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Unmet Need for a Factor Xa Inhibition Reversal Agent

INTRODUCTION

Anticoagulants, which are commonly used in outpatient settings, are associated with a risk of bleeding. In certain situations, there is an urgent need to reverse the effects of an anticoagulant drug; for example, in cases of life-threatening bleeding.[1] This article highlights available anticoagulant reversal agents, as well as unmet needs in anticoagulant reversal and late-stage clinical research in this area.

ANTICOAGULANT THERAPIES

Pharmacologic therapies commonly used for anticoagulation in outpatient settings include warfarin and several non–vitamin K oral anticoagulants (NOACs).[1-7] Available agents include the vitamin K antagonist warfarin[2], the direct thrombin inhibitor dabigatran (Pradaxa)[3], and the oral factor Xa (FXa) inhibitors rivaroxaban (Xarelto)[4], apixaban (Eliquis)[5], and edoxaban (Savaysa).[6] Parenteral FXa inhibitors are also available, such as enoxaparin (Lovenox).[8]

In terms of stroke prevention among patients with nonvalvular atrial fibrillation (NVAF), data from clinical trials and meta-analyses suggest that NOACs are as effective as warfarin, and in some cases more effective than warfarin. NOACs are also safer than warfarin in terms of reduced major bleeding.[9,10] In pivotal clinical trials evaluating NOACs in patients with NVAF, major bleeding occurred at an annual rate of 3.32% with dabigatran (at the US-approved dose for NVAF), 3.6% with rivaroxaban, 2.13% with apixaban, 2.75% with high-dose edoxaban (60 mg daily), and 1.61% with low-dose edoxaban (30 mg daily).[3,6,11-15]

BURDEN OF BLEEDING WITH ANTICOAGULANT THERAPY

As with all anticoagulants, a primary serious adverse event of concern with FXa inhibitors that affects uptake, use, and adherence is the risk of major uncontrolled bleeding and life-threatening bleeding events.[9,16] In pivotal trials and real-world registries of patients receiving FXa inhibitors for NVAF, both major bleeding and intracranial hemorrhage (ICH) are associated with high rates of mortality. For example, among patients receiving rivaroxaban in the ROCKET-AF trial, all-cause mortality at a median of 60 days (range: 8 to 246 days) was 48% in patients with an ICH and 20% in patients with any major bleed.[16,17] Similarly, among patients receiving apixaban in the ARISTOTLE trial, the 30-day mortality rate was 45% in patients with an ICH and 11% in patients experiencing any major bleeding.[18,19] Consistent with these findings, among patients receiving edoxaban in the ENGAGE-AF-TIMI trial, the 30-day mortality rate was 39% in patients with an ICH receiving high-dose edoxaban, 29% in patients with an ICH receiving low-dose edoxaban, and 7.7% to 8.3% in patients experiencing any major bleeding.[20]

Mortality related to FXa-associated bleeding is also seen in real-world registry data. Specifically, in the RASUNOA registry, overall ICH-related mortality was 28% (within 90 days of NOAC-associated ICH), and in the DRESDEN registry, the 90-day overall all-cause mortality rate was 10.2% in patients with rivaroxaban-associated major bleeding.[21,22]

Any major bleeding event may increase the risk of mortality.[20] These events may include bleeding at a critical site (eg, surgical, intraocular, pericardial, intraspinal, intraarticular, and/or intramuscular site), major bleeding associated with hemodynamic instability, or bleeding related to major blunt or penetrating trauma.[23-25] Notably, patients with major bleeding due to an ICH (eg, intracerebral, subdural, subarachnoid, extradural) are at especially high risk of mortality.[16,21] The clinical burden of bleeding associated with the use of FXa inhibitors is substantial, and there remains an unmet need for a reversal agent for use in cases of life-threatening or uncontrolled bleeding. Furthermore, with the increasing use of FXa inhibitors, the number of patients who require reversal of the anticoagulant effects is anticipated to rise.[26]

ANTICOAGULANT REVERSAL AGENTS AND UNMET NEED FOR FXa INHIBITOR REVERSAL

Pharmacologic therapies for reversal of anticoagulation include vitamin K for patients receiving warfarin[2] and idarucizumab (Praxbind) for patients experiencing bleeding associated with dabigatran[27] (TABLE[1,27-42]). For FXa inhibitors, no agent for reversal of FXa activity is currently approved.[26]

Existing strategies for management of major bleeding associated with FXa inhibitors include use of prohemostatic agents (eg, 3-factor prothrombin complex concentrate [PCC], 4-factor PCC, activated PCC, recombinant factor VIIa), fresh frozen plasma, red blood cells, tranexamic acid, and desmopressin.[1,4,5] None of these treatments are approved for use in patients treated with FXa inhibitors, and evidence for the use of these agents consists mostly of nonclinical data or preclinical data in healthy volunteers.[4-6,33,34] Additionally, PCCs and recombinant factor VIIa carry boxed warnings for thrombotic and thromboembolic events.[32,37,40]

Given that in clinical trials of healthy volunteers PCCs do not affect anti-FXa activity, the off-label use of procoagulant agents, which is not supported by studies in bleeding patients, suggests the continued unmet clinical need for a specific FXa inhibitor reversal agent.[34,35] A medicine to potentially address this unmet need is currently in late-stage development: andexanet alfa, a modified human FXa decoy protein for reversal of FXa inhibition.[26,43-45] In September 2016, researchers published a preliminary descriptive analysis of interim data from the ongoing ANNEXA-4 study, which is evaluating andexanet alfa in bleeding patients who were receiving FXa inhibitors.[45]

