

ON MY MIND

Specific Antidotes for Direct Oral Anticoagulant Reversal

Case Closed or Cold Case?

Direct oral anticoagulants (DOAC) are recommended as the preferred option for the treatment and prevention of thromboembolic events because of a favorable benefit–risk profile when compared with vitamin K antagonists. Nevertheless, the fear of bleeding owing to the lack of a specific antidote has been a major concern. Idarucizumab was marketed in 2018 for the reversal of the thrombin inhibitor dabigatran. Recently, after the publication of the ANNEXA-4 study, andexanet alfa, the antidote for factor Xa (FXa) inhibitors, was approved.¹ The results of this study question whether these antidotes fulfill an unmet need and improve DOAC-treated patient outcomes.

Major bleeding occurs annually in 1% to 3% of DOAC-treated patients and results in high mortality. The short half-life of DOACs compared with warfarin obviates the use of an antidote in most cases. However, anticoagulant reversal is unquestionably required in specific situations including urgent invasive procedures, overdose, or life-threatening traumatic or spontaneous bleeding. Because rapid vitamin K antagonist reversal reduces mortality of patients facing major bleeding and minimizes hematoma expansion after intracerebral hemorrhage, immediate reversal of DOAC should similarly improve outcomes.² This is based on the assumption that by reversing the anticoagulant effects, the antidote restores hemostasis, stops hemorrhage, and therefore reduces mortality. Ideally, the perfect antidote should induce immediate, complete, and sustained reversal of the anticoagulant activity correlated with clinical improvement, with no side effects, especially thromboembolic, should be user friendly, and should be available at an acceptable price.

Idarucizumab (Praxbind, Boehringer Ingelheim) is a humanized monoclonal antibody fragment with structural analogies with thrombin that specifically binds dabigatran with high affinity, forming complexes cleared by the kidneys. The Food and Drug Administration approved idarucizumab for dabigatran reversal in life-threatening or uncontrolled bleeding, or emergency procedures. Indeed, the single-arm RE-VERSE AD study (Reversal Effects of Idarucizumab on Active Dabigatran) demonstrated that intravenous infusion of 5 g idarucizumab provided immediate, effective (100% median maximum percentage reversal), and sustained reversal of anticoagulant activity in 503 dabigatran-treated patients who had uncontrolled bleeding or faced emergency surgery.³

Andexanet alfa (Andexxa, Portola) is a genetically modified FXa that acts as a decoy to bind FXa inhibitors, including apixaban, rivaroxaban, and edoxaban, but also low-molecular-weight heparins. It has no active site and is therefore catalytically inactive. It has no membrane-binding Gla-domain, so it is unable to assemble into the prothrombinase complex. The Food and Drug Administration granted accelerated approval for patients treated with apixaban or rivaroxaban, when reversal is needed because of life-threatening or uncontrolled bleeding, beginning in May 2018 after the intermediate analysis of the ANNEXA-4 study (The Andexanet

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Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors study). The European Medicine Agency waited for the full cohort results in 2019 to grant a conditional marketing authorization. This single-arm study confirmed that a bolus of andexanet followed by a 2-hour infusion markedly reduced anti-FXa activity (92% reduction) in patients with acute major bleeding receiving FXa inhibitors, mainly apixaban and rivaroxaban.¹

