Idarucizumab for the Reversal of Dabigatran

Michael Gottlieb, MD, RDMS*; Basem Khishfe, MD

*Corresponding Author. E-mail: MichaelGottliebMD@gmail.com, Twitter: @MGottliebMD.

0196-0644/$-see front matter

http://dx.doi.org/10.1016/j.annemergmed.2016.11.025

A **podcast** for this article is available at www.annemergmed.com.

[Ann Emerg Med. 2017;69:554-558.]

Editor's Note: *Emergency physicians must often make decisions about patient management without clear-cut data of sufficient quality to support clinical guidelines or evidence-based reviews. Topics in the Best Available Evidence section must be relevant to emergency physicians, are formally peer reviewed, and must have a sufficient literature base to draw a reasonable conclusion but not such a large literature base that a traditional "evidence-based" review, meta-analysis, or systematic review can be performed.*

INTRODUCTION

Dabigatran is a direct thrombin inhibitor used for preventing ischemic stroke and systemic embolization. It was approved by the Food and Drug Administration in 2010, with no antidote available. As with all anticoagulants, dabigatran increases the risk of bleeding. One study evaluating the use of dabigatran 150 mg received twice daily for atrial fibrillation demonstrated that 16% of patients had a bleeding episode during a 1-year period, with more than 1.5% having a life-threatening bleeding episode.[1]

Although heparin and warfarin have known reversal agents, the lack of an agent for dabigatran has prompted providers to use alternate approaches to treat life-threatening hemorrhage in patients receiving dabigatran. Hemostatic agents (eg, prothrombin complex concentrate, fresh frozen plasma, factor VII) have been suggested, but there have been concerns raised about their efficacy and safety (eg, thrombotic risk).[2,3] Hemodialysis has also been recommended, but can lead to critical delays in treatment and risk worsening of the hematoma.[4] Additionally, a rebound in dabigatran levels has been observed in patients with dabigatran-associated bleeding after receiving hemodialysis.[4]

Idarucizumab is a humanized monoclonal antibody fragment specifically directed at dabigatran that binds to the thrombin site with 350 times greater affinity than thrombin, resulting in near-irreversible binding until renal excretion.[5] It has a short half-life, allowing early resumption of anticoagulation after the episode resolves, and does not increase the risk of hypercoagulability.[6] After numerous animal studies,[5,7-10] several phase 1 studies,[6,11-13] and the interim results from a phase 3 trial,[14] idarucizumab was approved by the Food and Drug Administration[15] and the European Medicines Agency.[16] Recent guidelines from the Neurocritical Care Society and Society of Critical Care Medicine further support the use of this agent by recommending idarucizumab as a first-line agent for reversal of dabigatran-associated intracranial hemorrhage.[17]

The objective of this Best Available Evidence article is to provide a summary of the current evidence about the efficacy and safety of idarucizumab for dabigatran reversal in humans.

SEARCH STRATEGY

A PubMed search from 1946 to October 7, 2016, was performed with the key words and Medical Subject Headings "idarucizumab" or "Praxbind," with no limitations. The search yielded 135 results. Bibliographic references found in all relevant articles were examined to identify additional pertinent literature. Citations were independently reviewed by both authors. Only original, published, primary research articles assessing the efficacy of idarucizumab for reversal of dabigatran in humans were included. Case reports, case series, animal studies, and narrative summaries were excluded. We identified 5 original research articles that directly addressed our question.

ARTICLE SUMMARIES

Glund et al[11]

This was a phase 1, randomized, double-blind, placebo-controlled trial assessing the pharmacokinetic and pharmacodynamic aspects of idarucizumab. It was a single, ascending-dose study in which each group received a different dose of idarucizumab as an intravenous infusion. The study group consisted of healthy male volunteers aged

18 to 45 years and with a body mass index of 18.5 to 29.9 kg/m^2. Exclusion criteria included subjects with current illness or abnormal values for prothrombin time, activated partial thromboplastin time, or platelet count.

