Evidence for Idarucizumab (Praxbind) in the Reversal Of the Direct Thrombin Inhibitor Dabigatran: Review Following the RE-VERSE AD Full Cohort Analysis

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INTRODUCTION

Dabigatran (Pradaxa, Boehringer Ingelheim) is an oral anticoagulant approved for the prevention and treatment of venous thromboembolism (VTE), reduction in risk of stroke and systemic embolism in nonvalvular atrial fibrillation, and postoperative thromboprophylaxis.1–4 As a direct thrombin inhibitor, dabigatran impedes both free and fibrin-bound thrombin, thus inhibiting coagulation by blocking the effects of thrombin.1–4 Dabigatran inhibits thrombin-mediated effects including generation of fibrin monomers from fibrinogen; activation of clotting factors V, VIII, XI, and XIII; and platelet aggregation.1–4

Multiple studies have assessed bleeding risks associated with dabigatran. The RE-MODEL trial compared dabigatran 220 mg once daily or 150 mg once daily to subcutaneous enoxaparin 40 mg once daily for the prevention of VTE after knee replacement. The incidence of major bleeding did not differ significantly among the study arms: 1.5% in the dabigatran 220 mg once daily group (P = 0.82 compared with enoxaparin), 1.3% in the dabigatran 150 mg once daily group (P = 1.0 compared with enoxaparin), and 1.3% in the enoxaparin 40 mg once daily group.5 The RE-NOVATE trial compared dabigatran 220 mg or 150 mg once daily with subcutaneous enoxaparin 40 mg once daily for the prevention of VTE after total hip replacement and reported no significant difference in major bleeding rates with study doses of dabigatran compared with enoxaparin (P = 0.44 for dabigatran 220 mg once daily; P = 0.60 for dabigatran 150 mg once daily).6 The RE-LY trial compared dabigatran 110 mg or 150 mg twice daily to adjusted-dose warfarin for atrial fibrillation and reported that major bleeding occurred at an annual rate of 3.36% in the warfarin group compared with 2.71% in the 110 mg dabigatran group (P = 0.003) and 3.11% in the 150 mg dabigatran group (P = 0.31). Hemorrhagic stroke occurred at an annual rate of 0.38% in the warfarin group compared with 0.12% in the 110 mg dabigatran group (P < 0.001) and 0.10% in the 150 mg dabigatran group (P < 0.001).7 Gastrointestinal bleeding occurred at an annual rate of 1.02% in the warfarin group compared with 1.12% in the dabigatran 110 mg group (P = 0.43) and 1.51% in the dabigatran 150 mg group (P < 0.001).7 The increased rate of gastrointestinal bleeding in the dabigatran 150 mg group has been considered a major disadvantage for its utilization. Major bleeding episodes in the RE-COVER study—which compared dabigatran 150 mg twice daily to adjusted-dose warfarin for the treatment of acute VTE—occurred in 1.6% of 1,274 participants receiving dabigatran and in 1.9% of 1,265 participants receiving warfarin (hazard ratio with dabigatran, 0.82; 95% confidence interval, 0.45–1.48). Bleeding events were noted in 16.1% of dabigatran recipients and 21.9% of warfarin recipients in RE-COVER.8 Because major bleeding events occurred in all of the studies listed, the management of bleeding in dabigatran-treated patients during emergency situations and surgical procedures is warranted.

