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Andexanet alfa to reverse the anticoagulant activity of factor Xa inhibitors: a review of design, development and potential place in therapy

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Abstract
Direct oral anticoagulants are associated with rates of major bleeding which are not negligible, albeit lower than those associated with vitamin K antagonists. No specific reversal agent for factor Xa (FXa) direct inhibitors is currently available for clinical use. A modified activated human FXa decoy protein, andexanet alfa, is being developed that binds FXa direct inhibitors in their active site, thus reversing their anticoagulant effect. The purpose of this article is to review the design, development and clinical trials of andexanet alfa. Andexanet alfa was shown to reverse FXa inhibitors anticoagulant activity both in thrombosis animal models, healthy volunteers and patients with acute major bleeding. Andexanet alfa has been studied in double-blind, placebo-controlled phase II and III studies. A preliminary report of the phase III study showed that an effective hemostasis was obtained after andexanet alfa infusion in the majority of the patients with acute major bleeding associated with FXa inhibitors. Additional studies are ongoing and andexanet alfa is expected to be launched in the market in the near future.

Keywords Andexanet alfa · Bleeding · Rivaroxaban · Apixaban · Low molecular weight heparin · Reversal agent

Introduction

Scientists and clinicians are looking for improved anticoagulant agents which are effective in preventing thromboembolic events but devoid of significant bleeding risk. The direct oral anticoagulants (DOACs) are considered to be a relevant step in such a direction. Although DOACs seem to have a lower bleeding risk profile when compared with vitamin K antagonist (VKA) [1], major and minor bleedings still occur with DOACs with not negligible rates [1, 2]. In case of VKA associated bleeding, vitamin K and prothrombin complex concentrates (PCC) can be used for reversal [3]. Specific reversal agents were not available when DOACs were introduced in the market, and the lack of reversibility has been considered by clinicians as a limitation. In case of major bleeding due to accidents or traumas or of emergency surgery in subjects on anticoagulants, the prompt restoration of normal hemostasis with specific reversal agents, if available, may be critical [4, 5]. The Quarterwatch Annual Report in June 2016 showed an increase number of bleeding adverse events due to DOACs in parallel with the increase of their use in the everyday clinical practice [6]: they accounted for 34% of the oral anticoagulant market in 2016. Several cases of dabigatran associated fatal bleeding have already entailed US federal and state lawsuits against Boehringer. On 28 May 2014, the company announced that it had settled about 4000 cases for $650 m (£380 m; €480 m), but denied wrongdoing saying that it had settled the lawsuit to avoid lengthy litigation [7]. Similarly, several lawsuits against manufacturers of factor Xa (FXa) direct inhibitors are ongoing. The reversal agent for dabigatran, idarucizumab, was approved for use in the EU and USA in 2015. Although no specific reversal agents for FXa direct inhibitors are available, PCCs may be effective in most cases of major bleeding associated with rivaroxaban or apixaban [8]. In 2016, data from IMS Health Incorporated showed that rivaroxaban had 46.5%, apixaban 42.5%, edoxaban 0.5% of DOACs market share [9]. By contrast, dabigatran had 10.5% of the DOACs market. In fact, FXa inhibitors sharing more than 85% of DOACs market

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accounted for a large number of domestic, serious adverse event reports that the FDA received in 2015, due to their large increase in market share (45% increase over previous year). In the phase III trials for atrial fibrillation, the reported annual rates of major bleeding with rivaroxaban or apixaban were 3.6 and 2.13% [10], respectively, whereas the rates in phase III trials for venous thromboembolism were 1% [11] and 0.6%, respectively, during 6-month follow-up [12]. In the "real world" the incidence rate (per 100 person-years) of major bleeding requiring hospitalization was 4.57 for rivaroxaban and 2.35 for apixaban in atrial fibrillation patients [13]. The Dresden DOAC registry reported a rate of major bleeding of 3.1 per 100-patient years for patients on rivaroxaban for stroke prevention in atrial fibrillation and 4.1 for patients on rivaroxaban for venous thromboembolism [14]. Moreover, some real world data suggest that rivaroxaban and warfarin do not differ significantly in real-world rates of the composite outcome of stroke, systemic embolism and major bleeding [15]. These data represent a strong signal indicating that the improvement of oral anticoagulants safety should be a major priority in drug development. Patients may weigh bleeding and stroke risk differently from both physicians and clinical guidelines and fewer patients would receive anticoagulation treatment than may be expected on the basis of recommendations found in clinical guidelines [16]. Reversal agents could improve patient outcomes in case of major bleeding. As a result, a higher number of patients could be willing to accept the bleeding risk and could be treated with anticoagulants resulting in fewer thrombotic events in this population at risk.