A total of 110 subjects were randomized in a 3:1 ratio. The subjects were divided into 13 groups. Twenty-five percent of the subjects in each group received placebo and 75% received idarucizumab. The subjects in each of the first 10 groups received a set amount of idarucizumab ranging from 20 mg to 8 g infused intravenously during 1 hour, whereas the subjects in each of the last 3 groups received 1, 2, or 4 g of idarucizumab infused intravenously during 5 minutes. Blood samples were collected at 21 points during the first 72 hours after administration to study the pharmacokinetics and pharmacodynamics of idarucizumab. Peak concentration was attained shortly after infusion, with a half-life ranging from 39 to 54 minutes. Idarucizumab infusion demonstrated no significant effect on diluted thrombin time, ecarin clotting time, thrombin time, activated partial thromboplastin time, or activated clotting time. Adverse events occurred at similar rates between the placebo and idarucizumab groups; 44.4% of subjects in the placebo group experienced an adverse event, whereas 36.1% of subjects receiving idarucizumab experienced one. The most common adverse events were headache, nasopharyngitis, back pain, and skin irritation. All adverse events were of mild intensity, except migraine, which was of moderate intensity and occurred in 2 subjects in the treatment group.

The authors concluded that administration of idarucizumab to healthy adult men (with no dabigatran in their system) had no effect on coagulation parameters or endogenous thrombin generation potential. No relationship was observed between dose of idarucizumab and frequency of adverse events. Idarucizumab was well tolerated at all administered doses, regardless of the infusion rate.

Glund et al[12]

This was a randomized, placebo-controlled, double-blind, phase 1 trial investigating idarucizumab in a group of healthy volunteers pretreated with dabigatran. Healthy male volunteers aged 18 to 45 years and with a body mass index of 18.5 to 29.9 kg/m^2 were enrolled. Patients were randomly assigned to 1 of 4 groups in a 3:1 ratio of idarucizumab to placebo. All participants received dabigatran 220 mg twice daily for 3 days, with a final single dose of 220 mg on the fourth day. One hour 55 minutes after receiving the last dose, corresponding to the expected peak dabigatran concentration, either idarucizumab or placebo was administered. Participants assigned to the idarucizumab group received either a dose of 1, 2, or 4 g as a 5-minute intravenous infusion or a dose of 5 g plus 2.5 g given as two 5-minute infusions 1 hour apart.

There were 47 patients completing the study, with 9 assigned to each of the 1-g, 2-g, or 5 g plus 2.5-g idarucizumab groups, 8 assigned to the 4-g idarucizumab group, and 12 assigned to the placebo group. Demographic characteristics were similar between groups. The primary endpoint was incidence of drug-related adverse events. The secondary endpoint was the measurement of reversal of diluted thrombin time, ecarin clotting time, thrombin time, activated partial thromboplastin time, activated clotting time, and endogenous thrombin potential. At least 1 adverse event was reported in 31 (66%) of the 47 participants. Of these participants, only 7 events were deemed to be drug related, with 1 episode of infusion-site erythema and 1 episode of epistaxis in the idarucizumab group, 1 hematoma in the placebo group, and 4 bleeding episodes (eg, hematuria, epistaxis) after receipt of dabigatran pretreatment but before receipt of the intervention. All of the adverse events were of mild intensity and did not lead to cessation of treatment. After infusion of idarucizumab, immediate and complete reversal of the dabigatran-induced elevations of diluted thrombin time, ecarin clotting time, activated partial thromboplastin time, activated clotting time, and thrombin time was reported for all idarucizumab-dose groups. Reversal was sustained with the 2-, 4-, and 5 g plus 2.5-g doses. After placebo treatment, diluted thrombin time decreased at a rate consistent with normal clearance of dabigatran from plasma.

The authors concluded that there was no clinically significant difference in the incidence or intensity of adverse events between groups. There was also no relation between idarucizumab dose and the frequency of adverse events observed. Idarucizumab demonstrated immediate reversal of dabigatran-related elevations of multiple coagulation parameters.