Idarucizumab (Praxbind, Boehringer Ingelheim) is a humanized monoclonal antibody fragment indicated for the reversal of dabigatran.8 It binds to acylglucuronide metabolites of dabigatran with a 350-times greater affinity for dabigatran than that of thrombin.9 Idarucizumab neutralizes the effects of both free and thrombin-bound dabigatran.10 It is administered intravenously as two separate 2.5-g doses (administered no more than 15 minutes apart) for emergency surgical procedures or life-threatening, uncontrolled bleeding in patients receiving dabigatran for anticoagulation.9 Idarucizumab administration may be conducted in a critical care or emergency department setting, although it could be conducted in any setting based on emergent need; the patient’s condition will likely dictate transfer to a higher level of care if idarucizumab is administered emergently in a setting that cannot provide adequate monitoring. Idarucizumab administration in the setting of uncontrolled, life-threatening bleeding should occur in conjunction with hemostatic agents, such as blood products (e.g., whole blood, fresh frozen plasma, cryoprecipitate, packed red blood cells, platelets); plasma derivatives (e.g., three-factor prothrombin complex concentrate, four-factor prothrombin complex concentrate, recombinant factor VIIa, activated prothrombin complex concentrate), volume expanders; prohemostatic agents; albumin; and others.11 Dose adjustment is not necessary for renal impairment.8 The safety, efficacy, and tolerability of idarucizumab in the reversal of dabigatran-induced anticoagulation have been assessed in several clinical studies, including some that are ongoing.8

In October 2015, the Food and Drug Administration (FDA) granted expedited approval to idarucizumab for dabigatran-treated patients during emergency situations when dabigatran reversal is needed.12 This accelerated approval was contingent

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Evidence for Idarucizumab in the Reversal of Dabigatran: A Review

on further adequate and well-controlled clinical trials to verify and describe idarucizumab’s clinical benefit. Approval of idarucizumab was crucial because of the lack of specific reversal agents for dabigatran. Managing bleeding with direct thrombin inhibitors was previously limited to medication discontinuation, provision of supportive care, dialysis, or utilizing available blood products and clotting factor supplements. This review is intended to summarize the current literature for clinical practitioners, pharmacists, and other health care providers seeking information on idarucizumab for patient- and formulary-related decisions.

METHODS

The literature review sought randomized controlled trials, observational studies, case reports, and analyses of post-marketing data that assessed the safety and efficacy of idarucizumab in the reversal of anticoagulation effects of dabigatran. MEDLINE through Ovid, Embase, and International Pharmaceutical Abstracts (IPA) were used to perform a comprehensive search for relevant keywords. The search strategy included “idarucizumab” or “Praxbind” as keywords, and the search was limited to humans and English language. Review articles, editorials, and similar items were removed from the search results. Duplicate articles were eliminated from the final search results. Captured studies were assessed for inclusion based upon their quality of evidence: more specifically, whether power was set and met; appropriateness of statistical tests used; validity of inclusion and exclusion criteria; randomization resulting in similar groups; effectiveness of blinding; duration of the study; fair and comparable treatment regimens; validity of outcome measures; and degree of concordance of the authors’ conclusions with the study results.

In addition to searches conducted using MEDLINE, Embase, and IPA, the same keyword search was applied to the National Clinical Trials (NCT) database and European Union Clinical Trials Register to assess the current direction of research related to idarucizumab. Resulting entries were ignored if they were redundant to articles identified in MEDLINE, Embase, or IPA, or matched results provided in the idarucizumab prescribing information. Entries were ranked and reported by status, or degree of study completion, as per the NCT database.

Background information on idarucizumab was obtained and corroborated through Lexi-Comp, Micromedex, Drug Facts and Comparisons, and Clinical Pharmacology. The prescribing information, as prepared by Boehringer Ingelheim, was also referenced. The compiled background information included idarucizumab’s indication; dosing; formulations; warnings and precautions; adverse effects; and mechanism of action.

RESULTS

The search strategy resulted in a total of 212 reports regarding idarucizumab from MEDLINE, Embase, and IPA. Of those, 11 relevant reports were captured that assessed the safety, efficacy, and tolerability of idarucizumab when used in healthy volunteers administered dabigatran or dabigatran-treated patients. Thirty-nine reports were captured that presented case data on 59 patients who had received idarucizumab. An NCT database search identified seven studies in progress; two studies were captured using the European Union Clinical Trials Register and were found to be redundant to those captured in the NCT database.

