Role of agents for reversing the effects of target-specific oral anticoagulants

**Purpose.** The available clinical data on target-specific oral anticoagulant (TSOAC) reversal agents that are currently in development or have been approved by the Food and Drug Administration (FDA) are reviewed.

**Summary.** The development of TSOACs such as dabigatran, rivaroxaban, edoxaban, and apixaban has presented benefits and new challenges. One of the main challenges associated with the use of TSOACs is the lack of suitable agent-specific reversal agents. Several treatment options for the management of life-threatening bleeding events associated with TSOAC use, such as fresh frozen plasma, prothrombin complex concentrates, and recombinant coagulation factor VIIa, have been used, with inconsistent results. Currently, two potential reversal agents for oral direct factor Xa inhibitors (andexanet alfa and ciraparantag) are at various stages of clinical development. Idarucizumab, a reversal agent for the oral direct thrombin inhibitor dabigatran, was approved by FDA in October 2015. Idarucizumab and andexanet alfa have been reported to produce anticoagulation reversal effects within minutes of administration. Ciraparantag was demonstrated to decrease whole blood clotting time to within 10% of baseline values in 10 minutes or less, with a return to baseline hemostasis in 10–30 minutes. TSOAC reversal agents have been generally well tolerated in clinical trials.

**Conclusion.** Idarucizumab and other TSOAC reversal agents, such as andexanet alfa and ciraparantag, present the potential for consistent and effective treatment and management options when life-threatening or uncontrolled TSOAC-associated bleeding occurs or when emergency surgery is warranted in patients using TSOACs.

**Keywords:** anticoagulant, antidote, andexanet alfa, ciraparantag, idarucizumab, reversal

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Oral anticoagulants are frequently used to treat and decrease the risk of recurrence of thromboembolic events. Until recently, warfarin, a vitamin K antagonist, was the mainstay of oral anticoagulation treatment. With the emergence of target-specific oral anticoagulants (TSOACs)—apixaban, edoxaban, rivaroxaban, and dabigatran—treatment and prevention of thromboembolic events have been transformed. Dabigatran, a direct thrombin inhibitor, produces its potent antithrombotic effects by specifically blocking the activity of thrombin, the central enzyme in the process responsible for thrombus formation. The direct factor Xa (FXa) inhibitors apixaban, edoxaban, and rivaroxaban decrease thrombin formation by selectively binding and inactivating FXa, leading to inhibition of the conversion of prothrombin to thrombin. In comparison to warfarin, TSOACs have fewer drug-drug interactions and no drug-food interactions. Also, routine coagulation monitoring with subsequent dosage adjustments is not required with TSOAC use. However, for most TSOACs there is no medication-specific reversal agent.
All anticoagulant treatments are associated with an increased risk of bleeding and, in some cases, severe, life-threatening bleeding. Management of bleeding events in patients using TSOACs has been challenging. Agents such as prothrombin complex concentrates, fresh frozen plasma, and recombinant coagulation factor VIIa have been proposed as potential reversal agents, but their effectiveness has been unpredictable. Given this limitation, researchers have focused on the development of TSOAC reversal agents. A review of available clinical data on two potential reversal agents for direct FXa inhibitors, andexanet alfa (PROT6445) and ciraparantag (PER977), and clinical data on idarucizumab (Praxbind, Boehringer Ingelheim), a direct factor IIa inhibitor recently approved by the Food and Drug Administration (FDA), suggests that development of these agents may provide an efficient method of TSOAC reversal.

Idarucizumab

Need for a dabigatran reversal agent. To date, study results have indicated increased rates of bleeding in patients taking dabigatran, as compared with patients taking warfarin. The RE-LY trial investigators reported that rates of major bleeding with dabigatran and warfarin use were similar, with patients taking dabigatran experiencing more gastrointestinal bleeding events. A postmarketing study of Medicare patients also found higher bleeding rates with dabigatran use than with warfarin use; furthermore, results from this study indicated frequency rates of 32.7% versus 26.5% (p < 0.001) for any bleeding, 9.0% versus 5.9% (p < 0.001) for major bleeding, and 28.6% versus 23.6% (p < 0.001) for minor bleeding in patients taking dabigatran and warfarin, respectively. Reported patient demographics and clinical factors associated with an increased risk of bleeding while taking dabigatran were age of ≥75 years (as compared with <65 years), black race, chronic kidney disease, and antiplatelet use. Results from these studies documented the bleeding risk associated with dabigatran use and indicated the need for a dabigatran reversal agent.

