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Review Article

Reversal agents for NOACs: Connecting the dots

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ARTICLE INFO

Article history:

Received 3 November 2015

Accepted 16 November 2015

Available online 11 January 2016

Keywords:

SPAF

NOACs

Reversal agents

Idarucizumab

Adexanet alfa

ABSTRACT

Objective: The objective of this review is to provide an overview on the current development of the specific reversal agents for Non-vitamin K Oral Anticoagulants (NOACs).**Methods:** We conducted a systematic literature search strategy to identify potential studies on Medline, Embase, and the Cochrane register.**Conclusions:** These new reversal agents for NOACs, will help address the unmet need for the management of major or life threatening bleeds, and the management of emergency surgical procedures in patients taking NOACs. It will increase confidence in the use of NOACs; thereby extending treatment to a wider range of patients.

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1. Introduction

At present, many Non-vitamin K Oral Anticoagulants (NOACs) have become available for prophylaxis and treatment of venous thromboembolism, and stroke prevention in atrial fibrillation patients as an alternative to vitamin K antagonist (VKAs), such as warfarin and acenocoumarol. Though effective, VKAs pose critical challenges in clinical practice, such as narrow therapeutic index, increased risk of intra cranial hemorrhage (ICH) and slow onset and offset of action, which

limits their use in routine practice.^{1,2} Large clinical trials evaluating the NOACs across the spectrum of thromboembolic disorders have shown that they are at least as effective as VKAs, with additional benefit of reduced risk of ICH.³

An increased risk of bleeding is a known possible complication of all anticoagulant therapies.⁴ A meta-analysis by Wang & colleagues suggests that NOACs might be more efficacious and safe in Asians in comparison to non-Asians.⁵

Although the favorable efficacy and safety profile of all NOACs has been demonstrated in the absence of a specific reversal agent,³ certain clinical situations may arise in which

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Abbreviations: NOAC, Non vitamin K Oral Anticoagulant; VKA, Vitamin K Antagonist; ICH, IntraCranial Hemorrhage; PCC, Prothrombin Complex Concentrate.

<http://dx.doi.org/10.1016/j.ihj.2015.11.023>

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rapid reversal of anticoagulant activity is desirable. Due to the short duration of action of the drugs, the discontinuation of the drug is in most cases sufficient to control the problem. However, need for a reversal agent to neutralize these compounds in case of an overdose or serious bleeding, or when a rapid restoration of hemostasis is required (e.g. perioperative period) has been acknowledged since the clinical use of these anticoagulants began.

Adequate supportive care and temporary removal of all antithrombotic drugs constitute the basis for management of serious bleeding complications associated with NOACs.⁶ Pro-hemostatic agents such as 3 or 4 factor prothrombin complex concentrates (PCCs), and activated factor VII have been tried for the NOAC-related bleeding with varying degrees of success.⁶ Hemodialysis can remove up to 60% of circulating dabigatran, while administration of activated charcoal may be useful to reduce absorption of dabigatran if taken within 2 h of ingestion and rivaroxaban or apixaban if taken within 6 h after overdose or accidental ingestion.^{7–9}

The following reversal agents for NOACs and other anticoagulants are currently in development.

Andexanet alfa (PRT064445) is a modified recombinant derivative of factor Xa under development by Portola Pharmaceuticals, Inc. as a reversal agent for all direct small molecule FXa inhibitors (e.g. rivaroxaban, apixaban, edoxaban, and betrixaban), LMWHs, and fondaparinux.¹⁰

Ciraparantag (PER977, previously known as aripazine), a synthetic small molecule that binds to FXa inhibitors, dabigatran, and heparins is being developed by Perosphere Inc.¹¹

Idarucizumab (BI655075), a humanized mouse monoclonal antibody fragment (FAB), which binds to dabigatran with high affinity (Praxbind Injection, Boehringer Ingelheim Pharmaceuticals, Inc.).

2. Methods

We conducted a systematic literature search strategy to identify potential studies on Medline (1950–present), Embase (1980–present), and the Cochrane register for controlled trials using OVID interface. Publications from potentially relevant journals were also searched by hand.

3. Study selection

Using structured search for idarucizumab (BI655075), andexanet alfa (PRT064445), and ciraparantag (PER977) the studies were selected for this review.

