

REVIEW

Current Data on the Role of Specific Antidotes for the Reversal of Non-Vitamin K Oral Anticoagulant Action*Sokratis Pastromas, MD**Henry Dunant Hospital, Athens, Greece**E-mail: spastromas@yahoo.gr***Abstract**

The increasing use of the non-vitamin K oral anticoagulants during the recent years was associated with the need of development of targeted agents that could reverse the anticoagulative activity in cases of severe bleeding episodes or urgent high risk operations. Thus, several reversal agents are currently in development and the early results seem promising. Idarucizumab is a monoclonal antibody that can immediately and specifically reverse dabigatran action. Andexanet alfa is a recombinant modified factor Xa that can bind and reverse factor Xa inhibitors, including rivaroxaban, apixaban and edoxaban, and low molecular weight heparin. Aripazine is a universal reversal agent small molecule that can reverse the action of factor Xa inhibitors, unfractionated and low molecular weight heparin and possibly dabigatran. Currently, only idarucizumab has received approval from the United States Food and drug Administration for the reversal of the dabigatran. *Rhythmos 2016;11(3):70-72.*

Key Words: non-vitamin-K anticoagulants; oral anticoagulants; dabigatran; rivaroxaban; apixaban; antidotes; idarucizumab; andexanet alfa; aripazine

Abbreviations: AF = atrial fibrillation; dTT = dilute thrombin time; ECT = ecarin-clotting time; FDA = Food and Drug Administration; INR = International Normalized Ratio; LMWH = low molecular weight heparin; NOACs = non-vitamin K oral anticoagulants; VKAs = vitamin K antagonists

Introduction

For many years vitamin K antagonists (VKAs), such as warfarin and acenocoumarol, were the only clinically available anticoagulant agents for patients with atrial fibrillation (AF) or venous thromboembolism.¹ During the last several years, the use of non-vitamin K oral anticoagulants (NOACs), both direct factor Xa and thrombin inhibitors, in clinical practice is constantly growing since their effectiveness and safety have been proved to be similar or better compared to VKAs.² A major issue regarding the safety of NOACs is the reversal of their anticoagulation effect in emergency situations, such as a major bleeding event.³ Considering the non-availability of a quantitative measurement test for the extent of the anticoagulation effect of NOACs like the International Normalized Ratio (INR), there is great interest in developing novel agents that reverse the anticoagulative effect of NOACs. In patients receiving NOACs only one clotting factor is blocked, either thrombin or factor Xa,

although the plasma levels are within normal range. Currently only one specific reversal agent, idarucizumab, has been granted approval by the United States Food and Drug Administration (FDA), since there are data from clinical trials proving its effectiveness in the complete reversal of dabigatran action;^{4,5} while for andexanet alfa, FDA has accepted the Biologics License Application (BLA) for filing under a priority review. Andexanet alfa is designed to reverse the anticoagulant activity of factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban). Moreover, Aripazine (Ciraparantag) is the agent which has been tested less in clinical trials compared to the other agents.⁶

Idarucizumab

Idarucizumab (Praxbind[®], Boehringer Ingelheim, Inc., Ridgefield, CT, USA) is a humanized monoclonal antibody which binds both free and thrombin-bound dabigatran (**Table 1**). It has a high affinity for dabigatran about 350 times stronger than the affinity for thrombin and can reverse the anticoagulation effect at a 1:1 stoichiometric ratio in vivo and in vitro.⁷ Idarucizumab is administrated by intravenous infusion, the half time is ~45 min and finally the bound complex is eliminated mainly by renal excretion. Although idarucizumab has similar structure with thrombin, it does not have any prothrombotic activity.⁸ The estimation of its reversal effect can be obtained by measuring dilute thrombin time (dTT) and ecarin-clotting time (ECT), which are related with the unbound dabigatran concentration. In healthy volunteers who participated in a double blinded placebo controlled phase II trial, no serious adverse events have been reported.⁸ Only minor adverse events, such as erythema at the site of the drug administration, erythema and flu-like symptoms have been reported. The administration of 1, 2 and 4 g over 5 min resulted in a reduction of dTT by 74%, 94% and 98%, respectively. Dabigatran reversal was maintained over 72 hours with 2 g or higher doses of idarucizumab.⁹

