Current Evidence for Pharmacologic Reversal using Direct Oral Anticoagulants: What's New?

Running title: Changing Horizon for Reversal of DOACs

Shujuan Zhao[1], Xuejiao Hong[1], Jingjing Cao[1], Jing Zhang[2], Song Du[2], and Peizhi Ma[1*].

[1] Department of Pharmacy, People's Hospital of Henan Province, Zhengzhou, Henan 450003, China

[2] Department of Cardiovascular Medicine, People's Hospital of Henan Province, Zhengzhou, Henan 450003, China

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Requests for reprints: Peizhi Ma, Department of Pharmacy, People's Hospital of Henan Province, Zhengzhou, Henan 450003, China; 49800425@qq.com

Abstract

The use of direct oral anticoagulants (DOACs) is becoming increasingly common in clinical practice and has addressed many issues related to Vitamin K-dependent antagonists (VKAs). However, the lack of reversal in life-threatening situations raises concerns regarding patient safety. Thus, current research is aimed at developing reversal agents that can safely neutralize the effects of anticoagulants. In this brief article, we present the design, mechanisms of action, animal models, clinical trials, and current evidence supporting the use of these emerging reversal agents. Idarucizumab and andexanet alfa have been approved by the U.S. Food and Drug Administration (FDA), while others are in clinical trials and may soon be available on the market. These reversal agents allow a prominent step towards the widespread use of DOACs and contribute to the general management of anticoagulation and patient safety.

Keywords: Direct oral anticoagulants; Bleeding; Idarucizumab; Andexanet alfa; Ciraparantag

1. Introduction

Vitamin K-dependent antagonists (VKAs), such as warfarin, have been the only oral anticoagulants available for more than 50 years. However, clinical management of VKAs is difficult due to their narrow therapeutic index, which requires careful monitoring of the international normalized ratio (INR), as well as drug-drug and dietary interactions [1]. Since 2008, newer oral anticoagulants, also known as direct oral anticoagulants (DOACs), have emerged in North America, Europe, Asia, and elsewhere. Currently, DOACs include either the direct thrombin inhibitor (dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban and edoxaban). DOACs have been approved for the prevention of embolic stroke in patients with non-valvular atrial fibrillation (NVAF), as well as for the treatment and secondary prevention of venous thromboembolism (VTE) and prevention of VTE after major orthopedic surgery [2]. DOACs have been shown to have better efficacy and several advantages compared to warfarin, such as a quick onset of action, predictable pharmacodynamics, less drug interactions, less frequent monitoring, and decreased bleeding tendencies [3].

Notably, compared to VKAs, DOACs have been associated with lower rates of intracranial hemorrhage [4]. However, there is still some risk of bleeding with DOACs that cannot be ignored [5,6]. In clinical trials, DOACs confer higher rates of gastrointestinal bleeding, especially with dabigatran (150 mg b.i.d.), rivaroxaban, and edoxaban (60 mg o.d.) [7,8,9]. In addition, apixaban and rivaroxaban are associated with excessive menstrual bleeding [10]. With the short half-life and predictable pharmacokinetics of DOACs, bleeding can be resolved by cessation of anticoagulation while offering standard supportive measures [11]. Patients who require urgent surgery or suffer from serious bleeding due to accidents or traumas may need prompt reversal of the anticoagulation effects of DOACs. Intracranial hemorrhage increases the

risk of mortality and morbidity, necessitating the development of effective reversal agents. As such, there has been increased research on specific reversal agents. In this brief article, the clinical progress of DOACs-specific reversal agents will be discussed.

2. DOACs-specific reversal agents

Three specific reversal agents of DOACs - idarucizumab, andexanet alfa, and ciraparantag - are in different stages of development. Idarucizumab (Boehringer Ingelheim International GmbH, Ingelheim, Germany) acts as a reversal agent for dabigatran and has been approved by the U.S. Food and Drug Administration (FDA) and by the European Medicine Association (EMA). Soon, idarucizumab will also be approved by other national institutions worldwide. Andexanet alfa (r-Antidote, Portola Pharmaceuticals, Inc, South San Francisco, Calif) is a reversal agent that specifically binds to rivaroxaban, apixaban, and edoxaban, and was approved by the FDA in 2018. Ciraparantag (Perosphere Inc, Danbury, Conn), a general reversal agent that is active against both direct and indirect factor Xa inhibitors, as well as factor IIa inhibitors, is still under development [12,13,14]. The sites of action for these reversal agents are shown in Figure 1.