PHASE 1 STUDIES

Glund et al. conducted a randomized, placebo-controlled, phase 1 study (NCT01688830) that included a dose-escalation evaluation of idarucizumab alone (reported here) and an efficacy assessment of idarucizumab in participants pretreated with dabigatran (reported below); 110 healthy male volunteers 18 to 45 years of age met the inclusion criteria. During the first stage of the study, the men were broken into 10 dosing groups and received increasing doses of idarucizumab, ranging from 20 mg to 8 g, as a one-hour infusion; three additional dosing groups received doses of 1 g, 2 g, or 4 g of idarucizumab over a five-minute infusion. The participants were randomized 3:1 in each dosing group (idarucizumab or placebo). The study reported that peak and total exposure increased proportionally with increasing doses of idarucizumab. The reversal effects of dabigatran anticoagulation were evaluated during the second and third stages of the study (provided below). Peak plasma exposure was reached quickly and elimination followed in groups receiving ascending doses of idarucizumab via both one-hour and five-minute infusions. No clinical differences were noted in the overall adverse effects among participants receiving idarucizumab or placebo. Common adverse reactions included nasopharyngitis, headache, skin irritation, and back pain, but overall the drug was well tolerated at all administered doses for both the one-hour and five-minute infusions.

Additional data supporting these results in healthy participants are reported in the prescribing information and are available via the NCT database (NCT02028780). In further analysis of these two populations of healthy patients, idarucizumab did not demonstrate any procoagulant properties itself, merely the reversal of dabigatran. Glund et al. also conducted a randomized, placebo-controlled, double-blind, phase 1 trial in 47 healthy male volunteers (also registered under NCT01688830). The study included a dose escalation evaluation of idarucizumab alone (reported above) and an efficacy assessment of idarucizumab in participants pretreated with dabigatran. Participants within each dosing group were randomly assigned in a 3:1 ratio to idarucizumab or placebo; all participants received oral dabigatran 220 mg twice daily for three days and a final dose on the fourth day. Idarucizumab was administered two hours after the last dabigatran dose on day 4. Idarucizumab was given in doses of 1 g, 2 g, or 4 g as a five-minute infusion or doses of 5 g plus 2.5 g given as two five-minute infusions one hour apart. Immediate and complete reversal was obtained after infusion of idarucizumab in all dose groups as evidenced by a reduction in the mean ratio of day 4 area under the effect curve from two hours to 12 hours (AUEC2–12) to day 3 AUEC2–12 for diluted thrombin time (dTT) in a dose-dependent manner. Sustained reversal of dTT (for the 72-hour study period) was seen with idarucizumab doses of 1 g or greater. Sustained reversal for all parameters—including dTT, ecarin clotting time (ECT), thrombin time (TT), and activated partial thromboplastin time (aPTT)—for 72 hours was seen with 5 g plus 2.5 g idarucizumab doses. There was no clinical difference in the severity or frequency of adverse events among treatment groups. Idarucizumab was well toler-
Evidence for Idarucizumab in the Reversal of Dabigatran: A Review

Glund et al. further conducted a randomized, double-blind, placebo-controlled, crossover phase 1 trial (NCT01955720) in 46 patients 45 to 80 years of age; 16 were considered elderly (65 to 80 years of age) and 18 had mild-to-moderate renal impairment. The study objective was to investigate the safety, tolerability, pharmacological parameters, and effective dose for idarucizumab in the reversal of dabigatran. Participants received dabigatran 220 mg or 150 mg twice daily for three days and one dose on the morning of day 4. Participants were then randomized to receive either placebo or idarucizumab 1 g, 2.5 g, or 5 g administered as a rapid five-minute infusion two hours after dabigatran administration on day 4; patients then received either idarucizumab or placebo in a crossover fashion. Rapid and complete reversal was seen in a dose-dependent manner. Reductions were seen in ECT, dTT, and aPTT immediately after dabigatran administration in all groups. Age did not affect reversal based on ECT, dTT, and aPTT. Participants with mild (mean creatinine clearance [CrCl], 72.8 mL/min) and moderate (mean CrCl, 58.7 mL/min) renal impairment eliminated idarucizumab less effectively than subjects with normal renal function. Exposure was greater (P = 0.002 and P < 0.0001 in mild and moderate renal function impairment, respectively), clearance was decreased (P = 0.002 and P < 0.0001, respectively), and idarucizumab half-life was prolonged (P = 0.0099 and = 0.0003, respectively). Idarucizumab adverse effects were mild and not correlated with age, degree of renal impairment, or dose.