4. The ideal reversal agent to an anticoagulant

The ideal reversal agent to an anticoagulant should be:

- Predictable and efficacious
- Easy to use and with immediate action
- Sustained/Specific/Safe

5. Reversal agents for NOACs

Currently, three reversal agents for NOACs are in clinical development: (1) idarucizumab, (2) andexanet alfa, (3) PER977 (Ciraparantag). Each of these differs in specificity, mechanism of action, and the effect on recognized biomarkers of anticoagulant activity. Table 1 summarizes the pharmacological properties of these reversal agents.

5.1. Vitamin K

Vitamin K is frequently and misleadingly named an 'antidote' for the VKAs. An important requirement for an 'reversal agent' is to act rapidly, which is not the case with Vitamin K. When Vitamin K is given to a patient taking a VKA, the liver uses the Vitamin K to start producing fully functioning clotting factors. However, restoring the coagulation factors that require Vitamin K for their production is a slow and complex process with variable effects among patients, which means that the full effect is often not established before 24 h.^{12–14}

It is important to remember that warfarin, with its variable half-life of 20–60 h (dependent on individual patient characteristics), still remains in the circulation as an active drug after Vitamin K application. Thus, a re-dosing of Vitamin K may become necessary, depending on the warfarin level and

Table 1 – Pharmacological properties of reversal agents.

	Idarucizumab ^{17–19}	Andexanet alfa ¹⁰	Aripazine (PER977) ¹¹
Target	Dabigatran	FXa inhibitors	Universal: FXa inhibitors, dabigatran, and heparins
Mechanism of action	Specific Humanized Fab: specifically binds dabigatran	Non-specific recombinant modified activated FX: competitive affinity for direct FXa inhibitors	Non-specific synthetic small molecule: hydrogen bonds (NOACs); charge–charge interactions (heparin)
Direct prothrombotic signals	Absent	Present (clinically not relevant)	Absent
Administration	IV, bolus or short infusion	IV, bolus and/or continuous infusion	IV
Re-initiate anticoagulation	Possible	No data available	No data available
Inclusion criteria in patient trial	Uncontrolled bleeding or requiring emergency surgery/procedure	Uncontrolled bleeding only	No patient trial yet

on the individual VKA metabolism of the patient. In cases of severe bleeding, where rapid reversal is required, Vitamin K needs to be combined with PCC.^{12–14}

5.2. Andexanet alfa

Recombinant modified Factor Xa molecule is being developed as a reversal agent for patients receiving a Factor Xa inhibitor, who suffer a major bleeding episode or who may require emergency surgery. It acts as a Factor Xa decoy that targets and sequesters with high specificity both direct and indirect Factor Xa inhibitors (NOACs: rivaroxaban, apixaban and edoxaban; LMWH and fondaparinux) in the blood. Once bound with andexanet alfa, the Factor Xa inhibitors are unable to bind to and inhibit native Factor Xa, thus allowing for restoration of normal hemostatic processes. Membrane-binding domain of native FXa is deleted to decrease integration into the prothrombinase complex to minimize the pro-thrombotic effect. Unlike in the coagulation cascade with factor X, andexanet alfa did not require any activation steps by factors VIIa (from the extrinsic pathway) or IXa (from the intrinsic pathway). The affinity of FXa inhibitors to andexanet alfa and native FXa is similar. Andexanet alfa is quickly and actively eliminated (half-life 30–60 min).¹⁰ It does not exhibit detectable pro-coagulant or anticoagulant activity, as found in a clotting assay examining the effects of rivaroxaban and andexanet alfa on human plasma PT prolongation.¹⁰ Andexanet alfa dose-dependently reversed the inhibition of FXa by direct FXa inhibitors and corrected the prolongation of ex vivo clotting times by such inhibitors. Data are not yet available for andexanet alfa in a patient setting, but data from healthy volunteer studies have been published.