An antidote for both FXa direct inhibitors (rivaroxaban, apixaban, edoxaban, betrixaban) and FXa indirect inhibitors, such as low molecular weight heparin (LMWH) and fondaparinux, has been developed by Portola (andexanet alfa, PRT064445, AnnexaTM-A, Portola Pharmaceuticals, Inc., San Francisco, CA, USA). Andexanet alfa has been evaluated by the U.S. Food and Drug Administration as a Breakthrough Therapy due to unmet need of a reversal agent for FXa inhibitors associated bleeding [17]. The purpose of this article is to review the design, development and clinical trials of andexanet alfa.

Design and development

FXa direct inhibitors bind reversibly to FXa active site and attenuate the ability of the prothrombinase complex, which consists of FXa and its cofactor factor Va on a membrane surface, to convert prothrombin to thrombin. Fondaparinux and LMWH bind antithrombin and catalyze FXa inhibition, thus attenuating prothrombin activation. Andexanet alfa is a recombinant human FXa decoy protein that binds FXa inhibitors in their active site with high affinity and a 1:1 stoichiometric ratio [18, 19]. The amino acid serine at position 419 is replaced by alanine and the membrane-binding-carboxyglutamic acid domain (Gla domain) of native FX is lacking [20, 21]. The membrane-binding Gla-domain and active site serine are essential for FXa function. Alanine at position 419 leads to the absence of enzymatic activity but still allows andexanet alfa to bind both direct FXa inhibitors and heparin-antithrombin-complexes [21]. The Gla domains are responsible for the binding of FXa to phospholipids, the surface where the prothrombinase complex is assembled and the absence of the membrane-binding Gla-domain does not allow andexanet alfa, when bound to FXa inhibitors, to compete with FXa for incorporation into the prothrombinase complex (Fig. 1).

Andexanet alfa is able to reverse the anticoagulant effect of both FXa direct inhibitors and agents that inhibit FXa via antithrombin (LMWH or fondaparinux). Circulating andexanet alfa binds FXa inhibitors directly, whereas it competes with FXa for fondaparinux-activated or LMWH-activated antithrombin, restoring the capacity of prothrombinase to generate thrombin. Since andexanet alfa is able to reverse only the anti-FXa activity but not the anti-Factor IIa activity of heparin, it is only partial antidote for heparin [18].

Andexanet alfa is produced in Chinese hamster ovary cells and in-vitro studies have shown that it can exert a dose-dependent reversal of FXa inhibition provoked by betrixaban, rivaroxaban and apixaban [21]. It has been investigated in different animal models of bleeding [21, 22]. In rats, the administration of andexanet alfa dose-dependently and

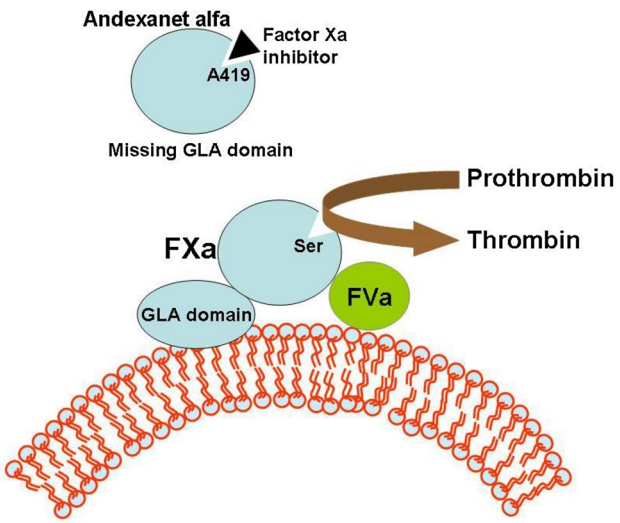

Fig. 1 Structure of andexant alfa. Andexanet alfa is a modified activated human factor Xa (FXa) that binds FXa with high affinity and a 1:1 stoichiometric ratio but does not have intrinsic catalytic activity (the amino acid serine at position 419 is replaced by alanine) and lacks the membrane-binding-carboxyglutamic acid domain (Gla domain) of native FX. The Gla domains are responsible for the binding of FXa to phospholipids

completely corrected bleeding provoked by antithrombin-dependent anticoagulation by enoxaparin or fondaparinux [21]. Andexanet reduced blood loss and anticoagulation markers in rivaroxaban-anticoagulated rabbits [22]. Andexanet alfa was well tolerated in monkeys: there was only one single episode of anaphylaxis and there was no histological evidence of prothrombotic activity, measured by clot and fibrin deposition in all major organs, with high-dose andexanet [22].

