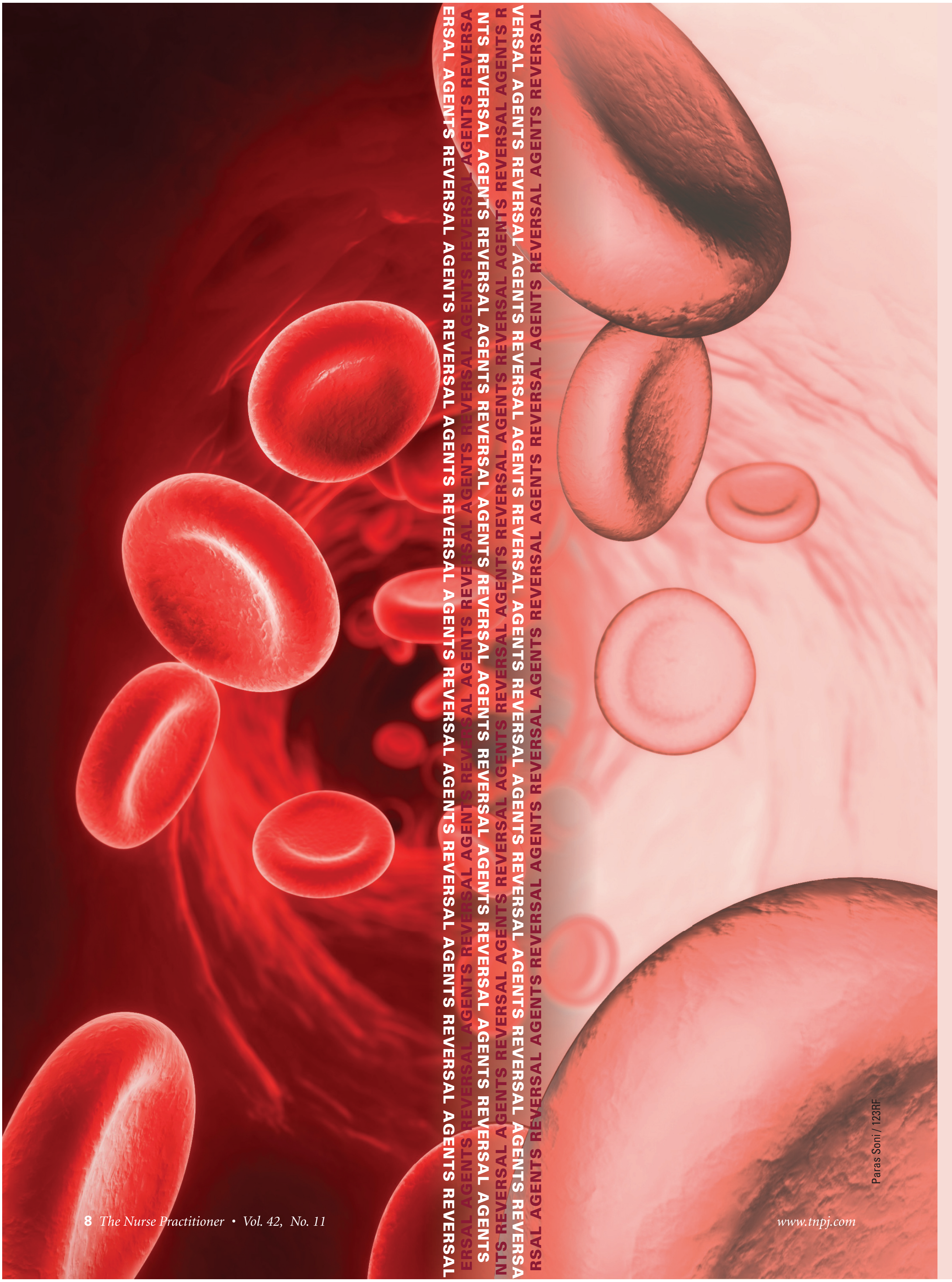

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Reversal agents for oral anticoagulants

Abstract: For more than half a century, warfarin, a vitamin K antagonist, has been the anticoagulant of choice. However, direct oral anticoagulants are rapidly gaining in popularity, which poses the need for efficacious reversal agents. This review article summarizes the strategies and agents used to reverse oral anticoagulants.