2.1 Idarucizumab (Praxbind)

Idarucizumab was the first FDA approved dabigatran-specific reversal agent. Idarucizumab is a humanized monoclonal antibody fragment that is structurally similar to thrombin, particularly at the dabigatran-binding site. Therefore, it is ineffective at reversing other anticoagulants. Unlike thrombin, idarucizumab lacks enzymatic activity, but it binds to dabigatran with an affinity that is ~350 times stronger than thrombin [15]. The mechanism of

action for idarucizumab is presented in Figure 2.

Animal models showed that idarucizumab can rapidly and dose-dependently reverse the effects of dabigatran for both internal and external bleeding [15, 16]. In healthy volunteers and renally impaired subjects, intravenous infusion of different doses of idarucizumab led to sustained reversal of dabigatran anticoagulant activity within 5 min [17, 18]. Remarkably, idarucizumab had no effect on coagulation parameters or endogenous thrombin potential when administered to dabigatran-naïve subjects, indicating that idarucizumab lacks intrinsically prothrombotic properties. Furthermore, the anticoagulant effect of dabigatran was restored 24 h after the last dose of idarucizumab [18].

The promising results of idarucizumab's risk-benefit profile supported further development of idarucizumab in the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE-AD, NCT02104947) phase III trial [19]. The study enrolled 503 patients from 173 sites (out of 369 initial sites) for the treatment of dabigatran. Group A included 301 patients with uncontrollable or life-threatening bleeding, and group B included 202 patients requiring surgery or other invasive procedures that could not be delayed for more than 8 h. All patients received a total of 5 g intravenous idarucizumab, administered as two 2.5 g doses, each given as a rapid infusion no more than 15 minutes apart. This dose was chosen due to its ability to reverse the total body load of dabigatran that correlated with the 99th percentile of the dabigatran levels measured in the RE-LY trial [20]. The study population consisted mainly of elderly patients (median age 78 years) with coexisting conditions, and more than 95% of the cases were treated for NVAF (95%). In group A, 137 (45.5%) patients had gastrointestinal bleeding, 98 (32.6%) patients had intracranial hemorrhage, and 78 (25.9%) patients had post-traumatic bleeding; the bleeding stopped with a median time of 2.5 hours after idarucizumab administration. In group B, 197 (97.5%) patients

required surgery or intervention. The median time from the first infusion to the initiation of the urgent surgery procedure was 1.6 hours, and periprocedural management of hemostasis was normal in 93.4% of the patients. Among both groups, 91.7% (276 in group A and 185 in group B) of the patients had a prolonged baseline diluted thrombin time (dTT) or ecarin clotting time (ECT) and were placed on primary efficacy analysis. The median maximum percentage reversal within 4 hours after idarucizumab administration was 100% (95% confidence interval, 100 to 100), based on either the dTT or the ECT. At 90 days, thrombotic events occurred in 34 of the 503 patients (6.8%; 19 in group A and 15 in group B), and the assessed mortality rate was 18.8% and 18.9% in groups A and B, respectively. Antithrombotic therapy was initiated in 72.8% of the patients in group A (mean of 13.2 days) and 90.1% of the patients in group B (mean of 3.5 days) during the 90-day follow-up. There were no serious safety concerns, and most events occurred as a worsening of the index event or coexistence. There did not appear to be any consistent pattern across the data.

Following these clinical trials, idarucizumab was subsequently approved by the FDA in October 2015 for use in dabigatran reversal in patients requiring emergency surgery or urgent situations and in those with life-threatening or uncontrolled bleeding [21]. In the same year, the EMA granted accelerated approval for idarucizumab [22]. Over the next three years, idarucizumab was scheduled to become available in most countries. As of June 2018, dabigatran has obtained regulatory approval from the China Food and Drug Administration (CFDA).

2.2 Andexanet alfa (ANDEXXA)

Andexanet alfa (also known as PRT064445) is a truncated recombinant variant of human factor Xa that is catalytically inactive due to a substitution of a serine residue for alanine at its

active-site, while still retaining strong affinity for factor Xa inhibitors. Competition of andexanet alfa with endogenous factor Xa for prothrombinase complex formation is prevented by eliminating the membrane-binding γ- carboxyglutamic acid (GLA) domain [23,24]. Therefore, andexanet alfa strategically serves as a decoy antidote by binding to factor Xa inhibitors, resulting in a rapid decrease in free plasma concentration, thereby neutralizing the anticoagulant effect. The mechanism of action for andexanet alfa is presented in Figure 3.