A proof-of-concept study, in healthy volunteers, the effect of a continuous infusion of andexanet alfa was evaluated in healthy volunteers ($n = 144$). Two minutes after completion of the andexanet alfa intravenous bolus, mean anti FXa activity decreased by >90% and was sustained throughout the infusion period for both regimens ($p < 0.0001$). For the 2-hour infusion cohort, complete reversal of inhibition of thrombin generation was sustained throughout the infusion and remained within the normal range for 2 h post cessation of infusion. Andexanet alfa was well tolerated with no serious or severe adverse events. Anti-FXa activity appeared to return to similar levels as in the placebo group within 2 h of the end of the andexanet alfa infusion.¹⁵ Phase 3 studies to assess the effects of andexanet alfa for reversal of anticoagulation with apixaban in healthy elderly volunteers are ongoing.¹⁶

5.3. Idarucizumab

A humanized mouse monoclonal antibody fragment (FAB), which binds to dabigatran with high affinity (350 times higher than that observed with native thrombin) and specificity.^{17–19} Idarucizumab potentially binds to both free and thrombin-bound dabigatran, thus neutralizing its activity.^{18,19} In first-in-human study, involving 110 healthy male volunteers aged between 18 and 45 years, the authors concluded that the pharmacokinetic profile of idarucizumab meets the requirement for rapid peak exposure and rapid elimination, with no effect on pharmacodynamic parameters. Idarucizumab was found to be safe and

well tolerated in healthy adult males.²⁰ In another placebo-controlled phase 1 trial, by *Stephan Glund and colleagues*, four groups of healthy male volunteers were anticoagulated with 220 mg dabigatran twice daily for 3 days, and then on day 4, they received an intravenous infusion of either placebo or 1–4 g idarucizumab, 2 h after the last dabigatran dose (time to peak plasma concentrations for dabigatran), or a 5 g dose 2 h after dabigatran ingestion followed by an additional 2.5 g idarucizumab after an hour. All idarucizumab doses immediately reversed the dabigatran effects in each clotting assay studied (i.e., diluted thrombin time, ecarin clotting time, activated partial thromboplastin time, thrombin time, and activated clotting time). With 1 g idarucizumab the effect was not sustained and anticoagulation effects reoccurred within 1–10 h of infusion. Endogenous thrombin potential, which was reduced by dabigatran, returned to normal values within 30 min after idarucizumab administration with doses of more than 2 g. Similarly, fibrin formation in blood from a standardized forearm incision returned to normal values in a dose-dependent manner.

In summary, shortly after administration of the reversal agent, plasma concentrations of total dabigatran increased, but without subsequent anticoagulant effects. This could be explained by diffusion of unbound extravascular dabigatran into the intravascular space, which is immediately bound by idarucizumab and inactivated. Thus, idarucizumab also eliminates dabigatran from tissue, followed by elimination of the dabigatran–idarucizumab complex by the kidneys. Even in patients with renal impairment, a reoccurrence of anticoagulation is not expected. The infusion of idarucizumab was well tolerated by all volunteers, though minor drug-related adverse events were reported in seven, but with no clinically significant difference in events between the groups.^{21,22}

Currently, the safety and efficacy of idarucizumab are being evaluated in phase III Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) clinical trial. The interim analysis of 90 patients who received idarucizumab authored by Pollack et al. was published in NEJM on August 6, 2015. The study included two groups of adults, 18 years of age or older, who were taking dabigatran. The patients in group A ($n = 51$) presented with overt, uncontrollable, or life-threatening bleeding that was judged by the treating clinician to require a reversal agent, whereas the patients in group B ($n = 39$) were those who required an urgent surgical intervention or other invasive procedures that could not be delayed for at least 8 h and for which normal hemostasis was required. These inclusion criteria were chosen to mirror the real world population in which the reversal agent would be used. The eligible patients were given 5 g (total) of intravenous idarucizumab as two 50 ml bolus infusions, each containing 2.5 g of idarucizumab, not more than 15 min apart. The primary end point was the maximum percentage reversal of the anticoagulant effect of dabigatran, as determined at any point from the end of the first idarucizumab infusion up to 4 h after the second infusion. This was assessed on the basis of the measurement of the diluted thrombin time or ecarin clotting time at a central laboratory. In this interim analysis, idarucizumab normalized the test results in 88–98% of the patients within minutes.

Hemostasis was restored at a median of 11.4 h in group A patients (35 patients). Among 36 patients in group B who

Table 2 – Design of the andexanet alfa and RE-VERSE AD™ studies.

