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Review

Evidence Supporting Idarucizumab for the Reversal of Dabigatran

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ABSTRACT

Idarucizumab is a monoclonal antibody fragment specifically targeted to dabigatran. It has demonstrated prompt and durable reversal of the anticoagulant effects of dabigatran in animal studies and phase 1 studies of young, elderly, and renally impaired volunteers. Although elective invasive procedures and most bleeding complications in dabigatran-treated patients can be managed by temporarily stopping dabigatran therapy and using supportive measures, there are rare clinical situations that require urgent reversal of the anticoagulant effect of dabigatran. The effectiveness and safety of 5 g of intravenous idarucizumab is being investigated in a prospective, open-label, single-cohort study in patients with serious bleeding or in those requiring an urgent procedure. In an interim analysis of the first 90 participants, idarucizumab rapidly and completely reversed the anticoagulant activity of dabigatran in 88%-98% of participants, and there were no safety concerns, with no deaths or serious adverse events being attributable to idarucizumab. Supported by these interim results, idarucizumab has been approved in the United States and the European Union for use when reversal of the anticoagulant effects of dabigatran is needed for emergency surgery/urgent procedures or in patients with life-threatening or uncontrolled bleeding. Clinical use of idarucizumab should follow the same processes as patient enrollment in this study, which is projected to be completed in 2016. The outcomes achieved with this specific reversal agent are likely to be of continued interest to treating physicians.

Dabigatran is a direct oral anticoagulant (DOAC) that inhibits the function of thrombin without dependence on vitamin K antagonism [1]. In the penultimate step of the normal coagulation cascade, thrombin catalyzes the conversion of fibrinogen to fibrin, resulting in clot stabilization. Patients treated with dabigatran have normal synthesis and levels of thrombin, but competitive inhibition of thrombin activity by dabigatran effectively prevents completion of the coagulation process. This mechanism of action has been harnessed to provide effective anticoagulation in patients with nonvalvular atrial fibrillation (NVAF) to reduce the risk of ischemic stroke and systemic embolization, and in patients with or at risk of venous thromboembolic disease [1]. In clinical trials, dabigatran has been associated with similar or reduced rates of the key safety end points of major and intracranial bleeding, depending on the dose and the indication, as well as similar rates of fatal bleeding compared with vitamin K antagonists (VKAs), such as warfarin [2-4]. Nonetheless, some risk of bleeding unavoidably accompanies the decision to use an anticoagulant in a patient, especially older patients with the comorbidities that typically accompany NVAF. Most bleeding complications associated with the use of dabigatran are minor or at worst moderate in severity and can be managed by simply temporarily withholding the drug and supporting the patient with general physical or pharmacologic hemostatic measures, replacement of shed blood, and observation [5,6]. The short half-life of dabigatran relative to VKAs, which inhibit the synthesis of multiple coagulation factors over days, is an important consideration in these strategies [1,7]. Typically, the effect of dabigatran–in the absence of acute renal failure or acute overdose–dissipates within 12 hours of a 150-mg dose, with steady-state dabigatran plasma concentrations decreasing to <100 ng/mL and activated partial thromboplastin time to approximately 1.5 times baseline levels in that interval [8,9].

Similarly, the short half-life of dabigatran facilitates the timing of elective invasive procedures. Withholding the drug for 1-5 days, depending on renal status and the magnitude of the bleeding risk associated with the procedure, allows the intervention to be accomplished with restored hemostasis [1]. Because the onset of action of dabigatran is–like its offset–rapid [10], re-initiation of anticoagulation can generally be accomplished as soon as postprocedural hemostasis is restored.

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In rare clinical situations, these general measures are insufficient to address bleeding complications or bleeding concerns in patients requiring emergent invasive procedures in the context of anticoagulation with dabigatran. In cases of uncontrolled or life-threatening hemorrhage or when an invasive procedure cannot be delayed long enough for natural decay of the anticoagulant effect of dabigatran, more definitive reversal of anticoagulation is desirable. If dabigatran was ingested within the preceding 2-3 hours, oral administration of activated charcoal may limit absorption of the most recent dose [8,11,12]. Elimination of dabigatran–which is 80% renal–can be maintained by vigorous fluid administration and resulting diuresis [1,5,8]. However, these approaches are of limited impact in most emergency situations. Unlike the other DOACs, dabigatran can be removed rather effectively from the circulation by hemodialysis, although data supporting this approach are limited [1,13,14]. Unfortunately, this is a cumbersome and logistically challenging approach in the emergency situation, in patients without established dialysis access.

Such patients, therefore, require urgent reversal of the anticoagulant effect of dabigatran (ie, normalization of thrombin activity in the presence of an effective antithrombin agent). It is not possible to administer pure thrombin to patients to overcome the competitive blockade of dabigatran. Exogenous thrombin can be given in combination with other coagulation factors using fresh frozen plasma or 3- or 4-factor prothrombin complex concentrates [12]. However, because levels of thrombin and other coagulation factors are presumably normal in dabigatrantreated patients, this approach introduces a concern for iatrogenic creation of a hypercoagulable or prothrombotic state, as has been demonstrated in an animal study [15], potentially trading one worrisome situation for another.