The ANNEXA-4 preliminary analysis included 67 patients in the safety analysis, of whom 47 were eligible for inclusion in the efficacy analysis. All patients in this preliminary analysis had experienced acute major bleeding within 18 hours of receiving a dose of FXa inhibitor. These patients received a bolus dose of andexanet alfa followed by a 2-hour infusion.[45] Investigators evaluated the anticoagulant effects of circulating FXa inhibitors through anti-FXa levels—a biomarker that directly measures anticoagulant activity and correlates with unbound anticoagulant plasma concentrations.[46,47] Andexanet alfa promptly and significantly reversed anticoagulant activity by 89% (95% CI, 58%-94%) in patients receiving rivaroxaban and by 93% (95% CI, 87%-94%) in patients receiving apixaban.[45] Reversal occurred at the first measurement after the end of the bolus.[45]

An independent adjudication committee rated hemostatic efficacy based on changes in hematoma volume in cases of ICH, changes in

TABLE. AVAILABLE ANTIHEMOSTATIC AGENTS—FDA-APPROVED INDICATIONS AND POTENTIAL USE IN PATIENTS WITH NOAC-ASSOCIATED BLEEDING[1,27-42]

Agent	FDA-Approved Indication(s)	Potential Use in Patients with NOAC-Associated Bleeding
Vitamin K (Mephyton)	Indicated for use in coagulation disorders due to faulty formation of factors II, VII, IX, and X when caused by vitamin K deficiency or interference with vitamin K activity.[28]	Vitamin K is not expected to be effective in major bleeding associated with NOAC use.[29]
Desmopressin acetate (DDAVP)	Antidiuretic replacement therapy in management of central diabetes insipidus, temporary polyuria and polydipsia following head trauma or surgery in the pituitary region, and primary nocturnal enuresis.[30]	Desmopressin acetate is an alternative option for management of major bleeding associated with dabigatran, apixaban, and rivaroxaban.[1]
Tranexamic acid (Cyklokapron)	Short-term use in patients with hemophilia to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction.[31]	Although tranexamic acid may be of use in traumatic hemorrhage not associated with NOACs, its use in cases of NOAC-related bleeding is generally not recommended. Tranexamic acid is an alternative agent in cases that do not respond to other treatments.[1,29]
4-Factor aPCC (FEIBA NF)	Control of spontaneous bleeding episodes or to cover surgical interventions in patients with hemophilia A or B with inhibitors.[32]	PCCs do not reverse anti-FXa activity in healthy volunteers, and there is no evidence for their hemostatic efficacy in FXa inhibitor–associated bleeds. These agents are not indicated for treatment of such bleeds.[1,33-35] In the absence of a specific reversal agent, some organizations advocate the use of PCCs for NOAC-related major bleeding despite the lack of evidence.[29]
4-Factor PCC (KCentra)	Urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist therapy in adult patients.[37]	
3-Factor PCC (Bebulin, Profilnine SD)	Prevention and control of hemorrhaging episodes in patients with hemophilia B.[38,39]	
rFVIIa (NovoSeven RT)	Treatment of bleeding episodes and perioperative management in adults and children with hemophilia A or B with inhibitors, congenital factor VII deficiency, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets; also indicated in treatment of bleeding episodes and perioperative management in adults with acquired hemophilia.[40]	No studies have been conducted with rFVIIa in NOAC–treated patients. Guidelines warn of the prothrombotic risks associated with use of rFVIIa. Despite this, use of rFVIIa has been suggested for treatment of NOAC-associated bleeding.[29,36]
Idarucizumab (Praxbind)	Indicated for use in patients treated with dabigatran (Pradaxa) when reversal of the anticoagulant effects of dabigatran is needed.[27]	Idarucizumab is the preferred reversal agent for dabigatran.[1]
Fresh frozen plasma (Octaplas)	Indicated for replacement of multiple coagulation factors due to liver disease, in patients with acquired deficiencies, in patients undergoing cardiac surgery or liver transplant, and for plasma exchange in patients with TTP.[41]	Fresh frozen plasma is insufficient to reverse the effects of NOACs.[42]

aPCC = activated prothrombin complex concentrate; NOAC = novel oral anticoagulant; PCC = prothrombin complex concentrate; rFVIIa = recombinant factor VIIa; TTP = thrombotic thrombocytopenic purpura.

hemoglobin and hematocrit levels in cases of nonvisible bleeding, and hemostasis in cases of visible bleeding. For patients with musculoskeletal bleeding, improvements in pain relief and objective signs of bleeding without an increase in swelling defined hemostatic efficacy. Twelve hours after infusion, hemostatic efficacy was rated as "good" or "excellent" in 79% of patients in the efficacy population (95% CI, 64%-89%). Over 30 days of follow-up, overall mortality was 15%, ICH-related mortality was 21%, and 18% of patients experienced thrombotic events.[45]

ONGOING RESEARCH AND ROLE OF THE PHARMACIST

Considering the substantial clinical burden of bleeding associated with use of FXa inhibitors, the lack of clinical data to support existing management strategies (eg, use of prothrombin complex concentrates, blood products, tranexamic acid, and desmopressin), and the fact that none of the currently used agents reverse anti-FXa activity, effective bleeding management for patients taking FXa inhibitors remains an unmet clinical need.[1,4,5,26] An investigational drug designed to address this unmet need, andexanet alfa, is currently in late-stage development.[26,43,44]

The use of FXa inhibitors is growing, and there is no specific antidote available for these drugs. This article has reviewed the importance of anti-FXa activity and the limitations of currently available agents for the management of bleeding related to FXa-inhibitor use. The landscape is evolving, however, and pharmacists must maintain awareness of agents in development, such as andexanet alfa, a FXa inhibitor reversal agent that may be approved in 2017.

References are available online at PharmacyTimes.com.