Glund et al[6]

This was a randomized, double-blind, crossover study that examined the pharmacokinetics, pharmacodynamics, and safety of idarucizumab for the reversal of dabigatran in volunteers who were elderly or had some degree of renal impairment. Forty-six subjects were studied, consisting of 12 middle-aged patients (45 to 64 years), 16 elderly patients (65 to 80 years), 12 with mild renal impairment (creatinine clearance of 60 to 90 mL/minute), and 6 with moderate renal impairment (creatinine clearance of 30 to

60 mL/minute). Subjects were pretreated with dabigatran 220 or 150 mg (in patients with renal impairment) twice daily for 4 days. Participants received either placebo or a dose of 1, 2, or 5 g, or 2 doses of 2.5 g given 1 hour apart. After a 6-day washout period, the groups were allocated to the opposite treatment (ie, idarucizumab or placebo).

Dabigatran-prolonged diluted thrombin time, ecarin clotting time, and activated partial thromboplastin time were all reversed to baseline after idarucizumab. There was no effect of age on pharmacokinetics. However, idarucizumab had decreased clearance and a prolonged half-life in patients with mild or moderate renal impairment. Dabigatran has also demonstrated prolonged half-life in patients with renal impairment. Overall, 31 subjects (67%) reported adverse events during the trial: 21 (46%) during pretreatment with dabigatran, 14 (30%) while receiving idarucizumab, and 12 (26%) while receiving placebo. All adverse events were of mild intensity and were not affected by idarucizumab dose, age, or degree of renal impairment.

The authors concluded that idarucizumab resulted in immediate and complete reversal of dabigatran-induced anticoagulation in this study. Age, sex, and renal function had no effect on the reversal of dabigatran-induced anticoagulation by idarucizumab. However, impaired renal function was associated with decreased clearance and a prolonged half-life of idarucizumab.

Glund et al[13]

This article investigated the restoration of dabigatran anticoagulation 24 hours after idarucizumab treatment, as well as the safety and effectiveness of a second idarucizumab treatment. There were 12 volunteers enrolled (6 men and 6 women aged 46 to 58 years, with creatinine clearances ranging from 81 to 127 mL/minute), who received dabigatran 220 mg twice a day for 3 days, with a single dose on day 4. Participants were then randomized to idarucizumab (2.5 or 5 g) or placebo, administered as a 5-minute intravenous infusion 1 hour 55 minutes after the final dabigatran dose. Dabigatran was restarted 24 hours after receipt of either idarucizumab or placebo and continued for 3 days. The anticoagulant effects of dabigatran and the reversal by idarucizumab were determined by the diluted thrombin time, ecarin clotting time, and activated partial thromboplastin time. Plasma concentrations of unbound dabigatran (representing active dabigatran) and idarucizumab were also measured.

Idarucizumab administration resulted in immediate reduction of dabigatran and normalization of the previously elevated diluted thrombin time, ecarin clotting time, and activated partial thromboplastin time. This was sustained for the entire observation period of 24 hours. Full reversal was achieved with both the 2.5- and 5-g idarucizumab doses. Reinitiation of dabigatran 220 mg twice a day after 24 hours led to similar levels of anticoagulation irrespective of previous treatment with idarucizumab or placebo.

The authors concluded that idarucizumab provides an option for rapid reversal of dabigatran-induced anticoagulation and allows reinitiation of dabigatran treatment 24 hours after a surgical intervention or after major bleeding to reduce subsequent thromboembolic risk.

Pollack et al[14]

This study was an interim analysis of a larger, prospective, cohort study assessing the efficacy and safety of idarucizumab in patients presenting with serious bleeding or the need for an urgent procedure. The study included adults aged 18 years or older who were receiving dabigatran and presented with either an overt, uncontrollable, or life-threatening bleeding event or who required surgery or other invasive procedures that could not be delayed for at least 8 hours or for which normal hemostasis was required. The primary endpoint was the maximum percentage reversal of anticoagulant effect of dabigatran (as measured by diluted thrombin time and ecarin clotting time) within 4 hours after administration of idarucizumab. Secondary endpoints included clinical hemostasis and adverse events.