The use of andexanet alfa has been reported in various animal bleeding models. In a rivaroxaban-anticoagulated rabbit liver laceration model, andexanet alfa reduced anticoagulation markers and bleeding loss by more than 85% [24]. In a rat model, andexanet alfa administration dose-dependently corrected bleeding caused by antithrombin-dependent anticoagulants [25]. In a phase II study, intravenous administration of andexanet alfa in healthy volunteers resulted in rapid reversal of anti-factor Xa activity of apixaban, edoxaban, and rivaroxaban in a dose-dependent manner without any major adverse effects [26]. In addition, andexanet alfa was reported to reverse the anti-factor Xa activity of rivaroxaban (ANNEXA-R, NCT02220725) and apixaban (ANNEXA-A) in older healthy volunteers in a double-blind, placebo-controlled study [27]. In both clinical studies, an initial decrease in anti-factor Xa activity was observed minutes after bolus injection, but the effect was transient because of the short half-life of andexanet alfa (~1 h). Inhibition of anti-factor Xa activity was sustained when andexanet alfa was administered as a bolus plus continuous infusion. Andexanet alfa was well-tolerated with no adverse effects, such as thrombosis or bleeding. The study had several advantages: the average age of the study participants was similar to the average age of those taking factor Xa inhibitors in clinical practice, and the study used widely accepted anticoagulation biomarkers. However, further research is needed for patients who require emergent or urgent reversal of factor Xa inhibitors.

The ANNEXA-4 (NCT 02329327) trial is a multinational, prospective, open-label phase III study of andexanet alfa in patients with acute major bleeding who were recently administered a factor Xa inhibitor. The trial is expected to recruit patients from Germany and continue to enroll patients from Japan in the beginning of 2019 to include both Asian patients and those taking edoxaban [28,29]. In 2019, the full study results were published based on 63 centers and 352 patients in North America and Europe [28]. Eligible patients with acute major bleeding received a bolus dose of andexanet alfa within a period of 15 - 30 minutes, followed by a continuous 2-hour intravenous infusion. Out of the 352 patients, 254 (72%) patients whose baseline anti-factor Xa activity was ≥ 75 ng/ml (or ≥ 0.25 IU/ml for those receiving enoxaparin) were included in the efficacy analysis. This cut-off reduced the likelihood that hemostasis would occur without reversal of anticoagulation. The average age of the patients was 77 years. Bleeding was mainly intracranial in 227 (64 %) patients or gastrointestinal in 90 (26 %) patients. The study showed that andexanet alfa markedly reduced the median value for anti-FXa activity from 149.7 ng/ml at baseline to 11.1 ng/ml (92% reduction) in 134 patients receiving an apixaban bolus, from 211.8 ng/ml to 14.2ng/ml (92% reduction) in 100 patients who received rivaroxaban, and from 0.48 IU/ml to 0.15 IU/ml (75% reduction) in 16 patients treated with enoxaparin. During the efficacy analysis, 249 out of the 254 patients could be assessed for hemostatic efficacy, and clinical hemostasis was judged as excellent or good in 204 patients (82%). During the 30-day follow-up, 34 patients (10%) experienced thrombotic events and deaths were reported in 49 patients (14%). It is not surprising that a majority of the events appeared in patients who delayed or did not resume the anticoagulation therapy; however, after restarting the anticoagulation therapy, no thrombotic events occurred during the 30-day follow-up. Reducing anti-factor Xa activity was not able to predict hemostatic efficacy but was able to modestly predict efficacy in patients with

intracranial hemorrhage. This could be due to the confusion of variation in bleeding source (venous or arterial), platelet function, different types of medications, and some other characteristics.

In May 2018, based on the interim results from the ANNEXA-4 study, the U.S. FDA approved andexanet alfa for clinical use to efficiently manage emergency reversal of both rivaroxaban and apixaban. There are two dosing regimens (Table 1). Since andexanet alfa has not been shown to be effective and is not indicated for the treatment of bleeding related to any factor Xa inhibitors, it can only be used for the reversal of apixaban and rivaroxaban rather than others [29].

2.3. Ciraparantag

Ciraparantag (PER-977 or aripazine) is a small, synthetic, water-soluble, cationic molecule developed by Perosphere Inc. It was designed as a universal antidote to directly neutralize DOACs, unfractionated heparin (UFH), low molecular weight heparins (LMWHs), and fondaparinux anticoagulant activity via non-covalent hydrogen bonding and charge–charge interactions [30], therefore eliminating them from their endogenous targets. In addition, ciraparantag does not bind to any human plasma proteins or clotting factors; thus, it has no anticoagulant or procoagulant effects. The mechanism of action for ciraparantag is presented in Figure 4.