The preferred approach in such situations, therefore, would be to use a specific reversal agent to remove the anticoagulant effect of dabigatran, disinhibiting native thrombin and returning the patient to his or her baseline coagulation status. An ideal reversal agent would be specific to the administered anticoagulant, engage in no other drugedrug interactions, have no inherent pro- or anticoagulant effect, have rapid and predictable onset of action, be readily prepared and administered, and be dosed in a simple fashion. Additionally, it should have a sufficiently durable effect that in cases of bleeding, coagulation can be maintained while definitive source management is being accomplished, and in preprocedural patients, the procedure can be completed without the additional bleeding risk wrought by anticoagulation.

Idarucizumab meets these criteria for patients treated with dabigatran who require immediate anticoagulation reversal [16]. Idarucizumab is a humanized monoclonal antibody fragment specifically directed at dabigatran [17]. The active site of idarucizumab is structurally similar to the dabigatran binding site of thrombin, although the antibody lacks enzymatic activity. Idarucizumab binds dabigatran with approximately 350 times the avidity with which thrombin binds dabigatran. As such, in sufficient doses, idarucizumab readily displaces dabigatran from thrombin and tightly binds it, thereby allowing fibrin formation to ensue normally. The antibody can bind free and thrombinbound dabigatran, as well as extravascular dabigatran, as it enters the central compartment after changes in the concentration gradient [18], thus preventing the anticoagulant from the periphery from subsequent binding to thrombin.

The interaction between idarucizumab and dabigatran is characterized by an extraordinarily rapid on rate (measured in milliseconds) and a very slow off rate, consistent with the high-affinity binding typical of an antibodyeantigen bond [17]. Binding is effectively irreversible, with very little dissociation of the idarucizumabedabigatran complex before renal excretion, even in patients with renal compromise [16-18]. When infused intravenously, peak plasma concentrations of idarucizumab are achieved almost immediately, allowing prompt binding to dabigatran [19]. The key clinical findings from volunteer studies of idarucizumab are reviewed in detail in the review article by Reilly et al. within this special issue and are summarized in Table [20].

Table
Key Clinical Phase 1 Findings with Idarucizumab in Healthy Volunteers

Objective	No. of Subjects	Findings
Reversal of anticoagulant effect of dabigatran in healthy young (age 18-64 y) volunteers	59	Dose-dependent decrease in ECT, dTT, aPTT, TT, and ACT
Reversal of anticoagulant effect of dabigatran in elderly (age 65-80 y) volunteers	16	Dose-dependent decrease in ECT, dTT, aPTT, TT, and ACT
Reversal of anticoagulant effect of dabigatran in subjects with creatinine clearance 44–79 mL/min	18	Dose-dependent decrease in ECT, dTT, aPTT, TT, and ACT
Pharmacokinetics of idarucizumab alone in healthy volunteers	110	Initial $t_{1/2}$ ~45 minutes
Pharmacokinetics of dabigatran in volunteers given idarucizumab	93	Unbound dabigatran concentrations determined using HPLC/MS parallel results of clotting tests
Re-initiation of dabigatran 24 h after idarucizumab administration	12	Full anticoagulant effect of dabigatran 24 h after idarucizumab administration
Re-exposure to idarucizumab 2 mo after initial administration	6	No hypersensitivity, 1 subject developed new anti-drug antibodies
Evaluation of potential procoagulant activity of idarucizumab	104	No increase in thrombin generation compared with placebo
Safety of idarucizumab	203	No dose-related adverse events, no serious adverse events

See references [19,22].
ACT = activated clotting time; aPTT = activated partial thromboplastin time; dTT = dilute thrombin time; ECT = ecarin clotting time; HPLC/MS = high-performance liquid chromatography/tandem mass spectrometry.
Reproduced with permission from Pollack et al. [21]

Animal studies of idarucizumab likewise showed a prompt and durable reversal of the anticoagulant effects of dabigatran, without prothrombotic effect [17,23]. In addition, phase I studies showed only a low level of antibody formation after single or repeat exposure to idarucizumab [16,18,19]. No severe or serious drug-related adverse events were identified [16,18,19,22]. The only side effect was a transient, doserelated increase in urinary protein levels, which was to be expected from the excretion of the antigeneantibody complexes via a saturable renal protein transporter [19].

1. Re-Verse AD, A Study in Patients

From all indications, then, idarucizumab seemed to be a promising specific reversal agent for dabigatran. A clinical study in patients to support registration was developed with input from various regulatory bodies, and ultimately the following key decisions were made concerning the design of this study of idarucizumab. An open-label, single-cohort design was selected. Although it was of course recognized, that a blinded, controlled study would represent better "science," this approach was not deemed feasible or appropriate for a study of idarucizumab. Blinded, placebocontrolled studies had already been conducted in healthy volunteers, demonstrating safety and efficacy according to reversal of clotting tests. The drug seemed to be so effective in these studies that it was not thought ethical to enroll a placebo-treated group. In addition, such a controlled study, with clinical outcomes as the primary end point, would require thousands of patients and could take 5-10 years to complete owing to the difficulties of finding, consenting, and treating eligible dabigatran-treated patients as soon as they appeared in emergency departments. Likewise, there seemed to be no rational comparator control, because there is no standard treatment for dabigatran-associated bleeding, and no studies have evaluated the effects of other reversal or repletion strategies for

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