By Carrie L. Griffiths, PharmD, BCCCP; Mark L. Vestal; Spencer J. Livengood; and Samantha Hicks, MSN, ACNP, CCRN

Anticoagulation therapy is indicated in patients who have had a venous thromboembolism, atrial fibrillation (AF), mechanical valve replacement, and other coagulation disorders (antiphospholipid antibody syndrome, Factor V Leiden). Since 2010, when the first direct oral anticoagulant was approved by the FDA, antithrombotic therapy has shifted away from the mainstay of therapy, the vitamin K antagonist, due to recent guideline recommendations in antithrombotic therapy.[1]

In AF, a $CHADS_2$ score or CHA_2DS_2-VASc score (an updated version), is used to determine the patient's stroke risk and need for anticoagulation therapy.[2] Several studies have shown a lower bleeding risk with direct oral anticoagulants (DOACs) over warfarin.[3-6] Therefore, clinicians are considering these agents more often for their patients. In addition to their improved safety and efficacy profile, DOACs do not require monitoring and have fewer drug interactions than warfarin.

DOACs do not require monitoring, so it is difficult to determine if the drugs are subtherapeutic, therapeutic, or supratherapeutic. This has led to a need for effectual antidotes in the case of an emergency.[1] Currently, only one reversal agent (idarucizumab for dabigatran) has been approved by the FDA, leaving other DOACs such as rivaroxaban, apixaban, and edoxaban without reversal agents.

However, warfarin has many reversal options, such as phytonadione (vitamin K), fresh frozen plasma (FFP), and prothrombin complex concentrate (PCC). These reversal agents allow warfarin to be an alternative option for patients at an increased risk of bleeding, and recent guidelines still recommend it for certain patients.[1] This article reviews key points regarding available oral anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban, edoxaban), available reversal agents (vitamin K, FFP, PCC, idarucizumab), and a new reversal agent (andexanet alfa), which is currently in phase III clinical trials.

Oral anticoagulants

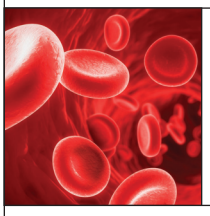
Warfarin

Approved by the FDA in 1954, warfarin is indicated for prophylaxis and treatment of venous thrombosis, pulmonary embolism, thromboembolic complications associated with AF and/or cardiac valve replacement, and reduction in the risk of death due to recurrent myocardial infarction and stroke. It works by inhibiting the synthesis of vitamin K–dependent clotting factors II, VII, IX, and X and the anticoagulant proteins C and S, ultimately leading to an anticoagulant effect.[7]

Although warfarin is an effective anticoagulant, managing therapy with warfarin is challenging due to the individual

Keywords: andexanet alfa, apixaban, dabigatran, direct oral anticoagulants, edoxaban, fresh frozen plasma, idarucizumab, phytonadione, prothrombin complex concentrate, reversal agents, rivaroxaban, vitamin K, warfarin

variations in dosage requirements that can result in over/under-anticoagulation. In addition, warfarin has a narrow therapeutic range, which must be monitored closely to prevent adverse reactions (such as bleeding). Warfarin's concentrations can also be affected by vitamin K–containing foods and other medications, such as amiodarone, fluconazole, and others.[8] However, even though warfarin interacts with many foods and medications, it is still commonly used for anticoagulation.[9]



Since the first DOAC was approved, antithrombotic therapy has shifted away from the mainstay of therapy, the vitamin K antagonist.

