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Reversal Agents in the Era of NOACs

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Abstract

The incidence and prevalence of atrial fibrillation (AF) is expected to more than double between 2010 and 2030. Accordingly, the use of non-vitamin K oral anticoagulant (NOAC) agents for thromboembolic stroke prevention is anticipated to increase. The development of effective and safe antidotes is needed to address the unmet need for rapid anticoagulation reversal. The immediate role for these novel antidotes is for reversal of NOAC activity in life threatening bleeding and urgent surgical intervention. In addition, reversal agents may play an important role in simplifying bridging protocols in the peri-procedural period for catheter ablation of AF and elective surgery. Currently, novel reversal agents are either decoy drug receptors or small molecule non-specific anticoagulant activity inhibitors. These agents are at various stages of FDA investigation and approval, with emerging prospective data for safety and efficacy. The purpose of this review is to outline the currently developed NOAC molecular antagonists, their potential clinical roles and future directions.

Introduction

The advent of NOACs has simplified the management of thromboembolic risk in non-valvular AF. Their use obviates the need for regular therapeutic monitoring whilst affording at least comparable efficacy and probably a superior safety profile, compared to traditional vitamin K antagonists (VKA)[1]-[4]. In the setting of catheter ablation of AF, uninterrupted VKA is an established strategy aimed at minimising the risk of peri-procedural thromboembolism [5], [6]. Likewise, the use of uninterrupted or minimally interrupted NOAC therapy in the peri procedural period has garnered traction, supported by case series and early prospective clinical studies[6]-[8]. However, the initial lack of reversal agents has been a hindrance in advancing the use of these agents in AF, both in general use and specifically in the ablation setting. A detailed understanding of NOAC molecular structure and function has enabled the design of antagonist drugs.

Overview of Non-vitamin K antagonists and the need for effective reversal agents

There are currently 4 NOACs available for clinical use. Dabigatran is a direct thrombin inhibitor while rivaroxaban, apixaban and edoxaban are factor Xa (FXa) inhibitors. Betrixaban is also a FXa activity inhibitor developed through the molecular iterative process, which has undergone phase II studies in AF[9]. An overview of the pharmacologic and pharmacokinetic characteristics of these agents is shown in [Table 1]

Between 2010 and 2030, the prevalence of AF is estimated to rise from 5 million to 12 million[10] . Correspondingly, between 2009 and 2014, the use of NOACs has increased to 4.21 million, and based on IMS Health Global Data, this figure is expected to continue to increase significantly [11] .The use of these agents in AF thromboembolic prevention is therefore expected to be accompanied by an increase in serious hemorrhagic complications. Rapid reversal of anticoagulation is particularly desirable in the event of intracranial haemorrhage and major gastrointestinal haemorrhage. TABLE 2 shows the incidence of life threatening hemorrhagic complications necessitating acute anticoagulation reversal in patients taking NOACs[1-4, 12, 13] . In addition, the annual acute care surgery rate is 1290 per 100,000 14 . These figures demonstrate a current and escalating future need for rapid, efficacious and safe NOAC specific reversal agents..

Pharmacology of Reversal Agents

Until recently, only bypass agents were available for bleeding on NOAC therapy. However, now direct molecular antagonists that inhibit the anticoagulant activity have been developed. The latter class of agents act by binding to and sequestering the active drug (Idarucizumab or Andexanet alfa) or occupying the anticoagulant drug's active site through non-covalent hydrogen bonding (Aripazine, Ciraparantag, [PER977]).

Bypass agents are pro-haemostatic clotting factors that can activate coagulation despite presence of coagulation inhibitors. Prothrombin Complex Concentrates (PCCs), activated PCCs (aPCCs) and recombinant FVIIa (rFVIIa) have been suggested for consideration within many local institutional bleeding management protocols. However it is important to note that efficacy testing for NOAC effect reversal has been limited to animal studies and small healthy

Key Words

Non-vitamin K antagonist anticoagulants, Reversal agents, Atrial Fibrillation.