It has been shown that ciraparantag significantly reverses the anticoagulant activity of rivaroxaban, apixaban, edoxaban, and dabigatran in animal bleeding models, and restores blood coagulation (measured as prothrombin time, thromboelastography, activated partial thromboplastin time) to baseline levels [31]. Two clinical trials involving healthy volunteers demonstrated the efficacy of ciraparantag for recovering whole-blood clotting time to baseline

values. Volunteers were given a single dose of enoxaparin 1.5 mg/kg or a single dose of edoxaban 60 mg. Ciraparantag reversed the anticoagulant activity of both enoxaparin and edoxaban in a dose-dependent manner, and this effect was sustained for 24 hours with no evidence of thrombotic or other severe adverse events [32,33]. Currently, two clinical trials (NCT 03172910, NCT 03288454) are recruiting healthy volunteers to assess the clinical therapeutic potential of ciraparantag for the reversal of rivaroxaban- and apixaban-induced anticoagulation.

The clinical efficacy of ciraparantag has yet to be established in bleeding patients and more data is required to examine the time to restart anticoagulation therapy after ciraparantag treatment, especially in patients who need an urgent procedure with extracorporeal support and immediate heparinization.

One of the challenges posed by ciraparantag is its influence on laboratory test results. Ciraparantag binds to contact pathway activators, such as Celite and Kaolin, and also binds to anticoagulants, such as citrate, EDTA and heparin. Thus, reversal can only be detected using the whole-blood clotting test. The point-of-care microfluidic device has been developed in an attempt to facilitate these measurements of anticoagulant activity in the presence of ciraparantag [2].

3. Critical Discussions

Presently, andexanet alfa is under regulatory review in some countries, and has a high likelihood of approval. Although ciraparantag is in the development phase, clinical evidence is still preliminary. There remain critical questions that need to be addressed pertaining to the limited information on pharmacokinetics/pharmacodynamics, reversal efficacy, safety, and accurate laboratory tests for detection of ciraparantag exposure. Since there is no additional data

available to support the inclusion of ciraparantag in the label at this time, many experts think that this antidote is far from gaining approval and will probably not enter the market.

Furthermore, relevant clinical associations may be required to support the broad availability of these specific antidotes in major and regional hospitals so that critical complications may be treated promptly. For smaller hospitals and rural medical facilities, decisions to keep stocks of these agents may rely on cost-benefit ratio, logistics, transportation systems, and local conditions.

4. Summary

Although DOACs do not require routine testing, assessment of reversal agents is challenging in patients with serious bleeding events. To date, idarucizumab is approved for patients with life-threatening or uncontrolled bleeding and emergency surgery/urgent procedures [21]. Andexanet alfa is indicated for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding [29]. As clinical evidence continues to evolve, the dawn of DOACs-specific reversal agents is now upon us. Future implementation of these specific agents will depend on performance in various clinical scenarios, when to re-initiate the anticoagulant strategies, how to identify suitable patients to receive them, and the reevaluation of post-marketing safety and effectiveness of these agents.

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Table 1. Doses recommendation of andexanet alfa

FXa Inhibitor	FXa Inhibitor Last Dose	Timing of FXa Inhibitor	Initial IV Bolus	Follow-On IV Infusion
Apixaban	More than 5 mg or unknown	Less than 8 h or unknown	800 mg over a period of 30 minutes	960 mg for up to 120 minutes
Rivaroxaban	More than 10 mg or unknown			
Otherwise	—	—	400 mg over a period of 15 minutes	480 mg for up to 120 minutes

Figure Legends

Figure 1. Coagulation cascade. Targets of anticoagulant agents and specific reversal agents. (Partial data from Mega J L, Simon T. Pharmacology of antithrombotic drugs: an assessment of oral antiplatelet and anticoagulant treatments. Lancet, 2015, 386(9990):281-291.)