Andexanet alfa patient study ¹⁵	RE-VERSE AD™ ²³
<p>Prospective, open-label design</p> <p>Estimated enrolment: 270 patients</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Patient taking a direct or indirect FXa inhibitor • Acute bleeding (life-threatening or critical organ or drop in hemoglobin (Hb) by ≥ 2 g/dL or below 8 g/dL) <p>Major exclusion criteria:</p> <ul style="list-style-type: none"> • Life-expectancy of <2 months from causes other than bleeding • Patients expected to undergo surgery in <1 day • Acute trauma where reversal of anticoagulation alone would not be expected to control the acute bleeding • History of a thrombotic event <1 month prior to screening • Treatment with enoxaparin (<1 mg/kg/day) or anticipated use of heparin within 24 h after andexanet alfa bolus <p>Excludes patients, who are expected to receive other interventions, such as PCC, FFP, or rFVIIa</p> <p>Primary endpoint: Proportion of patients with excellent or good hemostasis (stopping major bleed at 24 h from the start of andexanet alfa bolus)</p>	<p>Prospective, open-label design</p> <p>Estimated enrolment: 200–300 patients</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Patient taking dabigatran • Requiring emergency surgery or procedures, or • Uncontrolled bleeding, as deemed by the treating physician <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Minor bleeds that can be managed with standard supportive care • No clinical signs of bleeding • Surgery of procedure that is elective, with a low risk of uncontrolled or unmanageable bleeding, or that can be delayed for ≥ 8 h <p>No restrictions on use of FFP, PCC, aPCC, or rFVIIa</p> <p>Primary endpoint: Maximum reversal of dabigatran's activity, based on central laboratory measurements of dTT or ECT from end of first infusion up to 4 h after completion of last infusion</p>

underwent an emergency procedure, normal intraoperative hemostasis was reported in 33, while mild and moderate abnormality was reported in 2 patients and 1 patient, respectively. One patient had a thrombotic event which occurred within 72 h after idarucizumab administration.²⁴ Table 2 highlights the differences in trial design for andexanet alfa and idarucizumab studies.

In September 2015, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for the medicinal product Praxbind (idarucizumab), a specific reversal agent for dabigatran.²⁴

In October 2015, the U.S. Food and Drug Administration granted accelerated approval to idarucizumab (Praxbind Injection, Boehringer Ingelheim Pharmaceuticals, Inc.) for the treatment of patients on dabigatran, when reversal of the anticoagulant effects is needed for emergency surgery/urgent procedures, or in life-threatening or uncontrolled bleeding.²⁵

5.4. Ciraparantag

Ciraparantag (PER977) is a small (512 Da), synthetic, water-soluble, cationic molecule designed to bind all the NOACs (both F IIa and F Xa inhibitors) and heparins through non-covalent hydrogen bonding and charge–charge interactions. It prevents them from binding to their endogenous targets and thus helps in reversing their anticoagulant effect. Thus PER977 has the potential to be a universal reversal agent to different classes of anticoagulants currently available.

In rat model PER977 reversed the anticoagulant effect of all four NOACs.²⁶ In a phase I trial of 180 healthy volunteers, ciraparantag administered at a dose of 100–300 mg, immediately reversed anticoagulation effects exhibited by higher dose of edoxaban, which was sustained for next 24 h. No evidence of a pro-thrombotic effect was seen as determined by prothrombin fragment 1.2, D-dimer, or tissue factor pathway inhibitor.²⁷

6. Conclusion

Though NOACs have been proven to be safe and efficacious in their respective large phase 3 clinical trials, a proportion of at risk patients are still not receiving anticoagulation therapy because of fear of bleeding. This fear is present both with the clinician and the patient. However, the need for reversal of an anticoagulant is rare and the rapid offset of the NOACs obviates the need for such an agent in most situations. Despite that, reversal agents for the NOACs would benefit the small group of patients who require emergency surgery or interventions and those with life-threatening bleeds. These new reversal agents may provide reassurance regarding managing the risks of bleeding, and so extending treatment to a wider range of patients.

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript, except for Gaurav Chaudhry and Prashant Rana who were employees of Boehringer Ingelheim during the development of this review article.

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