Dabigatran

A direct thrombin inhibitor, dabigatran was approved by the FDA in 2010 for nonvalvular AF and was the first DOAC used as an alternative to the vitamin K antagonist.[10] This oral prodrug converted by serum esterase works by binding to both fibrin-bound and unbound thrombin, which ultimately negates the conversion of fibrinogen (factor I) to fibrin (factor Ia), preventing the formation of a thrombus.[3,10]

Currently, dabigatran is indicated for stroke and systemic embolism prophylaxis in nonvalvular AF, treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients who were previously treated with a parenteral anticoagulant for 5 to 10 days, risk reduction to prevent recurrence of DVT and PE in patients who were previously treated, and prophylaxis of DVT and PE in patients undergoing hip replacement surgery, which was approved by the FDA in 2014.[11]

Rivaroxaban

A factor Xa inhibitor, rivaroxaban was approved by the FDA in 2011 for nonvalvular AF and venous thromboembolism and was the first factor Xa inhibitor to be approved.[10] It exerts its pharmacologic effect by binding directly to free and clot-bound factor Xa, without requiring cofactors (antithrombin), thus preventing thrombus formation and platelet activation. Currently, rivaroxaban is indicated for risk reduction of stroke and systemic embolism in nonvalvular AF, treatment of DVT and PE, risk reduction to prevent recurrence of DVT and PE in patients who were initially treated for DVT or PE, and prophylaxis of DVT and PE in patients undergoing knee or hip replacement surgery.[12]

Apixaban

Approved by the FDA in 2012 for the treatment of nonvalvular AF needing anticoagulation, apixaban exerts its pharmacologic effect by binding to free and bound factor Xa in the body, thus preventing clot formation and platelet activation. Renal excretion accounts for 27% of apixaban elimination. This makes apixaban a viable option in patients with kidney impairment, although clinical judgment should be employed. Apixaban is currently approved for risk reduction of stroke and systemic embolism in nonvalvular AF and treatment of DVT and PE, risk reduction to prevent recurrence of DVT and PE after initial treatment, and prophylaxis of DVT after hip or knee replacement surgery.[13]

Edoxaban

A factor Xa inhibitor, edoxaban was approved by the FDA in 2015 for nonvalvular AF and is the newest factor Xa inhibitor to be approved. Like rivaroxaban and apixaban, it exerts its pharmacologic effect by binding directly to free and clot-bound factor Xa without requiring cofactors (antithrombin), thus preventing thrombus formation and platelet activation. Currently, edoxaban is indicated for reduction of stroke and systemic embolism in patients with nonvalvular AF and treatment of DVT and PE after 5 to 10 days of treatment with a parenteral anticoagulant.[14]

Consult the manufacturer's prescribing label for complete prescribing information including dose recommendations and dose adjustments for each drug.[7,11-14]

Reversal agents

Phytonadione (vitamin K)

Vitamin K reverses the anticoagulant effect of warfarin by promoting hepatic production of the vitamin K–dependent clotting factors II, VII, IX, and X. By promoting hepatic production of the vitamin K–dependent clotting factors, administering exogenous vitamin K I.V. or orally expedites the reduction of the international normalized ratio (INR). Between the two routes of administration, I.V. vitamin K causes a faster reduction in the INR within 6 to 8 hours after administration compared with oral vitamin K, which causes a reduction within 24 to 48 hours.[15]

The reduction in INR achieved after 24 to 48 hours is similar between the I.V. and oral routes. Therefore, there is no advantage to using the I.V. route when the need for warfarin reversal is not urgent. The I.M. and subcutaneous routes of administration are not recommended in patients requiring warfarin reversal due to erratic absorption; the

risk of anaphylaxis is a concern when vitamin K is administered via the I.V. route.[15,16]

The American College of Chest Physicians (ACCP) has specific recommendations that describe when vitamin K administration is appropriate.[16] First, the ACCP recommends against the routine use of vitamin K for warfarin reversal in patients with an INR between 4.5 and 10 and no bleeding; there is no advantage to administering vitamin K in this situation. Instead, warfarin should be withheld in these patients until the INR declines. Second, administering oral vitamin K and withholding warfarin are recommended for patients with an INR greater than 10 and no bleeding. Finally, in the presence of bleeding regardless of INR, a slow I.V. dose of vitamin K as well as withholding warfarin are recommended.[15,16]