Ninety patients who received idarucizumab were included in the study, consisting of 2 groups (51 patients with serious bleeding and 39 requiring an urgent procedure). The median age was 76.5 years and the median creatinine clearance was 58 mL/minute. The median time since the last dose of dabigatran was 15.4 hours. Among patients with serious bleeding, 18 had an intracranial hemorrhage, 20 had gastrointestinal bleeding, 9 had bleeding from trauma, and 11 had other causes of bleeding. Patients received 5 g of idarucizumab administered as 2 separate doses of 2.5 g given no more than 15 minutes apart. Among the 68 patients with an elevated diluted thrombin time and 81 patients with an elevated ecarin clotting time, the median maximum percentage reversal was 100%. Time to bleeding cessation was 11.4 hours among patients for whom this could be assessed. Among patients undergoing surgery or an invasive procedure, intraoperative hemostasis was reported in 33 (92%). There were 18 total deaths, although none were caused by the study medication. Twenty-one patients had serious adverse events, including the 18 deaths, 5 thrombotic events, and 2 gastrointestinal hemorrhages. Only 1 thrombotic event occurred within 72 hours after administration in a patient in whom anticoagulant treatment was not reinitiated.

The authors concluded that idarucizumab rapidly and completely reversed the anticoagulant effect of dabigatran in this single-cohort study. They also identified no safety concerns among the 90 patients receiving idarucizumab.

THE BOTTOM LINE

Idarucizumab is a direct antibody to dabigatran, with a high binding affinity in vitro, and has strong evidence from initial animal studies demonstrating improvement in coagulation parameters, blood loss, and mortality rates.[5,7-10] This has prompted further human studies, as outlined above, which have demonstrated decreased circulating dabigatran levels, improved bleeding parameters, improved hemostasis, and decreased bleeding during emergency procedures.[6,12-14] Additionally, idarucizumab has been demonstrated to have a low rate of drug-related adverse events and does not increase the risk of thrombosis.[11,12]

However, it is important to consider several limitations in regard to the above studies. Although the first 4 phase 1 studies assessed tolerability and coagulation parameters,[6,11-13] only 1 study actually assessed a clinically relevant outcome (ie, clinical hemostasis).[14] That study was not placebo controlled and clinical hemostasis was a secondary outcome. As their rationale for the study design, the authors stated that they believed it would be unethical to give these patients placebo when there is no known comparator and the patients have life-threatening bleeding.[14,18] However, without a placebo group, it is challenging to determine whether the outcomes are due to the study medication, cointerventions, or time itself. Furthermore, although the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study did demonstrate a complete reduction in blood dabigatran concentration to the lower limits of quantification and immediate correction of multiple coagulation parameters, the median time to bleeding cessation was 11.4 hours, and dabigatran levels became detectable in 6 patients at 12 hours and 16 patients at 24 hours, suggesting that hemostatic agents (eg, prothrombin complex concentrate, fresh frozen plasma, factor VII) may be valuable for immediate hemostasis and that a second dose of idarucizumab at 12 or 24 hours may be needed.[14] Additionally, the overall number of patients studied was small, comprising 305 total patients across all 5 studies. In the RE-VERSE AD trial, only 90 of the planned 300 patients were presented as part of the interim analysis.[14] It is possible that when the larger study is completed, the results will significantly differ. Furthermore, the decision to include 2 separate subgroups in the RE-VERSE AD trial (ie, patients with active bleeding and those requiring emergency surgery) broadens the external applicability at the expense of increasing clinical heterogeneity and further decreasing individual sample sizes. Given the short half-life of dabigatran, it is also important to consider the timing of the last dose because it is possible that dabigatran is no longer a contributing factor after several days. Although such funding is common for new medications, all of the studies were funded by the pharmaceutical company that developed both idarucizumab and dabigatran, which can increase the potential for bias. Finally, one should be aware that idarucizumab is expensive, with a single package costing $3,500 in the United States.[19,20]

In summary, the best available evidence is limited, and one must be cognizant of the existing data and weigh the risks and benefits when deciding whether to use idarucizumab for dabigatran-related bleeding. Often, the bleeding can be addressed by directed treatment and withholding of one or more doses of dabigatran. However, for life-threatening cases or when emergency surgery is necessary, one should consider idarucizumab as part of the reversal strategy.