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Table 1: Pharmacology and Pharmacokinetics of NOAC agents

	Dabigatran etexilate	Rivaroxaban	Apixiban	Edoxaban	Betrixaban
Mechanism of action	Reversible thrombin inhibitor. Indirectly inhibits thrombin-induced platelet aggregation	Competitive dose-dependent inhibition of free Factor Xa and prothrombinase activity as well as clot-bound Factor Xa. Indirectly inhibits thrombin-induced platelet aggregation			
Half-life (hrs)	7-9	5-9	~12	10-14	37
Time to maximum concentration (Tmax) (hrs)	1-2	2-4	3-4	1-2	3-4
Elimination	80% renally cleared unchanged; 20% active glucuronide-bound metabolites eliminated in stool	36% unchanged via renal secretion; 30% renal excretion of inactive metabolites; 34% hepatobiliary excretion	>50% excreted in stool; 12.5% recovered in urine unchanged; 12.5% inactive recovered in urine	60% excreted in stool; ~35% excreted in urine. >70% eliminated unchanged	<7% renal clearance; <1% hepatic metabolism. 82-89% unchanged hepatobiliary excretion via P-gp pump
Coagulation parameters (qualitative)	aPTT, TT	PT, anti-FXa	Anti-FXa	Anti-FXa	Anti-FXa

human volunteer studies[14]-[16] and to date there are no controlled clinical studies of reversal therapy in bleeding patients taking oral Xa inhibitors. Importantly, these agents carry an inherent pro-thrombotic risk and are expensive[17]-[19].

Ligand-specific and small molecule reversal agents are currently under investigation[20]. These agents are likely to be primarily used in life-threatening bleeding and emergent surgery. In addition, these agents may allow the safer implementation of uninterrupted or minimally interrupted NOAC protocols for elective surgery and catheter procedures. Notably, preliminary studies suggest that the ligand-specific reversal, idaracizumab, does not exhibit pro-thrombotic effects, in contrast to plasma protein derived bypass agents, and this may be important in pro-thrombotic states of AF and left atrial catheter ablation. However this observation requires confirmation by controlled trials. Aripazine (Ciraparantag, PER977) which potentiates FX activation by FIXa and platelet activation by adenosine diphosphate, may result in a pro-thrombotic state.

Idarucizumab is a monoclonal antibody that acts as a non-competitive irreversible inhibitor of unbound and thrombin-bound dabigatran and its active metabolites[21]. The compound has a high affinity and it is a specific inhibitor of Dabigatran action. The agent has a rapid onset mechanism of action and has been demonstrated to be safe and efficacious with a simple dosing regimen[22]. Laboratory evidence of reversal is observed within minutes. Idarucizumab has been approved by the FDA as well as the Australian and European regulatory bodies, and is widely incorporated into protocols for use in acute bleeding or emergent surgery[23].

Table 2: Incidence of serious hemorrhagic complications associated with NOAC use[1-3]

	Intracranial hemorrhage		Serious gastrointestinal hemorrhage	
	Incidence per year (%)	Estimated number per year	Incidence per year (%)	Estimated number per year
Dabigatran	0.3	900	0.4	1200
Rivaroxaban	0.5	4000	0.8	6400
Apixaban	0.4	2000	0.2	1000

Table 3: Bypass agents

Agent	Pharmacology	NOAC	Dosage and titration	Titration
3 factor PCC	Inactivated PCC (FII, FIX and FX)	Rivaroxaban, apixaban and Edoxaban. Variable evidence for Dabigatran	25-50IU/Kg	PT
4 factor PCC	Inactivated PCC (FII, FVII, FIX and FX)	Rivaroxaban, apixaban and Edoxaban. Variable evidence for Dabigatran	25-50IU/Kg	PT
Activated PCC	Activated FII, FVIIa, FIX and FX	Dabigatran, Rivaroxaban, Apixaban and Edoxaban	50 IU/kg. Maximum single dose of 100 Units/kg or maximum daily dose 200 Units/kg.	Not amenable to titration against standard coagulation assays
Recombinant FVIIa	Activated FVII	In-vitro data inconclusive for benefit in NOAC reversal	0.5-1mg/Kg	Currently not recommended due to poor in vitro efficacy and pro-thrombogenicity

PCC: Protein complex concentrate, F: coagulation factor, PT: Prothrombin time, NOAC: Non-vitamin K oral anti-coagulant

Andexanet-alfa is a recombinant modified human factor Xa decoy protein. It binds with high affinity to FXa inhibitors within 2 minutes of IV administration, but lacks enzymatic activity thereby neutralising the direct and indirect effects of FXa. A bolus dose is followed by an infusion with restoration of thrombotic activity being reflected by the change in thrombin generation and quantitative anti-FXa activity. Andexanet-alfa reverses the anticoagulant effects of small molecule anti-FXa agents (Rivaroxaban, Apixaban and Edoxaban) as well as low molecular weight heparin, and fondaparinux (the latter 2 being indirect FXa inhibitors)[24], [25].