Separately reported data described subgroups that were reinitiated on dabigatran 24 hours following idarucizumab administration as well as those later exposed to idarucizumab to assess antibody development (also registered under NCT01955720). Participants were safely restarted on dabigatran 24 hours following idarucizumab administration, although the number of patients in this subgroup analysis was limited to 12. Safety and efficacy of a second idarucizumab administration was assessed in six of these participants two months following the first exposure to idarucizumab. Participants demonstrated a similar degree of reversal relative to their first idarucizumab exposure and did not experience clinically relevant anti-idarucizumab antibody development; only one of the six patients had a low positive titer following re-exposure. Similar outcomes—specifically, a low rate of anti-idarucizumab antibody development prior to or following administration; low titers in those who did develop antibodies to idarucizumab; and the lack of clinically relevant adverse effects or reduction in efficacy in those with anti-idarucizumab antibodies who subsequently received idarucizumab—were corroborated by Norris et al. when data from 283 patients were pooled from available phase 1 studies.

PHASE 2 AND PHASE 3 STUDIES

Pollack et al. conducted a prospective cohort study—the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) trial—in 90 participants enrolled at 184 sites in 35 countries (NCT02104947). The objective of the study was to evaluate the safety and efficacy of idarucizumab in the reversal of anticoagulant effects in dabigatran-treated patients presenting with serious bleeding or requiring urgent surgery or an intervention that could not be delayed for eight hours. At the interim analysis, the study included two groups: group A consisted of 51 patients with life-threatening bleeding, and group B comprised 39 patients who required urgent surgery or other invasive procedures. The median age of participants was 76.5 years (range, 48–93 years); 56% were men. Median CrCl was 58 mL/min as calculated by Cockcroft-Gault. Participants received two infusions of 2.5 g intravenous idarucizumab. The 5-g idarucizumab dose used to reverse the effects of dabigatran was selected based on the highest range of plasma concentrations reported in the RE-LY trial. Sixty-eight participants had elevated dTT at baseline, and 81 participants had elevated ECT either before or after 72 hours. The results from these patients showed a median maximum percent reversal of 100% after four hours in both participant groups as assessed by dTT and ECT. Thrombotic events occurred in five patients, including VTE, non-ST segment elevation myocardial infarction, and ischemic stroke; mortality was reported as 20% (18 deaths). Among 35 of 51 participants in group A who could be assessed, the median time to cessation of bleeding was 11.4 hours. Among 33 of 36 participants in group B, normal hemostasis was achieved intraoperatively.

The full cohort analysis of the RE-VERSE AD trial included 503 patients (301 with uncontrolled, life-threatening bleeding [group A], 202 undergoing surgery or an invasive procedure [group B]) enrolled at 173 sites in 39 countries (also registered under NCT02104947). Most participants (95.7%) were receiving dabigatran for prevention of stroke in the setting of atrial fibrillation. The median age of participants was 78 years with a median CrCl of 50.8 mL/min as calculated by Cockcroft-Gault. The efficacy analysis included 461 patients with prolonged dTT or elevated ECT. Similar to the interim analysis, the median maximum percent reversal was 100% within four hours following idarucizumab administration based upon dTT or ECT. Baseline aPTT was prolonged in 373 of the 503 patients and reversed similar to the dTT. The median time to cessation of bleeding in those participants with overt bleeding was 2.5 hours. The median time to initiation of procedure in participants in group B was 1.6 hours, and hemostasis was assessed as normal in 93.4% of the participants.