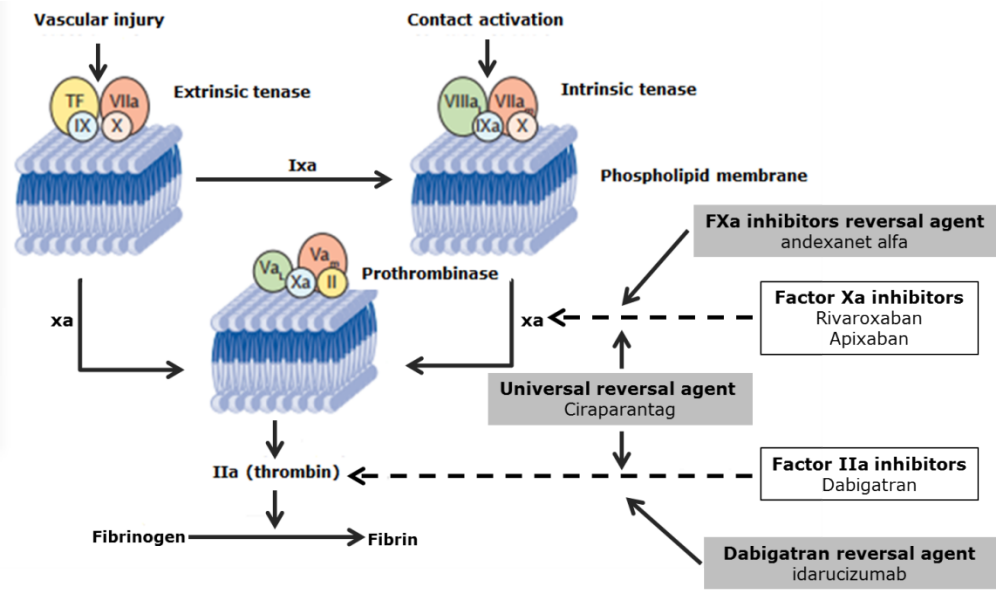

Figure 2. The mechanism of action of idarucizumab.

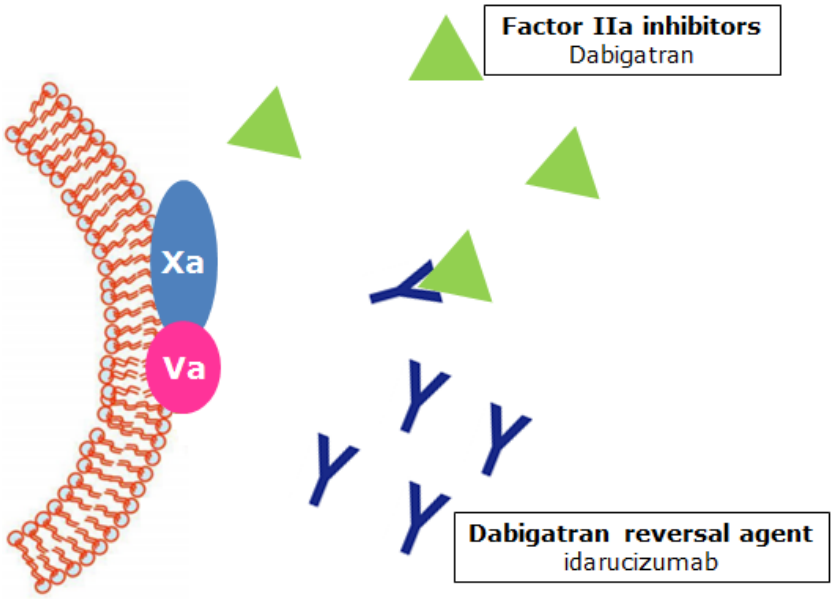

Figure 3. The mechanism of action of andexanet alfa.

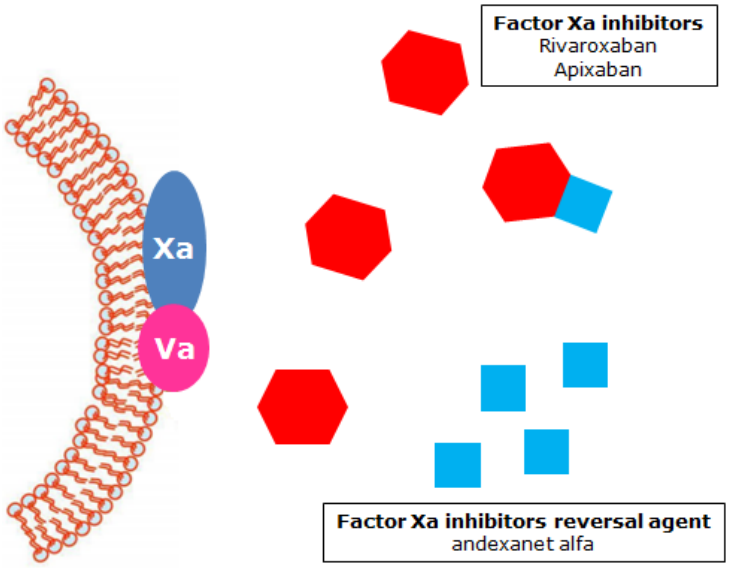

Figure 4. The mechanism of action of ciraparantag.