Phase I and II studies

In humans, andexanet alfa has a half-life of approximately 1 h and is administered as an intravenous infusion [23]. In a phase I study, 32 volunteers were randomized to andexanet alpha (between 30 and 600 mg; n = 24) or placebo (n = 8) during rivaroxaban treatment. In the presence of andexanet alfa, thrombin generation and rivaroxaban anti-FXa activity were reversed in a dose-dependent manner [24]. No thrombotic events or deaths were reported. The adverse events were: 1 pneumonia, 3 non-serious infusion-related reactions without anaphylaxis, 1 unplanned pregnancy occurred 10 days post-treatment, followed shortly by a spontaneous abortion [24]. The phase II studies showed that intravenous administration of andexanet alfa in volunteers who were receiving apixaban [25] or rivaroxaban [26] or edoxaban [27] at the steady state, resulted in a rapid dose-dependent reversal of the anticoagulant effect (within 2 min). The effect of andexanet alfa was assessed as anti-FXa activity, unbound FXa inhibitor concentrations, and thrombin generation [25–27]. Andexanet alpha at a dose of 420 mg neutralized 91% of the apixaban anti-FXa effect (compared to placebo) and 53% of the rivaroxaban anti-FXa effect. At a dose of 600 or 800 mg bolus, andexanet alpha decreased the anti-FXa activity in a dose dependent manner by 52 and 73%, respectively [27]. The anti-FXa activity returned to placebo levels in approximately 2 h after treatment in all the studies. In humans, andexanet has an effective half-life of approximately 1 h, and the reversal could be extended with a continuous infusion (a bolus plus a 1-to-2-h infusion), thus allowing drug activity throughout the infusion duration. No serious adverse reactions were reported, and no antibodies against FXa or FX were detected.

ANNEXA-A and ANNEXA-R were double-blind, placebo-controlled studies that were designed to evaluate the ability of andexanet to reverse anticoagulation with apixaban (ANNEXA-A) and rivaroxaban (ANNEXA-R) [28]. In the ANNEXA-A study, older healthy volunteers (the mean age of the participants was 57.9 years and 39% were women) received 5 mg of apixaban orally twice daily for 3.5 days. Three hours after the last dose of apixaban, andexanet alfa was administered as a 400-mg intravenous bolus or as a 400-mg intravenous bolus followed by a continuous infusion of 4 mg/min for 120 min (480 mg in total). In the ANNEXA-R study, healthy volunteers received 20 mg of rivaroxaban orally once daily for 4 days and then (at 4 h after the last dose of rivaroxaban) andexanet was administered as an 800-mg intravenous bolus or as an 800-mg intravenous bolus followed by a continuous infusion of 8 mg/min for 120 min (960 mg in total). In the apixaban group, the dose of 400 mg decreased the anti-FXa activity by 94% as compared with 21% among those who received placebo. In the rivaroxaban group, the dose of 800 mg decreased the anti-FXa activity by 92% as compared with 18% among those who received placebo [28]. In both studies, andexanet alfa increased thrombin generation above the lower limit of the normal range in all the participants, whereas in the placebo group, thrombin generation was restored in 25% of participants. No thrombotic events were observed.