The safety analysis included all 503 participants. The 30-day mortality rate was 13.5% in group A and 12.6% in group B; the corresponding 90-day mortality rate using the Kaplan-Meier method was 8.8% and 18.9%, respectively. Most deaths that occurred within five days after enrollment appeared to be related to the severity of the index event or to coexisting conditions. Thrombotic events occurred in 24 participants and included VTE, myocardial infarction, and ischemic stroke. Resumption of antithrombotic therapy was possible in 40.6% of participants within 72 hours of administration of idarucizumab. Nine participants received more than 5 g of idarucizumab due to recurrent bleeding or the need for a second urgent surgical procedure. The authors proposed that recurrent elevation in clotting time may have been due to redistribution of unbound dabigatran from the extravascular to the intravascular compartment. Antibodies against idarucizumab were noted in 28 patients, nine of whom developed those antibodies after idarucizumab administration. Anti-idarucizumab antibodies had no clinical effect on the efficacy of idarucizumab. Three events
that could be considered hypersensitivity reactions occurred. Serious adverse effects were reported in 117 patients; events that occurred at a frequency greater than 1% included delirium, cardiac arrest, sepsis, septic shock, cardiac failure, pulmonary edema, and respiratory failure. One of the limitations of the RE-VERSE AD trial is that it did not have a control group because of ethical considerations. Due to similar fatality rates in patients who have received standard care with or without prothrombin complex concentrate and participants who received idarucizumab in the RE-VERSE AD trial, inclusion of a control group in future studies may be warranted.

A resource utilization analysis of the RE-VERSE AD trial included 90 patients from the interim analysis (also registered under NCT02104947). The methods were those previously described in the RE-VERSE AD trial interim analysis. In regard to clinical outcomes, time to bleeding cessation could be assessed in 35 patients with uncontrolled bleeding (group A). The median time to cessation of bleeding was 11.4 hours, with 77% achieving cessation of bleeding within 24 hours of idarucizumab administration. The authors postulated that time to cessation of bleeding may not have been accurate in several participants due to the inability to visualize the site of bleeding. Group B consisted of 39 patients who received idarucizumab prior to surgery; their median time to surgery was 1.7 hours. Blood products or hemostatic agents were given to 63% of group A patients and 23% of group B patients. The most commonly utilized blood products were packed red blood cells (PRBC) and fresh frozen plasma (FFP). PRBCs were administered most frequently with a median volume of three units per patient infused. The median volume of FFP administration was two units per patient. Four patients received activated prothrombin complex concentrates. The median length of hospital stay for patients in both groups was seven days (range, one to 92 days). In group A, 17 patients had a documented intensive care unit (ICU) stay of at least one day; median ICU stay was four days (one to 44 days). The median length of stay in the ICU for group B was two days (one to 24 days).

**CASE REPORTS AND POST-MARKETING DATA**

Numerous case reports have been published since the approval of idarucizumab, as well as a retrospective national database review characterizing its use. Fifty-nine patient cases were documented between 2016 and 2017 reporting the use of idarucizumab: 18 cases for reversal due to uncontrolled major bleeding; 21 cases for reversal prior to surgery or intervention (e.g., lumbar puncture); 18 cases for reversal required prior to thrombolysis in stroke; and two cases with use of idarucizumab due to dabigatran overdose without major bleeding. Of the 59 patient cases, 94.8% reported successful reversal. Of these cases, 15 patients received additional products to achieve hemostasis. One patient developed an anaphylactic reaction after administration of the first idarucizumab dose but tolerated the second dose following pretreatment with steroids, epinephrine, and antihistamines; the patient was successfully reversed and survived. A few cases reported rebound of dabigatran levels after idarucizumab administration; however, dabigatran levels were not captured in all reports.

In a retrospective case-collection study performed using national reporting databases in Germany, 19 patients (median age, 78 years; 42% male) presenting with ischemic stroke and 12 patients (median age, 77 years; 50% male) presenting with intracranial hemorrhage received idarucizumab between January and August 2016. No bleeding complications were reported; 18 of the 19 stroke patients presented within the window to receive tissue plasminogen activator. Coagulation parameters normalized in all ischemic stroke patients where baseline data were available following administration of idarucizumab. In patients presenting with intracranial hemorrhage, 10 of the 12 patients had no hematoma growth after idarucizumab administration on follow-up computerized tomography scans. Two patients died, one from each group.