Pharmacology. Idarucizumab, the first-in-market agent for reversing the anticoagulant effect of the direct factor IIa inhibitor dabigatran, was approved by FDA in October 2015. It is indicated for use in patients treated with dabigatran in whom reversal of the anticoagulant effect is needed for emergency surgery or urgent procedures, life-threatening bleeding, or uncontrolled bleeding. Expedited approval of this indication was based on study results demonstrating a reduction in unbound dabigatran and normalization of coagulation parameters in healthy volunteers given dabigatran. Idarucizumab is a humanized monoclonal antibody fragment that binds to dabigatran with an affinity more than 350-fold higher than that of thrombin administered at a 1:1 molar ratio. Idarucizumab binds specifically to free and thrombin-bound dabigatran molecules, thus neutralizing their anticoagulant effect without interfering with the coagulation cascade. Idarucizumab does not seem to bind to known thrombin substrates, nor does it have any prothrombotic properties despite being similar in structure to thrombin. Once the complex of idarucizumab and dabigatran is formed in a lock-and-key manner, it is essentially irreversible, which is likely due to the very slow dissociation of dabigatran from idarucizumab. Schiele and colleagues reported that idarucizumab use did not shorten clotting time or increase the fibrin concentration or platelet aggregation and thus did not produce a hypercoagulable state.

Clinical studies. A study was conducted to evaluate the effectiveness of idarucizumab in reversing the anticoagulant effects of dabigatran in 35 healthy volunteers. Each participant in the study received idarucizumab 1, 2, or 4 g or a placebo administered as a five-minute i.v. infusion after administration of dabigatran 220 mg orally twice daily for four days. Blood was collected from an incision wound in order to explore restoration of wound-site fibrin formation by measuring fibrinopeptide A (FPA). Results of this study showed that there was a significant, dose-dependent return of fibrin formation with increasing doses of idarucizumab. Anticoagulation reversal allowed participants to reach 24%, 45%, and 63% of control FPA values at 30 minutes after administration of 1, 2, and 4 g of idarucizumab, respectively (p < 0.05 for all comparisons with placebo use). Upon reinitiation of dabigatran use 24 hours after the idarucizumab infusion, anticoagulation was achieved again. Idarucizumab’s effect generally lasts at least 24 hours. However, in a Phase III clinical trial, laboratory indicators of anticoagulation were reevaluated in a limited number of patients 12–24 hours after idarucizumab administration; in some patients, this reevaluation occurred as early as 1–4 hours after idarucizumab administration, potentially due to high initial baseline dabigatran con-

**KEY POINTS**

- Idarucizumab, a reversal agent for dabigatran that is an oral direct thrombin inhibitor, was recently approved by the Food and Drug Administration.
- Idarucizumab achieves a maximum percentage reversal of anticoagulant effect within four hours after administration.
- Six weeks after andexanet alfa administration to clinical trial participants, there were no reported occurrences of serious adverse events or thrombotic events.
- The potential for an increase in the prescribing of target-specific oral anticoagulants definitely exists.
centrations. Therefore, if clinically relevant bleeding occurs with elevation of these laboratory values after the recommended 5-g idarucizumab dose, administration of a second dose may be considered.