Supervising editor: Richard C. Dart, MD, PhD

Author affiliations: From the Department of Emergency Medicine, Rush University Medical Center, Chicago, IL (Gottlieb); and the Department of Emergency Medicine, Mount Sinai Hospital, Chicago, IL (Khishfe).

Authorship: All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

REFERENCES

1. Connolly SJ, Ezekowitz MD, Yusuf S, et al. RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139-1151.
2. Alikhan R, Rayment R, Keeling D, et al. The acute management of haemorrhage, surgery and overdose in patients receiving dabigatran. *Emerg Med J*. 2014;31:163-168.
3. Honickel M, Braunschweig T, van Ryn J, et al. Prothrombin complex concentrate is effective in treating the anticoagulant effects of

dabigatran in a porcine polytrauma model. *Anesthesiology*. 2015;123:1350-1361.
4. Singh T, Maw TT, Henry BL, et al. Extracorporeal therapy for dabigatran removal in the treatment of acute bleeding: a single center experience. *Clin J Am Soc Nephrol*. 2013;8:1533-1539.
5. Schiele F, van Ryn J, Canada K, et al. A specific antidote for dabigatran: functional and structural characterization. *Blood*. 2013;121:3554-3562.
6. Glund S, Stangier J, van Ryn J, et al. Effect of age and renal function on idarucizumab pharmacokinetics and idarucizumab-mediated reversal of dabigatran anticoagulant activity in a randomized, double-blind, crossover phase Ib study. *Clin Pharmacokinet*. 2016; http://dx.doi.org/10.1007/s40262-016-0417-0.
7. Grottke O, van Ryn J, Spronk HM, et al. Prothrombin complex concentrates and a specific antidote to dabigatran are effective ex-vivo in reversing the effects of dabigatran in an anticoagulation/liver trauma experimental model. *Crit Care*. 2014;18:R27.
8. Grottke O, Honickel M, van Ryn J, et al. Idarucizumab, a specific dabigatran reversal agent, reduces blood loss in a porcine model of trauma with dabigatran anticoagulation. *J Am Coll Cardiol*. 2015;66:1518-1519.
9. Honickel M, Treutler S, van Ryn J, et al. Reversal of dabigatran anticoagulation ex vivo: porcine study comparing prothrombin complex concentrates and idarucizumab. *Thromb Haemost*. 2015;113:728-740.
10. Na SY, Mracsko E, van Ryn J, et al. Idarucizumab improves outcome in murine brain hemorrhage related to dabigatran. *Ann Neurol*. 2015;78:137-141.
11. Glund S, Moschetti V, Norris S, et al. A randomised study in healthy volunteers to investigate the safety, tolerability and pharmacokinetics of idarucizumab, a specific antidote to dabigatran. *Thromb Haemost*. 2015;113:943-951.
12. Glund S, Stangier J, Schmohl M, et al. Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial. *Lancet*. 2015;386:680-690.
13. Glund S, Stangier J, van Ryn J, et al. Restarting dabigatran etexilate 24 h after reversal with idarucizumab and redosing idarucizumab in healthy volunteers. *J Am Coll Cardiol*. 2016;67:1654-1656.
14. Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373:511-520.
15. Food and Drug Administration. Idarucizumab. Available at: http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm467396.htm. Accessed October 7, 2016.
16. European Medicines Agency. EPAR summary for the public, Praxbind. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003986/WC500197464.pdf. Accessed October 7, 2016.
17. Frontera JA, Lewin JJ 3rd, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care*. 2016;24:6-46.
18. Pollack CV Jr, Reilly PA, Bernstein R, et al. Design and rationale for RE-VERSE AD: a phase 3 study of idarucizumab, a specific reversal agent for dabigatran. *Thromb Haemost*. 2015;114:198-205.
19. Eikelboom JW, Quinlan DJ, van Ryn J, et al. Idarucizumab: the antidote for reversal of dabigatran. *Circulation*. 2015;132:2412-2422.
20. Elia J. Dabigatran-reversal agent price set. Available at: http://www.jwatch.org/fw110754/2015/10/20/dabigatran-reversal-agent-price-set. Accessed October 7, 2016.