Phase III studies

ANNEXA-4 is an ongoing, multicenter, prospective, open-label, single-group study of andexanet alfa in patients with acute major bleeding. In 2016, the preliminary results were published [29], although it is ongoing with an estimated total enrollment of 350 patients with an expected officially declared completion date in November 2022. It was the interim report of 67 patients included in the trial. Inclusion criteria were: acute major bleeding and treatment with one of four FXa inhibitors—apixaban, rivaroxaban, edoxaban, or enoxaparin—within the past 18 h. The ANNEXA-4 enrolled only patients that meet major hemorrhage criteria defined as: potentially life-threatening acute overt bleeding with signs or symptoms of hemodynamic compromise, or acute overt bleeding associated with a decrease in hemoglobin of at least 2 g/dL or a hemoglobin level of 8 g/dL or less if no baseline hemoglobin level was available, or acute symptomatic bleeding in a critical area or organ (e.g., retroperitoneal, intraarticular, pericardial, intracranial, or intramuscular with the compartment syndrome). Patients received an andexanet alfa bolus during a period of 15–30 min, followed by a 2-h drug infusion [29]. Lower doses of andexanet alfa are needed to reverse apixaban than rivaroxaban or edoxaban, because FXa inhibitor concentrations depend on drug distribution volumes and time from the last drug dose. The half-live of edoxaban is approximately 10 h after multiple doses but the volume of distribution is > 100 L which is the rationale for the once-daily dosing regimen; the half-live of rivaroxaban is 5–9 h, but the large volume of distribution of rivaroxaban (approximately 50 L) allow for a longer period of anticoagulation than would be predicted on half-live alone. The half-live of apixaban is approximately 13 h and the volume of distribution is approximately 20 L, which is the rationale for the twice-daily dosing regimen. Thus, andexanet alfa doses varied according to FXa inhibitors type and time from the

last anticoagulant dose (Table 1): in case of apixaban or rivaroxaban taken > 7 h before the administration of andexanet alfa, the bolus dose was 400 mg and the infusion dose was 480 mg, otherwise (enoxaparin, edoxaban, or rivaroxaban 7 h or less before the administration of the bolus dose or at an unknown time), the bolus dose was 800 mg and the infusion dose was 960 mg. Of the 67 enrolled patients, 32 were receiving rivaroxaban, 31 were receiving apixaban, and 4 were receiving enoxaparin. Bleeding was gastrointestinal in 49% of participants, intracranial in 42% of participants, with other bleeding sites in 9%. All patients who received andexanet were included in the safety analysis, but only patients with baseline anti-FXa activity of ≥ 75 ng/mL (or 0.5 IU/mL for patients with enoxaparin) were included in the efficacy analysis (47 of 67 patients). The study confirmed the efficacy of andexanet alfa in reducing the anti-FXa activity by 89% from baseline among patients receiving rivaroxaban and by 93% among patients receiving apixaban. Of the 47 patients in the efficacy population, 37 were adjudicated as having excellent or good hemostasis (79%). Of the 10% of patients with the highest anti-factor Xa activity at the end of the infusion, 4 had received rivaroxaban and 1 had received apixaban; all received the lower dose of andexanet. In the "safety population", no patient had an infusion reaction or developed antibodies to FXa or FX, or neutralizing antibodies to andexanet. There were 10 deaths (15%), with 6 adjudicated as cardiovascular events and 4 as non-cardiovascular events. Thrombotic events during the 30-day follow-up were observed in 12 patients (18%) and included: 1 myocardial infarction, 5 strokes, 7 deep-vein thrombosis, and 1 pulmonary embolism [29]. Four patients had a thrombotic event within 3 days after andexanet alfa administration. Several limitations of the interim report of the ANNEXA-4 study should be acknowledged [30]. Firstly, the data were preliminary and the study was unblinded. Use of blood products or concomitant medications was not reported. The time span between andexanet alfa infusion and hemostasis assessment was unclear. There was no control group and one cannot be sure whether bleeding stopped spontaneously or because of andexanet alfa. Finally, the high rate of thrombotic complications is of concern and randomized clinical trials comparing current guideline recommendations vs. andexanet alfa administration in case of major bleeding could be advisable.

Table 1 Doses of andexanet alfa according to the different factor Xa inhibitor in ANNEXA-4 trial [29]

Drug	Bolus i.v.[a]	2-h infusion
Apixaban	400 mg	480 mg
Rivaroxaban, last administration > 7 h before	400 mg	480 mg
Rivaroxaban, last administration < 7 h before	800 mg	960 mg
Edoxaban	800 mg	960 mg
Betrixaban[b]	*NA*	*NA*
Enoxaparin	800 mg	960 mg
Fondaparinux	*NA*	*NA*

NA not available

[a]During a period of 15–30 min

[b]Phase I study ongoing (A Healthy Volunteer PK/PD, Safety and Tolerability Study of Andexanet After Betrixaban Dosing; ClinicalTrials.gov Identifier: NCT03330457)

