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REVIEW

Advances in oral anticoagulation therapy – What's in the pipeline?

P.S.S. Rao [a,*], T. Burkart [b,*]

[a] Department of Pharmaceutical Sciences, College of Pharmacy, The University of Findlay, Findlay, OH 45840, USA
[b] Department of Experiential Education, College of Pharmacy, The University of Findlay, Findlay, OH 45840, USA

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ABSTRACT

Approximately 900,000 people are affected by some sort of venous thromboembolic (VTE) event every year in the United States. VTE diagnosis used to mean treatment with medications that required routine lab monitoring for safety and efficacy. Activated factor X (FXa) inhibition has emerged as a convenient pathway for management of VTE and currently three FXa inhibitors are available for anticoagulation management - rivaroxaban, apixaban, and edoxaban. Continued development of medications utilizing this pathway may offer advantages via novel pharmacokinetic or pharmacodynamic properties that may minimize the adverse effects associated with traditional anticoagulant therapy. This review summarizes the available information regarding pharmacokinetic, pharmacodynamic, and early safety and efficacy data for three factor Xa inhibitors being developed - darexaban, betrixaban and nokxaban. The studies reviewed in this article suggests that three newer agents possess the potential for promise based on early phase I and II trials.

1. Introduction

Over the last decade, the discovery and use of direct oral anticoagulants (DOACs) has drastically changed the management of cardiovascular ailments. Amongst the various procoagulant factors, the importance of activated factor X in the clotting cascade and its role as a common point for both the intrinsic and extrinsic clotting pathways is well-documented [1,2]. Thus, inhibiting the activated factor X (FXa) is rationalized as an optimum strategy for the prevention of threatening blood clots. In this regard, scientific investigations have resulted in the successful clinical approval of three orally active FXa inhibitors – rivaroxaban, apixaban, and edoxaban. These U.S. Food and Drug Administration (FDA) approved FXa inhibitors are indicated for the treatment and/or prevention of venous thromboembolism (VTE).

Although the precise data is lacking, the Centers for Disease Control and Prevention (CDC) estimates that around 900,000 people in the United States are affected by VTE each year [3]. More importantly, around 60,000–100,000 American patients die each year because of VTE and related complications. The role of effective anticoagulant therapy, therefore, is critical in the management and survival of patients diagnosed or suffering with VTE. The DOACs, in particular, have provided clinicians a novel safe class of drugs with acceptable oral bioavailability for the management of VTE [4–6]. In addition, the available FXa inhibitors, unlike warfarin, are devoid of a narrow therapeutic index and do not require constant monitoring to ensure patient safety. In comparison to heparin and heparin derivatives, which require parenteral administration, the approved FXa inhibitors offer the convenience of oral administration to patients.

The therapeutic advantages offered through the inhibition of FXa, in addition to the lack of periodic monitoring and better safety profile, have supported the on-going investigations to develop newer FXa inhibitors. These efforts have resulted in some promising investigational FXa inhibitors which are currently in clinical trial or part of preclinical evaluations. In this review article, we have summarized the current and future clinical applications of anticoagulants for the management of thrombotic events. In particular, we have highlighted the recent findings with these promising FXa inhibitors and provided our opinion regarding the applicability and clinical justification of these investigational FXa inhibitors.

2. FDA approved anticoagulants: a brief overview

The pharmacology of FDA approved anticoagulants is well-known and has been described previously [7,8]. Broadly, the available anticoagulants can be classified based on either their route of administration or their primary target within the clotting cascade. Unfractionated heparin (UFH) and derivatives – low molecular weight heparin (LMWHs) and fondaparinux are available as parenteral formulations. On the other hand, warfarin, dabigatran and the approved FXa inhibitors (rivaroxaban, apixaban, and edoxaban) are orally administered anticoagulants. The prominent mechanism of action for the currently available anticoagulant includes inhibition of thrombin, inhibition of factor Xa, and inhibition of hepatic synthesis of activated clotting factors. Fig. 1

* Corresponding authors at: University of Findlay, College of Pharmacy, 1000 N. Main Street, Findlay, OH 45840, USA.
E-mail addresses: rao@findlay.edu (P.S.S. Rao), burkart@findlay.edu (T. Burkart).

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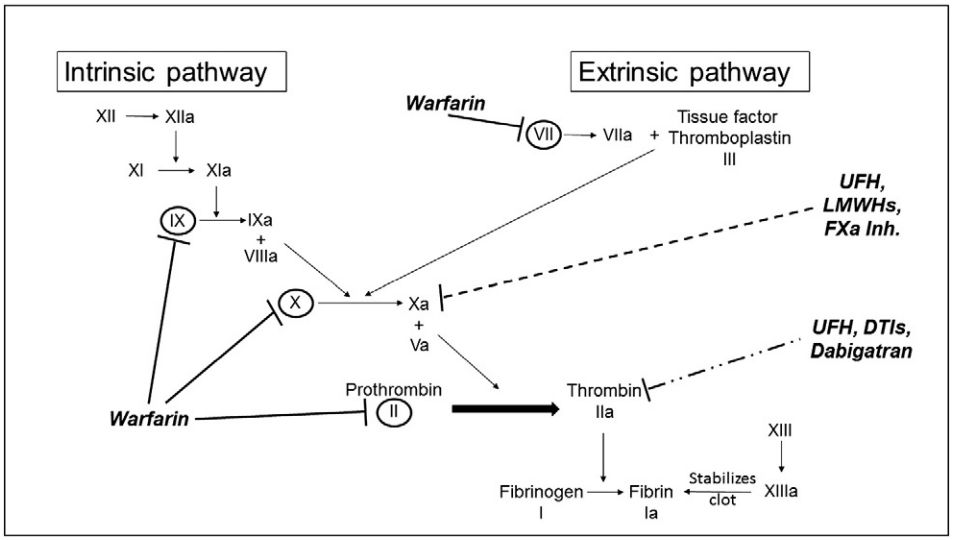

