of research and development by a number of pharmaceutical companies to develop a novel oral agent with acceptable toxicity and effective anticoagulation properties to replace the vitamin K antagonists. As a result, a number of new molecules have made their way into the various levels of clinical trials with promising results and encouragement for future clinical use and approval. Most of these new agents have targeted 2 major components of the clotting system, effectively halting the cascade of clotting factors, thus preventing the development of a thrombus. These 2 critical areas of the coagulation pathway that can be effectively inactivated are thrombin and factor Xa. Before proceeding, it is important to recognize the role that each of these factors play in the development of a thrombus (Figure 3).

Thrombin (IIa) is a direct result of the enzymatic activity of the prothrombin complex (prothrombinase), consisting of phospholipid Xa, its cofactor Va, and Ca++, on plasma prothrombin. Thrombin, having a more limited and specific enzymatic target, systematically cleaves small peptides from fibrinogen, its target plasma protein, at the arginine/glycine linkage. The result is an altered fibrinogen that forms a loose net-

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work with other altered molecules, forming a friable fibrin clot that subsequently becomes stabilized with covalent bonds by the action of factor XIII.\textsuperscript{11-15}

Factor X is a vitamin K dependent glycoprotein that plays a pivotal enzymatic role when activated in the clotting cascade. Activation of factor X occurs mainly by the enzymatic action of factors VIIa and IXa, both serine proteases.

It is important to point out that both factor Xa and thrombin are inhibited by heparin, both natural (unfractionated and low molecular weight) and synthetic preparations currently available for use in anticoagulation therapy. However, this inhibition can only occur when these agents are bound to antithrombin, a naturally occurring plasma protein that inhibits thrombin.\textsuperscript{16-18}

Thus, heparin is an indirect inhibitor of these serine proteases and by itself has virtually no anticoagulation activity. Therefore it differs significantly in its anticoagulation effect from the direct factor Xa inhibitors that will be discussed in this brief review (Table 1).

\textbf{Oral Direct Thrombin Inhibitors}

Direct thrombin inhibitors are a relatively new class of anticoagulants that do not require the presence of antithrombin to inhibit the enzymatic activity of thrombin. They also have the ability to inhibit fibrin-bound thrombin and prevent propagation of the thrombus. Intravenous preparations of direct thrombin inhibitors have been available for more than a decade, but only recently have oral preparations been introduced into clinical trials as a possible replacement or alternative for the vitamin K antagonists for long-term anticoagulation therapy. There are currently only 2 oral thrombin inhibitors actively in clinical trials. Ximelagatran is a prodrug that is rapidly absorbed from the gastrointestinal tract and biotransformed to its active metabolite, melagatran, when administered orally. It is a dipeptide analogue that is a potent competitive inhibitor of human thrombin. Melagatran has a plasma half-life of approximately 3 hours. After providing promising efficacy and low risk of bleeding in multiple clinical trials for primary and secondary prevention of thromboembolism, Ximelagatran has been withdrawn from further clinical trials after phase II studies showed a 6-7% incidence of elevated liver enzymes with long-term administration (SPORTIF II and THRIVE III).\textsuperscript{19-21}

Dabigatran etexilate, also a prodrug that is converted to dabigatran, is the most advanced oral thrombin inhibitor in clinical development and is currently being evaluated in phase III trials for primary prevention of veno-thromboembolic events (VTE). It is rapidly absorbed after oral administration and has a peak anticoagulant
effect at 2 hours. Its long half-life (15 hours), allowing once daily administration, provides an additional desirable feature to its oral route of administration. Odiparcil is an orally-active thioxyloside compound that inhibits activated thrombin (IIa) by inducing the synthesis of soluble glycosaminoglycans. The pharmacokinetics of this agent are somewhat unique in that its antithrombotic activity is dependent on plasma glycosaminoglycan levels that inactivate thrombin by enhancing heparin cofactor II activity. It is currently in clinical trials (phase II) to evaluate efficacy and safety in the prevention of thromboembolism in major orthopedic surgery patients. Adverse events associated with this agent have been primarily gastrointestinal and mild to moderate increases in hepatic transaminases.

**Oral Direct Factor Xa Inhibitors**

These new factor Xa inhibitors bind directly to the active site of factor Xa, inhibiting both free and bound Xa. Their inhibition of the procoagulant action of Xa in the clotting cascade (prothrombin complex) does not require binding to any of the naturally occurring anticoagulants, eg, antithrombin. Although none of these agents has yet been approved for clinical use by the Food and Drug Administration (FDA), several have provided data demonstrating effectiveness in primary and secondary prevention of VTE.