Overall, vitamin K is effective in the complete reversal of warfarin within 24 to 48 hours. Per the ACCP, intervention with vitamin K is not indicated when the INR is 10 or less unless the patient has significant bleeding or requires urgent surgery.[16] Administering vitamin K can result in the patient being refractory to warfarin when warfarin is reinitiated. Therefore, the lowest possible dose of vitamin K should be used to reverse warfarin to avoid further complications.[15]

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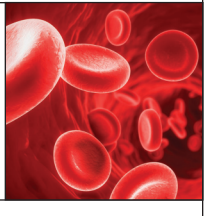

FFP

Prepared from single units of whole blood or plasma, FFP is a widely used agent that reverses warfarin in the event of serious bleeding and elevated INR. Within FFP, all of the clotting factors, plasma proteins, electrolytes, physiologic anticoagulants (protein C, protein S, antithrombin, tissue factor pathway inhibitor), and added anticoagulants exist, allowing FFP to reverse coagulopathies caused by warfarin.[17] Dosing is based on the patient's weight (10 mL/kg to 20 mL/kg), which produces a 20% to 30% increase in plasma levels of clotting factors.[15]

FFP carries risks, including disease transmission, fluid overload, and transfusion reactions, such as hypersensitivity reactions. It must be blood group–specific because it contains isohemagglutinins. FFP has to be thawed before use, which could delay treatment in the event of an emergency.[15] FFP is not effective to reverse the effects of DOACs and should not be used with reversal of DOACs.[10]

PCC

PCCs are typically composed of varying amounts of factors II, VII, IX, and X. Frequently used formulations of PCC include 3-factor PCC (3-PCC) and 4-factor PCC (4-PCC). Both products require activation by the clotting cascade to exert their effects within the body. PCCs are indicated for reversal of vitamin K antagonists, such as warfarin.[18]

The 3-PCC contains the factors II, IX, and X; 4-PCC contains a combination of coagulation factors II, VII, IX, X, and proteins C and S. Both of these products are indicated for patients requiring reversal of vitamin K antagonist due to acute major bleeding. The administration of PCC causes thrombotic or thromboembolic events in some patients treated with PCC. Vitamin K must be administered to patients receiving 4-PCC in order to maintain adequate factor levels in the body following administration when reversing warfarin.[19]

The risk of a thromboembolic event must be weighed against the risk of acute bleeding in patients receiving 4-PCC. Dosing of 4-PCC is given as a single dose based on the patient's weight and INR.[19]

PCCs are currently being studied as potential options for reversal of DOACs; however, the use of PCCs is currently off-label.[18] A meta-analysis by da Luz and colleagues concluded that PCCs partially reverse DOACs and should be considered as treatment options in case of severe bleeding for DOACs without a reversal agent. Studies for reversal of DOACs are limited and it is strongly encouraged to look at risks versus benefit (such as thrombosis) with PCC before considering using it as a reversal for these agents.[20]

Idarucizumab

To date, dabigatran is the only DOAC with an FDA-approved reversal agent. Idarucizumab, a humanized monoclonal antibody fragment, was approved by the FDA in 2015 as the reversal agent for dabigatran.[21] Due to promising results in clinical trials, idarucizumab received accelerated approval from the FDA, which allowed it to come to market sooner (see *Reversal agents for oral anticoagulants*).[22]

Idarucizumab, a humanized monoclonal antibody fragment, binds to dabigatran and its metabolites (affinity approximately 350 times higher than dabigatran for thrombin), thus neutralizing and reversing dabigatran's anticoagulant effect.[23] Because the mechanism of dabigatran differs from other DOACs, idarucizumab will only reverse the effects of dabigatran and should not be used to reverse other DOACs. Currently, FDA indications of idarucizumab include patients treated with dabigatran when the reversal of anticoagulant

effects is warranted for emergency surgery/urgent procedures, and/or life-threatening/uncontrolled bleeding.[21]