In a randomized, placebo-controlled, double-blind, proof-of-concept Phase I study, dabigatran was given twice daily for three days and once on day 4, and various doses of idarucizumab or a placebo were given two hours after the day 4 idarucizumab dose. Results of a variety of clotting assays demonstrated that idarucizumab effectively neutralized dabigatran in a dose-dependent manner and caused only mild adverse events (e.g., erythema) in healthy volunteers. No serious or severe adverse events were reported, and no adverse event led to discontinuation of treatment. Also, no clinically relevant between-group differences in frequencies of adverse events were noted. The investigators concluded that idarucizumab produced immediate, complete, and sustained reversal of dabigatran-induced anticoagulation in healthy men. Dilute thrombin time (dTT) assessments showed that the mean ratio of day 4 to day 3 values for area under the effect curve was 1.01 with placebo use, as compared with 0.26 with idarucizumab 1 g (a 74% reduction), 0.06 with idarucizumab 2 g (a 94% reduction), 0.02 with idarucizumab 4 g (a 98% reduction), and 0.01 with idarucizumab 5 g given as two 2.5-g doses (a 99% reduction). The researchers also concluded that idarucizumab was well tolerated, with no unexpected or clinically relevant safety concerns, and that further testing was warranted.

An ongoing multicenter, prospective cohort study (the RE-VERSE AD trial) is evaluating the reversal effects of idarucizumab on active dabigatran. Study results for the first 90 enrolled patients showed that idarucizumab reversed dabigatran’s effects within minutes in patients requiring urgent procedures or with serious bleeding complications. In the study, patients taking dabigatran (median age, 76.5 years) who were admitted to the emergency department with uncontrolled or life-threatening bleeding or required an invasive procedure (e.g., surgery) that could not be delayed at least 8 hours were given 5 g of i.v. idarucizumab (two 2.5-g infusions administered no more than 15 minutes apart); this dose was calculated to reverse the total body load of dabigatran associated with the 99th percentile of dabigatran levels measured in the RE-LY trial. The primary endpoint was the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after administering idarucizumab. A secondary endpoint was the restoration of hemostasis. The broad inclusion criteria for the study ensured that the most severely ill or injured patients requiring urgent reversal of dabigatran, such as patients with sepsis or a severe intracranial hemorrhage, were enrolled. Patients were categorized into two groups. Group A (n = 51) consisted of patients with uncontrolled or life-threatening bleeding complications, such as intracranial hemorrhage or severe trauma after a car accident. Group B (n = 39) consisted of patients who required emergency surgery or an invasive procedure, such as surgery for an open fracture after a fall. The degree of reversal of the anticoagulant effect of dabigatran produced by 5 g of idarucizumab over 4 hours was measured by dTT and ecarin clotting time (ECT) testing. Eighty-one patients had elevated ECT values at baseline. The study results demonstrated that the primary endpoint was met, with achievement of a median maximum reversal of 100% (95% confidence interval, 100–100%). Reversal was evident after administration of the first vial of idarucizumab and was complete in all but 1 patient at both 4 and 12 hours. Laboratory tests showed normal coagulation levels in 90% of patients, and normal blood clotting during surgery was reported in 92% of the patients who required surgery or invasive procedures. Among the 35 patients in group A who could be assessed, hemostasis (as determined by local investigators) was restored at a median of 11.4 hours. Among the 36 patients in group B who underwent an invasive procedure, normal intraoperative hemostasis was reported in 33 patients, and mildly or moderately abnormal hemostasis were reported in 2 and 1 patient, respectively. There were no potential signs of a procoagulant effect after administration of idarucizumab. Thrombotic events occurred in 5 patients in the study (1 patient each at 2, 7, 9, 13, and 26 days after idarucizumab administration); none were receiving antithrombotic therapy at the time of the events. There were 18 deaths in the study, 9 in each group. Ten deaths were due to vascular causes, including 5 fatal bleeding events. Mortality within 96 hours of treatment appeared to be related to the events and conditions prompting emergency room admission, while all later events appeared to be related to comorbidities. As the study lacked a control group, it is unclear how these event rates would compare with outcomes in similar patients not given idarucizumab; perhaps this could be evaluated in future postmarketing studies. Other adverse events that occurred were gastrointestinal hemorrhage (in 2 patients), postoperative wound infection, delirium, right ventricular failure, and pulmonary edema (1 patient each), with some patients experiencing more than one event.