These encouraging results come with caveats. First the immediate biological efficacy is questionable. The aim of reversal is to reduce anticoagulant activity below a safety hemostatic threshold, usually defined by international normalized ratio <1.3–1.5 for vitamin K antagonists and 50 ng/mL for DOACs.⁴ After reversal, dabigatran activity was nearly undetectable in 99.4% of the patients in RE-VERSE AD, whereas more than a quarter of the rivaroxaban-treated patients in ANNEXA-4 maintained concentrations above the threshold, suggesting a limited binding capacity of andexanet.^{1,3} Another issue is the anticoagulation rebound (ie, the reappearance of biological anticoagulant activity after neutralization). In RE-VERSE AD, late anticoagulation rebound was observed in 23% of the patients, mainly after 12 hours, and was associated with recurrent or continued bleeding in 9% of them, leading the investigators to consider readministration of idarucizumab.³ This rebound results from dabigatran moving from extravascular compartment into plasma in response to the concentration gradient occurring after reversal. In contrast, in ANNEXA-4, anticoagulation rebound occurred shortly after andexanet administration and was massive: 4 hours after the end of andexanet infusion, 75% of the patients had rivaroxaban concentrations above 50 ng/mL, and more than 50% even above 100 ng/mL.¹ Here, the rebound results from the short half-life of andexanet. Once the perfusion is completed, anticoagulant activity rises to placebo levels because andexanet neutralizes FXa inhibitors but does not eliminate them. Nevertheless, sustained correction of coagulation is required for several hours after bleeding, and even days in case of intracerebral hemorrhage. This time is needed for the initial platelet clot to make a stable fibrin clot able to resist further assault of anticoagulation. This was illustrated in RE-VERSE AD where reincrease in dabigatran concentration after reversal induced the recurrence of bleeding. This is also clearly stated in the guidelines for perioperative management that recommend delaying therapeutic anticoagulant resumption for 24 to 72 hours after scheduled surgery to prevent bleeding from the surgical site. The extremely brief reversal of FXa inhibitors with andexanet is therefore a strong limitation.

These antidotes also put potential thromboembolic risk into question. In RE-VERSE AD and ANNEXA-4, thrombotic events were reported in 4.8% and 10% of the patients within 30 days after reversal, respectively.^{1,3}

In the absence of controlled groups, it is impossible to state whether thromboembolic events reflect the inherent effect of the antidote or any hypercoagulable state related to patient underlying conditions, increased by DOAC interruption, inflammation, immobilization, or transfusion. However, it is worth noting that whereas idarucizumab had no procoagulant activity in animal models and in healthy volunteers, andexanet transiently increased markers of thrombin formation, including levels of D-dimer and prothrombin fragments 1+2.⁵ This has been attributed to the ability of andexanet to inhibit the activity of tissue factor pathway inhibitor, resulting in increased tissue factor-activated generation of FXa and thrombin. Until receipt of further data, the Food and Drug Administration issued a black box warning for andexanet regarding the increased risks of thrombotic events, cardiac arrest, and sudden death.

Finally, limitations regarding practical aspects must be considered. Whereas idarucizumab is administered as a single dosage of 2 vials for \$3880, andexanet is administered according to complex schemes including bolus then infusion based on the DOAC, dosage, and timing of the last dose, resulting in low or high regimens requiring the preparation of many vials, announced for \$24 750 and \$49 500, respectively. Such prices and initial limited supply may reduce andexanet accessibility. Rationalization of antidote use must be anticipated. DOAC concentration measurement can help to avoid unnecessary reversal when a concentration is already below the hemostatic threshold, which affected more than 25% of the patients in RE-VERSE AD.³

Both antidotes received Food and Drug Administration accelerated approval. This program allows approval based on a surrogate end point that is reasonably likely to predict a real clinical benefit but requires confirmatory studies to validate the anticipated benefit because surrogate markers do not always translate into clinical outcomes. This is apparently the case in ANNEXA-4 because reduction in anti-FXa activity was not predictive of hemostatic efficacy.¹ Portola is now conducting a randomized trial (<https://www.clinicaltrials.gov>; Unique identifier: NCT03661528) to evaluate andexanet versus standard of care in patients with intracerebral hemorrhage receiving FXa inhibitors.¹ This trial will definitively adjudicate the benefit of andexanet. For other agents, uncertainty will persist: idarucizumab is fully approved without an ongoing confirmatory controlled trial; activated and nonactivated prothrombin complex concentrates, although recommended when specific antidotes are not available, have never been rigorously assessed.

The availability of specific antidotes provides reassurance, but whether DOAC reversal translates into clinical improvements remains unknown and leaves clinicians in an awkward position. In the absence of a robust evaluation, the case is not closed.

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