Aripazine (Ciraparantag, PER977) is a small molecule non-specific antidote for all NOACs and heparins. The pan-antagonist has hydrogen bonding sites that bind NOAC agents' active moieties, heparin and LMWH (but not VKA), thereby preventing their anticoagulant function. Current phase II studies have employed a single IV bolus, with laboratory evidence of reversal observed by 30 minutes[26].

[Table 3] and [Table 4] detail the pharmacological properties of the currently developed pro-haemostatic reversal agents. [Table 5] summarises the key clinical data for the ligand-specific and small molecule NOAC reversal agents.

Current state of reversal agents and future directions

The projected AF epidemic will increase the use of currently available NOACs for thromboembolic prevention. Specific (Idarucizumab and Andexanet alfa) and non-specific small molecule (Aripazine) reversal agents may improve the safety profile of these agents particularly in the setting of acute hemorrhagic complications and emergent surgery. Idarucizumab approved by the FDA for the specific reversal of dabigatran, based on interim analysis of the first 90 patients in the REVERSE-AD study [27]. This was a cohort uncontrolled study as it was considered unethical to randomly assign patient to placebo. The results demonstrated rapid, effective reversal of dabigatran in 88 to 98% of patients with fixed dosage idaracizumab. Of note:

Table 4: Direct Reversal agents

Agent	Pharmacology	NOAC	Dosage and titration	Titration	Time to onset	Adverse reactions
Idarucizumab	Monoclonal antibody fragment with high affinity to Dabigatran (free and bound)	Dabigatran	2.5g IV x2 administered 15 minutes apart.	TT and serum dabigatran levels	2-3 minutes (TT). Initial half-life 45 minutes. Terminal half-life 10.3 hours. Renal clearance	Headache, hypokalaemia, fever, constipation, pneumonia
Andexanet alfa	Modified recombinant factor Xa (rFXa). Decoy receptor for oral FXa inhibitors devoid of enzymatic activity	Rivaroxaban, Apixaban, Edoxaban	Apixaban: 400mg IV bolus and 4mg/min infusion over 120 minutes Rivaroxaban: 800mg IV bolus and 8mg/min infusion over 120 minutes	Plasma FXa activity	2-5 minutes (FXa activity). Initial half-life 15 minutes Pharmacodynamic half-life ~1 hour	Thrombotic events in 18% however controlled studies are required
Aripazine (Ciraparantag, PER977)	Pan-antagonist small cation with multiple non-covalent binding sites	Dabigatran, Rivaroxaban, Apixaban, Edoxaban, Heparin and LMWH	Edoxaban: IV 100-300mg bolus (dose titration study)	Whole blood clotting time	Rapid onset within 10 min. Duration of effect 24 hrs. (WBCT)	Peri-oral and facial flushing. Dysgeusia.
Modified thrombin (T-S195A-IIa)	Trypsinized derivative of site mutated thrombin. Sequestration of dabigatran	Dabigatran	Proof of concept. 6mg/kg IV restored thrombus formation in dabigatran treated mice	Dabigatran reversal in vitro (bleeding time) and thrombus restoration in vivo (mice)	Investigational, pre-clinical	Investigational, pre-clinical

TT: Thrombin time, WBCT: whole blood clotting time, F: coagulation factor

the primary outcome in this trial was pharmacological reversal of drug with clinical outcomes as secondary endpoints. Among the 36 patients who underwent a procedure, normal hemostasis was reported in 92% with no pro-coagulant effects identified. Patients who were subsequently found not to have measurable dabigatran levels who received idaracizumab did not have adverse outcomes. Of note, five thromboembolic events that occurred in the study, were in patients who did not have anticoagulation restarted, highlighting the fact that the population requiring reversal has baseline high risk for thrombo-embolic events. Full recruitment has completed with the results expected to be published in 2017.