In the interim analysis of the RE-VERSE AD trial, the investigators evaluated data on a total of 123 dabigatran-treated patients who were administered idarucizumab due to the need for emergency surgery or an urgent invasive procedure or for bleeding that was life-threatening or uncontrolled. Adverse events reported at frequencies of ≥5% were hypokalemia (7%), delirium (7%), constipation (7%), pyrexia (6%), and pneumonia (6%). Twenty-six patients died, 11 within the first day after administration of idarucizumab; each of the deaths was attributed to either a complication of the primary event
that prompted presentation to the hospital or comorbidities.

Prescribing considerations. The available pharmaceutical formulation of idarucizumab contains sorbitol as an excipient, presenting serious concerns for patients with hereditary fructose intolerance (HFI). When the drug is administered at the recommended dose, sorbitol exposure can be up to 4 g. Patients with HFI who receive idarucizumab can experience hypoglycemia, hypophosphatemia, metabolic acidosis, increased uric acid levels, acute liver failure, and death. Also, since idarucizumab is a monoclonal antibody, the risk of an immunologic reaction exists.14

According to the prescribing information for idarucizumab, the anticoagulant effect of dabigatran was fully reversed in 89% of trial participants at 4 hours after the administration of a dose of 5 g of idarucizumab.14 However, it is recommended that if there is no urgent need for reversal of dabigatran, whose elimination half-life is ~12–17 hours, clinicians should refrain from administering idarucizumab and allow for dabigatran to be cleared by the patient. In patients taking dabigatran for disease states that predispose to underlying thromboembolic events, reversal of dabigatran therapy can lead to an increase in thrombotic risk. To reduce this risk, it is recommended that restarting anticoagulation therapy as soon as is medically possible should be considered. Therefore, patients expected to resume dabigatran therapy can start receiving the drug as early as 24 hours after administration of idarucizumab.

In summary, idarucizumab has the potential to benefit both patients and providers by reversing the anticoagulant effects of dabigatran without establishing a procoagulant state.7 Future studies to determine the safety and effectiveness of additional idarucizumab doses administered after the recommended dose of 5 g in a subset of patients in whom initial dosing is not effective may be warranted.18

Andexanet alfa
Pharmacology. Andexanet alfa is an agent in development for the reversal of the effects of direct and indirect FXa inhibitors. It is a modified recombinant form of the human coagulation factor X that lacks a membrane-binding γ-carboxyglutamic acid (GLA) domain associated with a mutation of the serine residue of the protease catalytic triad (substitution of alanine for serine) that results in catalytic inactivity and the prevention of prothrombin cleavage.20 Removal of the GLA domain removes the ability of the protein to bind with the prothrombinase complex, which eliminates any anticoagulant activity. Andexanet alfa binds with high affinity to direct FXa inhibitors (apixaban, rivaroxaban, and edoxaban) and binds with the complex formed by antithrombin III, thereby reducing the anticoagulant activity of the antithrombin III–dependent indirect FXa inhibitors enoxaparin and fondaparinux. It is important to note that andexanet alfa does not interfere with normal FXa function in hemostasis. Due to this lack of interference with tissue factor–initiated thrombin generation, andexanet alfa does not possess any anticoagulant activity.

Clinical studies. A randomized, double-blind, placebo-controlled Phase II trial examined the anticoagulation reversal activity of andexanet alfa in healthy subjects taking rivaroxaban, apixaban, edoxaban, or enoxaparin.22 Each medication was studied using up to six different cohorts, with dosing at a ratio of andexanet alfa to placebo of 2:1. For six days, patients received treatment with apixaban 5 mg twice daily, rivaroxaban 20 mg daily, edoxaban 60 mg daily, or enoxaparin 40 mg daily. On day 6, three hours after receipt of an anticoagulant dose, patients were administered an i.v. placebo or i.v. andexanet alfa.22 Andexanet was administered as either an i.v. bolus of 210–420 mg or an i.v. bolus of 400–800 mg followed by a one- to two-hour continuous infusion at a rate of 4–8 mg/min. The study results demonstrated dose-dependent rapid reversal of anti-FXa activity, with no detection of FXa or factor X antibodies, and restoration of thrombin generation to normal levels after infusion of andexanet alfa. Of note, infusions were well tolerated, without the development of thrombotic events or serious adverse reactions.21,22