**STUDIES IN PROGRESS**

As expedited FDA approval of idarucizumab was contingent upon further adequate and well-controlled clinical trials to verify and describe clinical benefit, additional studies are being conducted to assess the safety and efficacy of idarucizumab. Seven additional studies pending commencement or publication of results were identified through the NCT database and are briefly reviewed here for objectives and study design. One study has been completed and is awaiting publication. One study has completed recruitment but is ongoing. Five studies are recruiting or awaiting recruitment per the NCT database.

Boehringer Ingelheim has conducted a study (NCT02831660) to assess drug-related adverse events following idarucizumab administration. This was a phase 3, interventional, single-arm, nonblinded compassionate-use study. Adult Japanese men and women were enrolled if they were taking dabigatran and had uncontrolled or life-threatening bleeding or a condition requiring emergency surgery where adequate hemostasis was required. Participants were excluded if bleeding was absent, considered minor, or could have been managed with standard supportive care. Participants were also excluded if the surgery or procedure was elective or if the risk of uncontrolled or unmanageable bleeding was considered low. Drug-related adverse events were tallied for up to 10 days following administration. The study was completed in September 2016, and results have yet to be reported.

Boehringer Ingelheim is conducting a phase 1, interventional, open-label study (NCT03086356) to assess the pharmacokinetics and pharmacodynamics of idarucizumab alone and in combination with dabigatran. Healthy adult Chinese men and women were enrolled. Exclusion criteria were extensive and exclude individuals with gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological, and hormonal disorders and those receiving concurrent medications that could not be discontinued prior to enrollment. Pharmacokinetic and pharmacodynamic parameters will be reported following idarucizumab administration alone and idarucizumab after dabigatran reaches steady state.
Evidence for Idarucizumab in the Reversal of Dabigatran: A Review

Boehringer Ingelheim is recruiting for a post-marketing study (NCT02946931) intended to assess the effectiveness and safety of idarucizumab in Japanese participants. This study will be an observational retrospective cohort study. Adult men and women will be eligible if they are prescribed idarucizumab. Exclusion criteria have yet to be defined. Any suspected adverse drug reactions, serious adverse events, or adverse events for important potential risks such as hypersensitivity and thrombotic events will be reported.

Cardioangiologisches Centrum Bethanien of Germany is recruiting participants for a study (NCT01722786) to assess in-hospital mortality up to 30 days after admission in participants taking oral anticoagulants. This study will be a prospective, observational, noninterventional, open-label, multicenter, case report registry analysis. Male and female participants 18 to 99 years of age receiving a direct oral anticoagulant (including dabigatran) or a vitamin K antagonist who have acute bleeding or who require urgent surgical intervention will be included in the registry. In addition to in-hospital mortality, the difference in outcomes in those receiving reversal agents compared with those not receiving reversal agents will be assessed. Reversal agents or antidotes will include various blood products, idarucizumab, vitamin K, desmopressin, tranexamic acid, and hemodialysis.

Boehringer Ingelheim is recruiting pediatric participants for a study (NCT02815670) to assess the safety of idarucizumab. This study will be a phase 2b/3, single-dose, open-label, uncontrolled safety trial. Male and female participants taking dabigatran (in the context of a clinical trial) up to 18 years of age will be enrolled if they experience overt bleeding or have a condition requiring emergency surgery where adequate hemostasis is required. Participants will be excluded if bleeding is absent or considered minor, if the risk of unmanageable bleeding is low, or if they weigh less than 2.5 kg. Drug-related adverse events, immunological reactions, development of treatment-emergent anti-idarucizumab antibodies, and all-cause mortality will be assessed.

Boehringer Ingelheim is conducting another study to assess the safety of idarucizumab in pediatric participants (NCT02798107) that has yet to begin recruitment. This study will be a noninterventional, observational chart review. Male and female participants up to 18 years of age will be included if they are given idarucizumab. Participants will be excluded if they are enrolled in an alternate idarucizumab or dabigatran clinical trial. Drug-related adverse events, thromboembolic events, hypersensitivity and anaphylactic reactions, and all-cause mortality will be assessed.