Idarucizumab has been tested in a multicenter prospective single cohort study (RE-VERSE AD study) at a dose of 5 g in patients who had serious bleeding or required an urgent procedure. The primary endpoint was the maximum percentage reversal effect of the dabigatran within 4 hours after the infusion of the idarucizumab as assessed by the dTT or ecarin clotting time. An interim analysis was recently published which included 90 patients who received idarucizumab and the median time of the bleeding cessation was 11.4 hours in patients with serious bleeding. In patients who underwent an urgent procedure, intraoperative hemostasis was achieved in 92% of the cases. The mortality rate was reported at 20% with half of the occurred deaths due to the primary cause of

hospitalization. Only one thrombotic event occurred within 72 hours after idarucizumab administration in a patient in whom anticoagulant therapy had not been restarted.⁴ Data derived from 123 patients enrolled in the same study (RE-VERSE AD) were presented at the American College of Cardiology Congress on April 2016 and did not differ significantly from those published previously regarding the effectiveness and safety rates.¹⁰ Taking into account the results of the clinical trials of idarucizumab regarding its effectiveness and safety, in October 2015, the FDA approved its clinical use for cases requiring emergency reversal of dabigatran anticoagulation activity.¹¹

Andexanet alpha

Andexanet alpha is a universal reversal agent that is designed to neutralize the anticoagulant effects of both direct and indirect factor Xa inhibitors (Table 1). It acts as a recombinant modified human Factor Xa decoy protein that binds to factor Xa inhibitors with high affinity and a 1:1 stoichiometric ratio. Moreover, it binds both low molecular weight heparin (LMWH) and fondaparinux-activated antithrombin III which act as indirect Xa inhibitors.¹² Although andexanet alpha has similar properties to factor Xa, it has not been shown to have procoagulant catalytic activity. This is assessed by measurement of thrombin generation and anti-factor Xa activity which reflects the anticoagulant activity.^{13,14} In patients who were under rivaroxaban treatment with 20 mg daily for 6 days, the administration of 210 and 420 mg of andexanet alpha produced a reduction of factor Xa activity by 20% and 53% respectively without any serious adverse events. The discontinuation of andexanet alpha infusion resulted in normalization of factor Xa levels 2 hours later.¹⁵

The clinical effectiveness of the drug was tested in the phase III ANNEXA trials which enrolled healthy subjects anticoagulated either with apixaban (ANNEXA-A) or rivaroxaban (ANNEXA-R). Anti-factor Xa activity of apixaban and rivaroxaban was immediately reversed after a bolus injection of 400 mg and 800 mg, respectively. Thrombin generation was normalized without a rebound effect in the andexanet alfa group and there were no thrombotic events in these trials. The reversal effect was maintained for 2 hours after a bolus injection and for a longer duration with a continuous infusion of 4 mg/min for rivaroxaban and 8 mg/min for apixaban.⁵ An ongoing prospective open label trial is evaluating the hemostatic efficacy of andexanet alfa in patients receiving a factor Xa inhibitor who are experiencing an acute major bleed.¹⁶

Aripazine (Ciraparantag/PER977)

Aripazine is a synthetic molecule that can bind and reverse the action of unfractionated and low molecular

weight heparins, direct factor Xa inhibitors and direct thrombin inhibitors in a dose-dependent manner⁶ (Table 1). In a preliminary study which enrolled 80 healthy subjects, who received orally 60 mg of edoxaban, the infusion of 100-300 mg of aripazine restored hemostasis within 10-30 minutes with a sustained efficacy for 24 hours. In the placebo arm of the study the clotting time reached baseline levels after 12–15 hours.⁶ Data from large scale clinical trials are scarce and moreover the exact mechanism of action is not yet completely understood. Phase III clinical trials especially with edoxaban are underway.¹⁷

Conclusion

The development of specific antidotes for NOAC reversal augments the safety for patients who suffer from serious bleeding or undergo an urgent operation related to high bleeding risk.¹⁸ The fact is that most bleeding episodes can be managed by interruption of NOAC therapy and/or supportive measures. Currently, only idarucizumab has been approved by FDA targeting dabigatran action reversal but in the near future more agents with a universal action are likely to receive approval. The high cost of those reversal agents requires a thorough assessment in order to select eligible patients who will benefit from the use of these drugs.