Two Phase III parallel-group, randomized, double-blind, placebo-controlled trials (the ANNEXA-A and ANNEXA-R trials) involving a total of 145 healthy volunteers were conducted to evaluate the safety and efficacy of andexanet alfa in the reversal of the anticoagulant effects of apixaban and rivaroxaban, respectively.23 Both studies were completed in two consecutive phases. In the first phase, an i.v. andexanet alfa bolus was compared with placebo use alone; in the second phase, an i.v. andexanet alfa bolus followed by a 120-minute continuous infusion of andexanet alfa was compared with placebo use. The primary efficacy endpoint of both the ANNEXA-A and ANNEXA-R studies was the percentage change in anti-FXa activity from baseline (i.e., prior to andexanet alfa bolus or placebo administration) to nadir (i.e., after bolus or placebo administration). Secondary efficacy endpoints included the proportion of patients achieving an 80% or greater reduction in anti-FXa activity from baseline to nadir, the change in unbound rivaroxaban or apixaban levels from baseline to nadir, the change in thrombin generation (measured as the change in endogenous thrombin potential) from baseline to peak after andexanet alfa administration, and the occurrence of endogenous thrombin potential above the lower limit of the range of baseline-derived values at its peak. Additional safety outcomes of symptomatic thrombosis and bleeding were monitored throughout the trials.

The ANNEXA-A trial. In the first phase of the ANNEXA-A trial, 33 healthy volunteers ranging in age from 50 to 75 years received apixaban 5 mg twice daily for four days and then were randomly assigned in a 3:1
ratio to receive andexanet alfa 400 mg by i.v. bolus (30 mg/min) or a placebo three hours after the last dose of apixaban.26 In the second part of the study, participants received an 400-mg i.v. bolus of andexanet alfa followed by a 4-mg/min continuous infusion for 120 minutes (480 mg of andexanet alfa) or a placebo. With regard to the primary endpoint, after administration of an andexanet alfa bolus alone, there was a significantly greater mean reduction in anti-FXa activity within 2–5 minutes than was observed with placebo use (94% versus 21%, p < 0.001). Administration of both a bolus dose and a continuous infusion of andexanet alfa also resulted in a significantly greater mean reduction in anti-FXa activity than placebo use (92% versus 33%, p < 0.001).

With regard to the secondary endpoints, all patients who received andexanet alfa but no placebo recipients had a greater than 80% reversal of anti-FXa activity (p < 0.0001).26 Within 2–5 minutes after a 400-mg andexanet alfa bolus, the mean reduction in the concentration of unbound apixaban was significantly greater than that observed with placebo use (9.3 ng/mL versus 1.9 ng/mL, p < 0.0001). Also, after continuous infusion of andexanet alfa, the mean plasma concentration of unbound apixaban was significantly reduced relative to the concentration with placebo use (6.5 ng/mL versus 3.0 ng/mL, p < 0.0001). Compared with placebo use, andexanet alfa bolus administration resulted in a significantly greater mean rebound in thrombin generation previously inhibited by apixaban treatment (1323.2 nM·min versus 88.2 nM·min, p < 0.0001). Thrombin generation increased to the lower limit of normal in all study participants who received an andexanet alfa bolus but in just 11% of placebo recipients (p < 0.0001). Administration of a bolus plus a continuous infusion of andexanet alfa resulted in a significantly greater mean change in thrombin generation than was observed with placebo use (1193.1 nM·min versus 189.4 nM·min, p < 0.0001), and thrombin generation increased to the baseline-derived lower limit of normal in all patients receiving andexanet alfa, as compared with 25% of placebo recipients (p < 0.0001).

Safety data were monitored for up to six weeks after andexanet alfa administration.28 There were no occurrences of serious adverse events or thrombotic events during the study. Reported mild-to-moderate infusion reactions that did not lead to study discontinuation consisted of one occurrence of urticaria, four occurrences of flushing, and three occurrences of feeling hot. In addition, study participants receiving andexanet alfa did not have immunologic responses, as evidenced by the lack of development of antibodies to factor X or FXa.