Of the agents listed in Table 1, rivaroxaban has completed phase II and III studies that show its superior ability to prevent thromboembolism in large international trials when compared with standard anticoagulation therapy. Pooled analysis of results of these studies have shown a superior outcome in both primary and secondary endpoints (deep venous thrombosis, pulmonary embolism, and thromboembolic-related mortality) at all rivaroxaban dose levels compared to enoxaparin-treated controls. Two recent, large international trials published in the *New England Journal of Medicine* have confirmed the efficacy and safety of rivaroxaban in primary prevention of deep venous thrombosis in total hip and knee replacement surgery. The oral bioavailability of this agent is approximately 80%, and its peak anticoagulant effect occurs within 3 hours. Its biological half-life is approximately 7 hours, requiring twice daily doses.

Apixaban is a novel, oral factor Xa inhibitor that has completed phase II VTE prevention study in patients undergoing total knee replacement surgery and has shown superior efficacy at all dose levels when compared with enoxaparin or warfarin. Because of its half-life of approximately 10 hours, once daily dose and bid dose schedules have been evaluated in clinical trials.

This agent is currently being evaluated in an international, randomized phase III study for primary prevention of VTE in acutely ill hospitalized patients during and after hospitalization. The drug is being prescribed at a fixed dose without monitoring and continued for 30 days and compared with standard enoxaparin prophylaxis.

Razaxaban, 1 of the direct factor Xa inhibitors studied earlier, was shown to be as effective as standard anticoagulation therapy for reducing the risk of thromboembolism in patients following orthopedic surgery in a phase II randomized, double-blind, controlled dose response study. However, dose escalation has been associated with an increased risk of postoperative bleeding, preventing its approval for phase III trials.

Other agents listed in Table 1 are less further along in their development and are currently in phase II clinical trials. Ly 517717 is an oral factor Xa inhibitor with a long half-life of approximately 24 hours that can be given once daily. This drug in various doses has been compared with standard prophylactic doses of enoxaparin in patients undergoing total hip or knee surgery and has provided similar efficacy at higher doses to the enoxaparin treatment arm. YM150 has been evaluated in various doses for primary prevention in a small number of patients undergoing hip arthroplasty surgery and showed a dose response similar to that of enoxaparin without major bleeding. It continues to be evaluated in phase II trials for primary prevention in orthopedic surgical patients. DU1766 showed inferior efficacy at 2 different doses when compared to enoxaparin in a small phase II study of patients undergoing elective knee arthroplasty.

### Table 1. New Oral Anticoagulants

<table>
<thead>
<tr>
<th>Oral Thrombin Inhibitors</th>
<th>Oral Direct Factor Xa Inhibitors</th>
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<tbody>
<tr>
<td>Ximelagatran (Astra-Zeneca)—Prodrug metabolized to melagatan</td>
<td>Rivaroxaban (Bristol Myers Squibb)</td>
</tr>
<tr>
<td>Dabigatran etexilate (Boehringer Ingelheim)—Prodrug metabolized to dabigatran</td>
<td>Apixaban (Bristol Myers Squibb)</td>
</tr>
<tr>
<td>Odiparcil (Glaxo-Smith-Kline)—Induces synthesis of soluble glycosaminoglycans</td>
<td>Razaxaban (Bristol Myers Squibb)</td>
</tr>
<tr>
<td>LY517717 (Lilly)</td>
<td>YAM 150 (Astellas)</td>
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<tr>
<td>PRT054021 (Protola)</td>
<td>DU-176b (Daiichi)</td>
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*No longer in clinical trials.*

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The direct factor Xa inhibitors appear to increase the prothrombin time, activated partial thromboplastin time, and anti-factor Xa activity in a dose dependent manner and metabolism, and elimination is mainly by the liver. However, because clinical trials with all these agents listed are ongoing, with the exception of ximelagatran and raxaban, details of efficacy and safety of each agent along with its metabolism, dosage, and monitoring of anticoagulation levels can be found in the various trials cited in the references provided.

CONCLUSION

Although none of the agents listed in Table 1 are available for clinical use, mounting data provided by phase II and III clinical studies have provided evidence that support the effectiveness and safety of some of these novel agents. However, additional information on the efficacy and safety of these agents is critical and necessary before FDA approval will allow their use as alternatives for safe and effective anticoagulation therapy. The direct thrombin inhibitors have been associated with increases in liver enzymes with long-term use, and this issue will need to be resolved before they can be considered for long-term or chronic anticoagulation therapy. Another important issue that must be addressed before widespread use of these agents can be approved is having available the means to provide effective reversal of their anticoagulation effects. The direct factor Xa inhibitors are small molecular weight compounds that are readily absorbed in the gastrointestinal tract and provide prompt anticoagulation effect. Clinical trials with these agents for primary and secondary prevention of VTE continue in an effort to find the optimum dose and schedule with acceptable safety for short and long-term anticoagulation treatment.

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REFERENCES


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