Two methods of administration may be used. The first is a continuous infusion by hanging the vials, and the second method is providing bolus injections by injecting both vials consecutively via syringe.[21] Once the solution has been drawn up via syringe for bolus injections, idarucizumab must be administered within 1 hour. A preexisting I.V. line may be used for administration, but the line must be flushed with sterile 0.9% sodium chloride injection prior to infusion, and no other infusion should be administered via the same I.V. line.[21]

Idarucizumab has four warnings that should be considered before administration. First, reversing dabigatran exposes patients to risk of developing a thrombus due to the underlying disease (AF). To reduce this risk, restarting anticoagulation should be considered as soon as medically appropriate, and dabigatran may be reinitiated in a patient as early as 24 hours after administration of idarucizumab.

Second, in a small number of patients in clinical trials, elevation of coagulation parameters (activated partial thromboplastin time and/or ecarin clotting time [ECT]) has been observed after the administration of idarucizumab (between 12 and 24 hours post administration). If there is reappearance of clinically relevant bleeding with elevated coagulation parameters, it may be warranted to administer another dose of idarucizumab, but the safety and efficacy of readministration have not been established.[21]

Third, few reports in clinical trials have noted a hypersensitivity reaction, and the risk of reaction should always be considered. However, it is important to always determine the risk versus benefit when deciding if a patient should receive idarucizumab. Finally, if patients with the condition of hereditary fructose intolerance have had a previous reaction to sorbitol, it is important to note that idarucizumab contains 4 g of sorbitol as an excipient and should be considered when administering idarucizumab.[21,22]

During the phase III clinical trial, the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study, efficacy and safety of idarucizumab were established. In the RE-VERSE AD study, patients age 18 or older who had uncontrollable and/or life-threatening bleeding (group A) or who required a surgery or other invasive procedures that could not be delayed for 8 hours (group B) received idarucizumab. The primary endpoint was the percentage reversal of the anticoagulant effect of dabigatran, which was determined within 4 hours after the infusion of idarucizumab on the basis of the measurement of dilute thrombin time (dTT) or ECT by a central lab (dTT and ECT were chosen as markers of idarucizumab's percentage reversal

Reversal agents for oral anticoagulants[1,15,18,19,23,27]

Anticoagulant	Reversal agent	Mechanism of action	Important facts
Warfarin	Vitamin K	Cofactor for hepatic synthesis of factors II, VII, IX, and X	Recommended when a patient is bleeding or has an INR >10
	FFP	Repletes all plasma proteins and clotting factors	May transmit diseases; must be blood type–specific because FFP contains isohemagglutinins; may cause fluid overload, which could be problematic in patients with heart failure
	3-PCC	Repletes vitamin K–dependent clotting factors II, IX, and X	Must coadminister vitamin K with dose; some products contain heparin and are contraindicated in patients with heparin-induced thrombocytopenia (HIT); refer to package insert for dosing, as this depends on the product
	4-PCC	Repletes vitamin K–dependent clotting factors II, VII, IX, X as well as proteins C and S	Dose is determined by the patient's predose INR and body weight; must coadminister vitamin K with dose; preferred over FFP in cases of major bleeding; contains heparin and is contraindicated in patients with HIT
Dabigatran	Idarucizumab	Binds to and reverses dabigatran and its metabolites	Must administer both vials in package for complete reversal of dabigatran
Rivaroxaban Apixaban Edoxaban	Andexanet alfa	Binds to and reverses effects of factor Xa inhibitors	Currently in phase III clinical trials and pending FDA approval

effect because these markers are highly correlated with the concentrations of unbound dabigatran). Of note, dTT and ECT may not be readily available. Many different secondary endpoints were evaluated, but the major secondary endpoint was hemostasis restoration.[23]