The ANNEXA-R trial. In the first phase of the ANNEXA-R trial, 41 healthy volunteers 50–75 years of age received rivaroxaban 20 mg daily for four days and were then randomly assigned 2:1 to receive an 800-mg i.v. andexanet alfa bolus (30 mg/min) or an i.v. placebo.26 In the second phase, study participants received the same andexanet alfa bolus followed by a continuous infusion of andexanet alfa 8 mg/min for 120 minutes (960 mg) or were assigned to placebo use. Comparing the reversal effects of andexanet alfa after administration of apixaban 5 mg in the ANNEXA-A trial and after administration of rivaroxaban 20 mg, higher doses of andexanet alfa were required to reverse the effects of rivaroxaban; this was due to relatively higher initial plasma target-drug concentrations and a relatively larger volume of distribution.

Evaluation of data on the primary endpoint showed a significantly greater mean reduction in the anticoagulant activity of rivaroxaban with administration of an andexanet alfa bolus versus placebo use (92% versus 18%, p < 0.001).28 Participants who received both a bolus and an infusion of andexanet alfa had a significantly greater mean reduction in anti-FXa activity than placebo recipients (97% versus 45%, p < 0.001). Evaluation of data on secondary endpoints demonstrated a greater than 80% reduction in anti-FXa activity in all of the patients who received an andexanet alfa bolus alone but in none of the placebo recipients (p < 0.0001); with andexanet alfa bolus administration, the mean change in thrombin generation was significantly greater (1314.2 nM·min versus 173.9 nM·min with placebo use, p < 0.0001), thrombin generation increased above the lower limit of normal in a high percentage of volunteers (96% versus 7% with placebo use, p < 0.001), and there was a significantly greater reduction in the mean free rivaroxaban concentration (23.4 ng/mL versus 4.2 ng/mL, p < 0.0001). Relative to placebo recipients, study participants receiving both a bolus and an infusion of andexanet alfa had a significantly greater mean change in thrombin generation (1510.4 nM·min versus 264.4 nM·min, p < 0.0001) and a significantly greater mean reduction in unbound rivaroxaban (30.3 ng/mL versus 12.1 ng/mL, p < 0.0001). Six weeks after andexanet alfa administration, safety outcomes were similar to those reported in the ANNEXA-A trial. There were no reported serious adverse events, thrombotic events, or development of factor X or FXa antibodies. Mild-to-moderate infusion reactions included one incident of urticaria, two incidents of flushing, and one incident of feeling hot.

The outcomes of the ANNEXA-A and ANNEXA-R trials demonstrated reversal activity within 2–5 minutes and sustained reversal of anti-FXa activity for up to 120 minutes after administration of andexanet alfa via bolus or infusion, which is consistent with the drug’s half-life.29 Patient recruitment for an additional study, the ANNEXA-4 trial, is currently underway; that study will evaluate the effects of andexanet alfa in patients experiencing an acute bleeding event while taking FXa inhibitors such as apixaban, rivaroxaban, edoxaban, and enoxaparin.27
Ciraparantag

In April 2015, FDA granted ciraparantag a fast-track designation in order to facilitate the drug’s development and expedite the review process.

Ciraparantag is a small synthetic water-soluble molecule that binds fondaparinux, low-molecular-weight heparins (LMWHs), unfractionated heparin (UFH), and TSOACs. The reported mechanism of the reversal effect of ciraparantag is direct binding of TSOACs and heparins through noncovalent hydrogen bonding and charge–charge interactions to neutralize anticoagulant activity.

A double-blind, placebo-controlled Phase I study of 80 healthy patients was performed to evaluate the safety, tolerability, and pharmacokinetic and pharmacodynamic effects of a single i.v. dose of ciraparantag ranging from 5 to 300 mg after administration of a 60-mg dose of edoxaban. The study results indicated that a single i.v. dose of 100–300 mg of ciraparantag produced a decrease in whole blood clotting time (WBCT) to within 10% of baseline values in 10 minutes or less (in placebo recipients, a similar WBCT reduction took 12–15 hours). A return to baseline hemostasis occurred within 10–30 minutes after administration of 100–300 mg of ciraparantag and continued for 24 hours. Although numerical values for adverse-event frequencies were not reported, potential treatment-related events consisted of transient, mild perioral and facial flushing and abnormal distortion of the sense of taste. One patient experienced a moderate headache and another experienced a moderate muscle cramp and elevations of creatinine phosphokinase levels, which were not considered to be related to the study medication. Phase II clinical studies of ciraparantag are ongoing. Therefore, sufficient research data to evaluate ciraparantag’s safety and effects in a large patient population are not available.

