First Reversal Agent on the Direct Oral Anticoagulants: Idarucizumab (Praxbind®)
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Introduction
Oral anticoagulation with vitamin K antagonists requires frequent drug monitoring due to multiple drug-drug and drug-food interactions. Dabigatran (Pradaxa®) is a reversible, direct thrombin inhibitor that inhibits free and fibrin-bound thrombin. Direct oral anticoagulants (DOACs) such as dabigatran do not require laboratory monitoring.1 Cumulative evidence suggests bleeding complications associated with dabigatran are less frequent than with warfarin, but life-threatening bleeding can occur.2-4 Patients on anticoagulation may need urgent reversal at times of surgical intervention as perioperative bleeding is increased in these patients.

Recommendations for management of major bleeding for those on dabigatran include supportive care, packed red blood cells, and/or activated prothrombin complex concentrates. Activated charcoal can be administered following recent ingestion. Hemodialysis can also take place.5-7 Patients taking warfarin can be reversed with vitamin K or fresh frozen plasma while reversal agents for the other DOACs, factor Xa inhibitors, have not yet been approved.

The FDA has approved the first specific reversal agent for dabigatran for life-threatening or uncontrolled bleeding or when an emergency surgery or urgent procedure is required. Idarucizumab (Praxbind®) for injection is a humanized monoclonal antibody fragment (Fab) that has undergone accelerated approval due to its ability to bind free and thrombin-bound dabigatran and restore hemostasis in most patients.8,9

Clinical Pharmacology
Idarucizumab is a humanized monoclonal antibody fragment (Fab) that binds to unbound dabigatran and its metabolites in a 1:1 ratio with an approximately 350 times greater binding affinity than that of dabigatran to thrombin, thereby neutralizing dabigatran’s anticoagulant effects.9,10 Once the dabigatran-idarucizumab complex is formed in the blood, dabigatran is inactivated. To reestablish equilibrium, dabigatran is forced to leave the tissues and reenter circulation where it will bind with idarucizumab, further inactivating its anticoagulant effects. The neutralizing action of idarucizumab was found to be dose-dependent using markers such as diluted thrombin time (dTT), ecarin clotting time (ECT), activated partial thromboplastin time (aPTT), and thrombin time (TT).10

Pharmacokinetics and Pharmacodynamics
The volume of distribution (V_d) of idarucizumab was 8.9 L and displayed multiphasic and limited extravascular distribution. The drug was found to be excreted 32.1% unchanged in the urine after six hours after administration of 5 grams IV, with a total body clearance of 47 mL/minute. The initial half-life of the parent compound was found to be 47 minutes with a terminal elimination half-life of 10.1 hours. Idarucizumab was not found to have procoagulant effects.10,11

Early Clinical Efficacy Data
Clinical data for idarucizumab comes from the ongoing phase III RE-VERSE AD trial. The trial is a prospective, open-label, multi-center trial investigating two different groups of patients taking dabigatran.9 Patients in group A experienced overt, uncontrollable, or life threatening bleeding which required a reversal agent while patients in group B required surgery or invasive procedures which could not be delayed for 8 hours. Patients were able to receive blood products and other supportive care
throughout the study. All patients received two infusions of idarucizumab 2.5 g up to 15 minutes apart to achieve a total dose of 5 g. The primary endpoints for the trial were the maximal percentage reversal of dabigatran up to 4 hours after the last infusion of idarucizumab based on the dTT or ECT. Secondary endpoints included the proportion of patients achieving complete reversal of the dTT and ECT within four hours after idarucizumab infusion, and the reduction in the concentration of unbound dabigatran. The extent of bleeding, hemodynamic stability, hemostasis during interventions performed in group B, and thrombotic events or deaths within 90 days were additional secondary endpoints.

The interim analysis of the RE-VERSE AD trial contained 90 patients with 51 in group A and 39 in group B. The median time from last dabigatran dose for patients was 15.4 hours. The median maximum percentage reversal in patients with elevated dTT or ECT at baseline was 100% (95% CI, 100-100). The dTT was normalized in 98% of patients in group A and 93% of patients in group B while the ECT was normalized in 88% of patients in group A and 89% of patients in group B. Reversal of these lab values was rapid occurring within minutes of the idarucizumab infusions. At 24 hours, dabigatran levels were <20 mg/mL (essentially undetectable) in 79% of patients. In group B, 36 patients underwent a procedure and only three patients did not have normal intraoperative hemostasis after receiving idarucizumab.

Safety and Tolerability
The RE-VERSE AD trial looked at hemostasis as a secondary endpoint finding normal hemostasis in 92% of participants and mild to moderate impairment for the remainder of participants with a median time of 11.4 hours. There were nine patients in each study arm who had fatal events, including five bleeding events. There were five patients who experienced thrombotic events and one patient was found to have a thrombotic event within 72 hours after the administration of idarucizumab 5 g IV, but had not been restarted on anticoagulant therapy. No contraindications have been established at this point. Established precautions include hypersensitivity reactions, hepatic considerations regarding increased coagulation parameters 12 to 24 hours after the first dose (may consider administering a second dose), and hereditary fructose intolerance due to idarucizumab being formulated with sorbitol. Reported adverse events were fever (6%), delirium (7%), thromboembolic events, antibody development (4%), pneumonia (6%), constipation (7%), and hypokalemia (7%). Thromboembolic events were likely due to comorbid conditions and most events occurred seven days after treatment with one occurring two days after treatment. None of these patients had been receiving antithrombotic therapy.

Discussion
Idarucizumab’s effectiveness was shown in three trials, and it was approved under the FDA’s accelerated approval program. Efficacy for idarucizumab was based on 3 clinical trials with a total of 283 healthy subjects who were taking dabigatran. Trials have concluded that idarucizumab immediately reduced unbound plasma dabigatran levels lasting more than 24 hours.

Idarucizumab approval was also based on the ongoing RE-VERSE AD clinical trial. RE-VERSE AD included 90 patients taking dabigatran who took idarucizumab for emergency surgery or uncontrolled bleeding. Idarucizumab reversed the anticoagulant effect of dabigatran within 4 hours in a median of 100% of patients with elevated dTT or ECT at baseline. The 5 gram dose chosen for the RE-VERSE AD trial was chosen on the basis of the highest plasma concentrations measured in the RE-LY trial. Of note, there were no comparator groups in the RE-VERSE AD trial so it is unknown if idarucizumab performs better than supportive agents at reducing clinical outcomes.

Conclusion
Idarucizumab is the first reversal agent for one of the DOACs and was given breakthrough status by the FDA, which facilitated their speedy approval based on ongoing phase III clinical trials. Given that
idarucizumab promises reversal of dabigatran, while other available options have only shown some benefit, this is an exciting development.5–7
References