To provide idarucizumab to patients as soon as possible, an interim analysis from the RE-VERSE AD study was published in June 2015. Overall, idarucizumab completely reversed the anticoagulant effect of dabigatran in 90 patients within minutes of administration. Among the 68 patients who had elevated dTT and 81 who had elevated ECT, the medium maximum percentage reversal was 100% (95% confidence interval [CI], 100 to 100), which was evident on the first sample taken after the first infusion of idarucizumab. Therefore, since the interim results indicated that idarucizumab was an effective reversal agent for dabigatran, idarucizumab received accelerated approval from the FDA in October 2015, which was contingent upon the results of the full cohort analysis.[23]

In August 2017, the full cohort analysis of the RE-VERSE AD study was published, which continued to show that idarucizumab was an effective and safe reversal agent for dabigatran. Among the 503 patients in the trial, 461 patients (91.7%, 276 in group A and 185 in group B) had an elevated ECT or a prolonged dTT at study entry. Within 4 hours after administering idarucizumab, 100% (95% CI 100 to 100) of dabigatran's anticoagulant effect was reversed based on the ECT and dTT measurement. Furthermore, unbound (active) dabigatran concentrations remained less than 20 ng/mL (a level that produces little or no anticoagulant effect) for the majority of patients for 24 hours. Of note, reemergence of levels greater than 20 ng/mL occurred in 114 of 497 patients (23%), but only 10 patients experienced recurrent or continuous bleeding. Regarding restoration of hemostasis, in group A, 134 patients (98 patients had intracranial bleeding and could not be assessed) had confirmed bleeding cessation within 24 hours, and the median investigator-reported time to cessation of bleeding was 2.5 hours.

In group B, 197 patients underwent urgent procedures, and normal intraoperative hemostasis was reported in 184 patients (93.4%). Regarding safety, 117 patients (23.3%; 66 in group A and 51 in group B) had serious adverse events within 5 days of idarucizumab administration. However, no consistent pattern developed, and the majority of events were due to worsening of their underlying conditions.[24]

Andexanet alfa

Patients taking factor Xa inhibitor anticoagulants are at an increased risk of bleeding in emergency situations, such as trauma or surgery. Currently, there are no approved agents for the reversal of factor Xa inhibitors. Andexanet alfa is a new agent seeking FDA approval that completely reverses direct and indirect factor Xa inhibitors, such as rivaroxaban, apixaban, edoxaban, and enoxaparin.[25]

Andexanet alfa is a recombinant modified human factor Xa decoy protein, which exerts its effects by binding to factor Xa inhibitors and preventing their anticoagulant effects within the body. Administration in clinical trials has included a bolus dose followed by a 2-hour infusion of andexanet alfa. Because andexanet alfa has not yet been approved for use, the dosing and administration information have not been established.[25]

Andexanet alfa is currently undergoing a third phase III clinical trial to test its effectiveness in the reversal of these agents in direct and indirect factor Xa inhibitors. Two additional phase III trials showing the efficacy of andexanet alfa have already been completed. The ANNEXA-A trial only tested the reversal agent's effectiveness in apixaban, whereas the ANNEXA-R trial showed its effectiveness when reversing rivaroxaban.[26] The apixaban and rivaroxaban trials did not report any thromboembolic events caused by the administration of the reversal agent.[26]

One patient was reported to have an anaphylactic reaction upon administration.[26] While the last phase III trial has not yet been completed, a preliminary analysis has been recently published. This analysis reported andexanet alfa to be effective in the rapid reversal of factor Xa agents in 67 patients. However, 12 of the 67 patients (18%) reported having thrombotic events after being treated with andexanet alfa.[25]

Conclusion

Prescribing of DOACs is on the rise due to their efficacy and safety that has been seen in many clinical studies, and the need for effective antidotes is warranted. Currently, the only FDA-approved reversal agent for a DOAC is idarucizumab for dabigatran, which leaves the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban without effective reversal agents. However, andexanet alfa has shown efficacy in the reversal of factor Xa inhibitors and is currently in phase III clinical trials.[27] NP

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