Likewise, recruitment for the ANNEXA-4 study evaluating

Table 5: Key clinical studies evaluating various NOAC reversal agents

Study	Design	Population studied	Key findings	Comments
Idarucizumab				
REVERSE AD (NCT02104947)	Prospective multi-centre cohort	Serious bleeding or urgent surgery. Dabigatran overwhelmingly for AF	Reversal achieved within 10 min. Median time to bleeding cessation 11.4 hrs. Clinical hemostasis evident at up to 48 hrs.	Laboratory hemostasis correction and diminished Dabigatran levels. No serious adverse reactions. Study currently ongoing
NCT01688830	Randomised, placebo-controlled, double-blind phase 1 study	Healthy male volunteers	Dose-dependent high efficacy immediate, complete and sustained Dabigatran neutralisation	Well tolerated. No clinically relevant adverse effects
NCT02815670	Open label uncontrolled safety trial	Paediatric population with serious bleeding or urgent surgery. Dabigatran for venous thromboembolism	Currently recruiting	Primary, drug-related adverse events. Secondary, bleeding parameters
Andexanet alfa				
ANNEXA-A (NCT02207725)	Prospective randomised double blind: Andexanet alfa vs placebo	Healthy volunteers taking Apixaban 5mg bid, 50-75 years of age	Sustained suppression of FXa activity and diminished unbound Apixaban levels	Bolus and infusion required for sustained suppression
ANNEXA-R (NCT02220725)	Prospective randomised double blind: Andexanet alfa vs placebo	Healthy volunteers taking Rivaroxaban 20mg daily, 50-75 years of age	Sustained suppression of FXa activity and diminished unbound Rivaroxaban levels	Bolus and infusion required for sustained suppression
ANNEXA-4 (NCT02329327)	Multi-center, prospective, open-label, single-group study	Major bleeding in patients taking FXa inhibitors. Mean age 77 years	Reduced FXa activity and effective clinical hemostasis in 79% of patients	Study currently ongoing.
Aripazine (Ciraparantag, PER977)				
NCT01826266	Double-blind, placebo-controlled trial	Healthy persons Edoxaban 18-45 years	100-300mg IV dose restored hemostasis within 10-30 minutes. Effects sustained for 24 hours	Phase II studies of re-anticoagulation with Edoxaban ongoing
NCT02205905	Phase I, open label	Single IV dose in healthy volunteers	Pharmacokinetics study, ongoing	C-14 radiolabelled Aripazine 200mg IV dose
NCT02206087	Phase I/II	Healthy volunteers. Reversal of standard UFH dose using PER977 or placebo	Dose escalation study for UFH dose	Dose determination for efficacy, safety tolerability and adverse events
NCT02207257	Phase II	Healthy subjects administered Edoxaban. Reversal using PER977 or placebo	Pharmacodynamic and pharmacokinetic study	Dose determination study for Edoxaban reversal, followed by re-anticoagulation with Edoxaban

F: coagulation factor, AF: Atrial fibrillation, UFH: Unfractionated heparin

Andexanet-alfa for reversal of FXa inhibitors including rivaroxaban, apixaban, edoxaban and enoxaparin is currently ongoing. The interim analysis of the first 63 patients was reported in 2016[28] demonstrating pharmacological reversal and achievement of haemostasis in 89% individuals. Drug was delivered as a bolus during a period of 15 to 30 minutes, followed by a 2-hour infusion with doses dependent on time since last dose of anti-FXa agent (within 7 hours of bolus or prior). The primary outcome demonstrated pharmacological reversal by anti-FXa levels during infusion, with partial return of anti-FXa levels to pre-treatment levels at 4-4.5 hours after infusion. Thrombotic events occurred in 18% of patients including myocardial infarction, ischaemic stroke and venous thromboembolism and it was noted at the end of the interim report that a controlled study would be required to assess whether the frequency of thrombotic events exceeded that expected in this at risk patient population.

Aripazine (Ciraparantag, PER977) has been granted fast track designation by the FDA.

Availability of these novel reversal agents will also facilitate protocols in the peri-procedural setting potentially adding an extra safety net for patients who proceed without interruption to NOACs during catheter ablation, however, the safety data will need to be carefully assessed.

While the availability of reversal agents is likely to further tilt the scales in favour of NOAC over traditional vitamin K antagonists, unresolved issues remain including clinical availability, cost and confirmation of efficacy and safety by large clinical trials.

Disclosures

None.

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