Discussion

As reversal agents for TSOACs receive FDA approval, potential increases in their use warrant consideration of the impact on clinical practice and prompt questions that may lead to further study into their uses. Currently, therapeutic options in critical situations, such as active bleeding and emergency surgery, in patients taking vitamin K antagonists include discontinuation of the anticoagulant and administration of phytonadione with or without infusion of blood products or derivatives. Intravenous phytonadione therapy in sufficient doses can initiate a reduction in International Normalized Ratio (INR) values within 2 hours, with INR normalization generally seen within 24 hours. The newer reversal agents idarucizumab and andexanet alfa have been reported to produce anticoagulation reversal effects within minutes of administration (Table 1).

Table 1. Agents for Reversing Effects of Various Anticoagulants

<table>
<thead>
<tr>
<th>Reversal Agent</th>
<th>Target Anticoagulant(s)</th>
<th>Structure Type</th>
<th>I.V. Dosage</th>
<th>Common Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andexanet alfa</td>
<td>Oral FXa inhibitors, LMWHs, fondaparinux</td>
<td>Modified recombinant FXa protein</td>
<td>For apixaban: 400-mg bolus followed by 4-mg/min continuous infusion for 2 hr For rivaroxaban: 800-mg bolus followed by 8-mg/min continuous infusion for 2 hr</td>
<td>Mild-to-moderate infusion reactions</td>
</tr>
<tr>
<td>Ciraparantag</td>
<td>Oral FXa inhibitors, dabigatran, UFH, LMWHs, fondaparinux</td>
<td>Synthetic small molecule</td>
<td>Undetermined</td>
<td>Transient mild perioral and facial flushing, distortion of sense of taste</td>
</tr>
<tr>
<td>Idarucizumab</td>
<td>Dabigatran</td>
<td>Human monoclonal antibody fragment</td>
<td>5 g (two 2.5-g infusions no more than 15 min apart)</td>
<td>Infusion-site erythema, hypokalemia, delirium, constipation, pyrexia, pneumonia</td>
</tr>
</tbody>
</table>

FXa = clotting factor Xa, LMWH = low-molecular-weight heparin, UFH = unfractionated heparin.

*All reversal agents given i.v.; idarucizumab is the only listed drug with Food and Drug Administration marketing approval.*
reversal agent did not maintain an unbound dabigatran concentration above the lower limits of the desired range.\textsuperscript{18} Therefore, more studies may be needed to determine if an additional dose or doses of idarucizumab are warranted in such patients and, if so, what effect they might have on measured unbound dabigatran concentrations. In addition, as plans for additional research on andexanet alfa's effect in patients experiencing acute bleeding events are made, assessment of the potential need to administer an additional dose or doses in the population of patients in whom thrombin generation values within the target range are not attained within two hours should be considered.

In addition, physician prescribing practices may change with the approval and continued development of TSOAC reversal agents. Prior to the approval of idarucizumab, an 18-month retrospective review at an academic hospital identified 160 patients who had received a TSOAC prior to hospitalization.\textsuperscript{10} Of the evaluated patients, 53.1% ($n = 85$) had received rivaroxaban, 43.8% ($n = 70$) had received dabigatran, and 3.1% ($n = 5$) had received apixaban. Therefore, in light of the availability of reversal agents, the potential for an increase in TSOAC prescribing definitely exists.

**Conclusion**

Idarucizumab and other TSOAC reversal agents, such as andexanet alfa and ciraparantag, present the potential for consistent and effective treatment and management options when life-threatening or uncontrolled TSOAC-associated bleeding occurs or when emergency surgery is warranted in patients using TSOACs.

**Disclosures**

The authors have declared no potential conflicts of interest.

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