Table 1. Data regarding the effectiveness and the safety of the three reversal agents

Drug	Mechanism of action	Indicated dose	Time to reversal	Possible adverse events
<i>Idarucizumab</i>	Binds free & thrombin-bound dabigatran	5 g (2.5 g x 2) i.v. bolus within 15 min	dTT & eCT normalize after first infusion Median time to bleeding cessation 11.4 h	Skin irritation, headache No prothrombotic effect
<i>Andexanet alpha</i>	Binds factor Xa inhibitors: apixaban, rivaroxaban & edoxaban	400 mg iv bolus ± 2 h i.v. (4 mg/min)	Mean 94±2% decrease in anti fXa activity after 2-5min Reversal activity persists 1–2 hours	No prothrombotic effect
<i>Aripazine (Ciraparantag)</i>	Universal reversal agent, binds direct thrombin & Xa inhibitors & unfractionated & LMW heparin	100 mg single i.v dose	30 min: restoration of wBCT & mean fibrin diameter	Facial flushing, dysgeusia (scarce data) No prothrombotic effect

dTT = dilute thrombin time; eCT = ecarin clotting time; fXa = factor Xa; LMWH = low molecular weight heparin; wBCT = whole blood clotting time

REFERENCES

1. Mueller RL, Scheidt S. History of drugs for thrombotic disease. Discovery, development, and directions for the future. *Circulation* 1994;89:432–449.
2. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383:955–962
3. van der Hulle T, Kooiman J, Den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. *J Thromb Haemost* 2014;12:320–328.
4. Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for Dabigatran Reversal. *N Engl J Med* 2015;373:511-520.
5. Siegal DM, Curnutte JT, Connolly SJ, Lu G, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. *N Engl J Med* 2015 ;373:2413-2424
6. Ansell JE, Bakhru SH, Laulicht BE, et al. Use of PER977 to reverse the anticoagulant effect of edoxaban. *N Engl J Med* 2014, 371:2141-2142.
7. Schiele F, van Ryn J, Canada K, Newsome C, Sepulveda E, Park J, et al. A specific antidote for dabigatran: functional and structural characterization. *Blood* 2013;121:3554–3562.
8. 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.
9. 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.
10. Pollack C, Reilly P, Eikelboom J, et al. Idarucizumab for reversal of the anticoagulant effects of dabigatran in patients in an emergency setting of major bleeding, urgent surgery, or interventions. *J Am Coll Cardiol* 2016;67(13_S):664.
11. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm467300.htm>
12. Lu G, DeGuzman FR, Hollenbach SJ. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. *Nat Med* 2013;19: 446–451.
13. Crowther M., Lu G, Conley P.B., Reversal of factor Xa inhibitors-induced anticoagulation in healthy subjects by andexanet alfa. *Crit Care Med* 2014;42: A1469-A1469.
14. Lu G, Lin J, Coffey G, Curnutte JT, Conley PB. Interaction of andexanet alfa, a universal antidote to fXA inhibitors, with tissue factor pathway inhibitor enhances reversal of fXA inhibitor-induced anticoagulation. *J Thromb Haemost* 2015;13:634–635.
15. Crowther M, Vandana M, Michael K, et al. A phase 2 randomized, double-blind, placebo-controlled trial demonstrating reversal of rivaroxaban induced anticoagulation in healthy subjects by andexanet alfa (PRT064445), an antidote for fxa inhibitors (Abstract). *Blood* 2013;122:3636.
16. <https://clinicaltrials.gov/ct2/show/NCT02329327?term=andexanet+alfa&rank=3>
17. <https://clinicaltrials.gov/ct2/show/NCT02207257?term=PER977&rank=3>
18. Manolis AS, Melita H. Management of major bleeding with the non-vitamin K oral anticoagulants: the role of antidotes. *Rhythmos* 2016;11:1-7.