Fig. 1. An overview of the blood clotting cascade and the common sites of action for the approved anticoagulants. Warfarin, a vitamin K antagonist, inhibits the hepatic activation of several key clotting factors including factors VII, IX, X, and II. Unfractionated heparin (UFH) and heparin derivatives (low-molecular weight heparins, fondaparinux) are known activators of the endogenous anticoagulant, antithrombin (AT). Activation of AT results in inactivation of clotting factor Xa (UFH, LMWHs) and inactivation of thrombin (UFH). Dabigatran is a novel orally available direct thrombin inhibitor.

summarizes the major sites of action for anticoagulants within the blood clotting cascade.

UFH and other heparin derivatives possess no direct activity but rather increase the activity of an endogenous anticoagulant, antithrombin (AT) [9]. Following binding to UFH, the ability of AT to inhibit thrombin as well as other major clotting factors (including factor Xa) is dramatically increased thereby, eliciting an anticoagulant effect. On the other hand, LMWHs, upon binding to AT, produce a greater degree of FXa inactivation compared to thrombin inhibition. Reduction in chain length below 18 saccharide units within LMWHs renders them incapable of binding to both AT and thrombin simultaneously and decreasing their ability to inactivate thrombin. Three LMWHs have been approved for their antithrombotic effects – enoxaparin, dalteparin, and tinzaparin [10]. Fondaparinux is a synthetic pentasaccharide in which the AT binding region of heparin has been conserved. Following this structural modification, fondaparinux bound AT is capable of efficiently inactivating FXa only and fondaparinux has no effect on the AT-thrombin interaction [11]. Dabigatran, as opposed to UFH and heparin derivatives, is an orally active, reversible inhibitor of thrombin and acts independent of AT.

Warfarin is an orally available anticoagulant that interferes with the gamma carboxylation of vitamin K-dependent clotting factors [12]. Clotting factors responsible for both the intrinsic and extrinsic pathways (factors II, VII, IX and X, as well as the anticoagulant proteins C and S) are dependent on the availability of the reduced form of vitamin K for their posttranslational modification and activity [13,14]. By blocking the enzyme vitamin K epoxide reductase, warfarin inhibits the regeneration of reduced form of vitamin K in the liver and subsequent gamma carboxylation of newly translated clotting factor protein thereby, diminishing their activity. Apart from warfarin and dabigatran, inhibitors of FXa (discussed in Section 1) are the other orally active anticoagulants.

Although effective in managing and/or reducing the incidence of thrombotic events, the available anticoagulants are not devoid of adverse effects or limitations. UFH, for instance, suffers from its inability to neutralize thrombin that is bound to fibrin clot, propensity to induce thrombocytopenia, difficulty to dose (based on weight and via injection), and the need for monitoring due to variable pharmacokinetic properties [9]. Warfarin, in its more than 60 years of clinical use, has been widely used for its anticoagulant properties but is known to be associated with severe side effects as well. Major bleeding, owing to the narrow therapeutic index, remains the most significant adverse effect associated with warfarin use [15]. Skin necrosis, hair loss and risk for potential CYP-based drug-drug interactions are additional limitations associated with the use of warfarin [16]. In combination, these observations have bolstered the selection and inclusion of DOACs for the treatment of thrombotic events.

3. Investigational factor Xa inhibitors

In the following subsections, clinical findings for three promising investigational FXa inhibitors – darexaban, betrixaban, and nokxaban, have been reviewed. The three compounds are currently in various stages of drug development process and overall, emphasize the sustained interest of the pharmaceutical industry in exploring newer and possibly better FXa inhibitors.

3.1. Darexaban (YM150)

Darexaban is an investigational competitive inhibitor of FXa which has shown promising clinical anticoagulant activity [17]. Developed by Astellas Pharma Inc., initial studies with darexaban demonstrated a dose-dependent and predictable pharmacokinetic profile [18]. Upon oral administration, darexaban is quickly metabolized to darexaban glucuronide (YM-222714), an active metabolite which is equipotent to the parent drug [17,18]. In fact, clinical data has revealed the plasma levels of darexaban to be less than 1% of its glucuronide metabolite suggesting the clinical effectiveness of this drug to be a result of the active metabolite (darexaban glucuronide). Glucuronidation of darexaban is primarily catalyzed by two UDP-glucuronosyltransferase (UGT) - UGT1A9 in human liver and UGT1A10 in intestine [19].

The antithrombotic effects of darexaban have been assessed in Caucasian as well as Japanese patients [20]. Darexaban treatment, in single and multiple dose, was associated with favorable pharmacokinetic properties and no relevant differences based on gender and race were observed in this study. Furthermore, the elimination half-life of darexaban glucuronide was found to range from 14 to 20 h and the renal clearance rate for darexaban glucuronide was approximately 2.0 L/h in healthy, non-elderly Japanese and Caucasian subjects. Importantly, clinical studies have reported no significant effect of ketoconazole and rifampicin, known inducers of cytochrome P450 (CYP) 3A and P-glycoprotein (P-gp), on the pharmacokinetic profile of darexaban