Boehringer Ingelheim has amended its post-marketing study for dabigatran in light of the approval of idarucizumab (NCT03175198); the study has yet to begin recruitment. This study will be an observational, retrospective cohort study. Any individual who has not received dabigatran in the past will be eligible. Exclusion criteria have yet to be defined. Incidence of adverse drug reactions will be reported. Per the NCT entry, “Even after the availability of idarucizumab, appropriate use of [dabigatran] will continue. The patient population who receive [dabigatran] and the safety profile of [dabigatran] is not expected to change.”

DISCUSSION

Idarucizumab, a humanized monoclonal antibody fragment, is the first reversal agent approved for the direct thrombin inhibitor dabigatran. The recommended dose of idarucizumab is 5 g and is supplied as two single-use vials, each containing idarucizumab 2.5 g/50 mL. It is administered intravenously as two separate 2.5-g doses for emergency surgical procedures or for rapid reversal of uncontrolled bleeding in dabigatran-treated patients. In addition to idarucizumab, supportive care for uncontrolled, life-threatening bleeding should include administration of hemostatic agents. There are no known significant drug interactions related to idarucizumab; however, patients should be monitored for coagulation parameter re-elevation and thromboembolic events. Common adverse effects of idarucizumab identified in clinical trials include headache, hypokalemia, delirium, constipation, and pneumonia. Some serious adverse events associated with idarucizumab include risk for hypersensitivity reactions, thromboembolism (although idarucizumab has not been shown to have procoagulant properties), re-elevation of coagulation parameters, and risk of serious reactions in patients with hereditary fructose intolerance due to sorbitol excipients. There are no controlled studies of idarucizumab’s use during pregnancy or lactation. The drug’s risk for causing fetal harm is unknown; idarucizumab’s ability to cross the placenta has not been measured. For patients with renal impairment, no dose adjustment is required. Studies have not been conducted in patients with hepatic impairment. The average wholesale price per package of two idarucizumab 2.5 g/50 mL vials is $4,200.

The trials included in this review report on the coagulation parameters TT, dTT, ECT, and aPTT. Boehringer Ingelheim recommends utilizing dTT over TT due to calibration available with dTT. Both dTT and TT correlate with dabigatran plasma concentrations (quantitative and specific): a normal dTT or TT indicates no anticoagulant effects due to dabigatran. An elevated aPTT has been used to determine the presence of excess coagulation due to dabigatran but is less sensitive than dTT (semiquantitative, semispecific). Direct thrombin inhibitor activity may also be measured specifically by ECT: An elevated ECT has been used to denote an increased risk of bleeding due to dabigatran and may be more sensitive at higher levels of dabigatran than dTT (quantitative and specific). Each of these parameters may not be available in all institutions. When considering the addition of a coagulation parameter at an institution, dTT may be the most clinically useful as it relates to dabigatran and the effect of idarucizumab.

The FDA and the Committee for Medicinal Products for Human Use of the European Medicines Agency have approved the use of idarucizumab to reverse the anticoagulant effects of dabigatran. Anticoagulants such as dabigatran are beneficial for reducing the risk of thromboembolic events, but in the setting of uncontrolled bleeding or urgent surgery, reversal is needed in dabigatran-treated patients. Idarucizumab is only useful for patients treated with dabigatran. In the future, head-to-head studies of idarucizumab versus alternate agents for the reversal of the anticoagulant effects of dabigatran would be beneficial in assessing the complete efficacy and safety profile of idarucizumab. In preclinical studies, ciraparantag (investigational, Perosphere, Inc.) demonstrated the potential to reverse
Evidence for Idarucizumab in the Reversal of Dabigatran: A Review

direct thrombin inhibitors, including dabigatran.11 As additional reversal agents for dabigatran become available, it is important to have a summary of the existing evidence for idarucizumab so that comparisons may be made among reversal agents.

REFERENCES

Evidence for Idarucizumab in the Reversal of Dabigatran: A Review