Place in therapy

Major guidelines such as those of the European Heart Rhythm Association or European Society of Cardiology recommend that in case of non-life threatening bleeding, stopping DOACs allows the normalization of hemostasis in 12–24 h for their short half-life in the majority of cases, while supportive measures can be applied such as local hemostatic measures, fluid replacement, transfusional support [31, 32]. In case of life threatening or uncontrolled bleeding, that is leading to hemodynamic compromise or threatening a vital organ (eg, central nervous system or spinal cord, intraocular, intrapulmonary, retroperitoneal, or intramuscular with compartment syndrome) or unresponsive to conventional measures or potentially leading to disability, the immediate neutralization of the anticoagulant activity is recommended to obtain hemostasis normalization [31]. Vitamin K can be used for reversal in cases of bleeding due to VKA that act by inhibiting the synthesis of vitamin K-dependent factors (II, VII, IX, X) while PCC can be used, if immediate reversal is mandatory. VKAs act by inhibiting the vitamin K epoxide reductase complex 1 leading to non-carboxylated factors that are less active. Rapid restoration of functionally normal vitamin K-dependent factors with PCC is the primary goal in the management of acute major or life-threatening hemorrhage and infusion of PCC provides a prompt but transient correction in coagulopathy. Due the half-live of PCC (FVII 6 h, others 24–72 h) relative to the anticoagulant effects of VKAs (36–42 h), a prolonged correction of coagulopathy requires the administration of vitamin K for the restoration of intrinsic hepatic carboxylation of vitamin K-dependent factors (half-lives of FX: approximately 40 h, FII: approximately 60 h). Recently, the American College of Cardiology Task Force on Management of Bleeding in Patients on Oral Anticoagulants suggested 4-factor prothrombin complex concentrate (4F-PCC) containing FII, FVII, FIX, FX, and protein C and S as first line as reversal agent for VKA, and only 3-factor PCCs or plasma only if 4F-PCC is unavailable [33]. A specific reversal agent is only available for dabigatran among the DOACs [32]. The guidelines of the European Society of Cardiology recommend the use

of PCC (either activated or non activated) also for DOACs associated bleeding [31], whereas the guidelines of the American College of Cardiology recommend 4F-PCC as first choice, and activated PCC as second line [33]. Studies in healthy volunteers have demonstrated the reversal of laboratory abnormalities and bleeding time induced by rivaroxaban and edoxaban after the administration of PCCs [34–36]. PCC are nonspecific reversal agents and their clinical usefulness was studied in case of bleeding during VKA [34]. Recently, the UPRATE study enrolled 84 patients and investigated the 4F-PCC efficacy for the management of major bleeding during rivaroxaban or apixaban [8]. Bleeding was gastrointestinal in 15.5% and intracranial in 70.2% of participants. 4F-PCCs were effective in 69% of patients, while 32% of patients died within 30 days. Thrombotic events were observed in 3 patients and included: 2 strokes, and 1 pulmonary embolism [8]. The use of 4F-PCC in life-threatening or major bleeding associated with FXa inhibitors is reasonable but the use of a specific reversal agent as andexanet alfa may theoretically reverse FXa inhibitors anticoagulant effect without increasing the thromboembolic risk associated with supraphysiologic concentrations of clotting factors. The use of PCC might shift the hemostatic balance toward hypercoagulability, whereas andexanet alfa might only restore haemostasis. However, some data suggest that andexanet may bind to the tissue factor pathway inhibitor (TFPI), natural anticoagulant inhibitor, leading to a less active form of TFPI complex. This may provoke a transient increase in the levels of prothrombin fragment 1.2, thrombin–antithrombin complexes, and D-dimer. The binding to such natural anticoagulant inhibitor, could produce a procoagulant effect theoretically leading to an increased thromboembolic risk [37]. The availability of a specific reversal agent may render PCC less indicated or even obsolete for FXa inhibitors reversal, however a direct comparison of andexanet alfa vs. PCC may be needed to assess their place in clinical routine.

In case of emergency surgery or invasive maneuvers, DOACs reversal is also required and data on the use of PCC and andexanet alfa are lacking. Since exclusion criteria of the ANNEXA-4 trial included the scheduling of surgery within < 12 h after the enrollment [29], data will still be lacking for emergency surgery even after approval of andexanet alfa for reversal of FXa inhibitor associated bleedings. While no data on andexanet alfa is available for patients receiving FXa inhibitors, patients receiving dabigatran who require emergency surgery or urgent procedures may receive idarucizumab that has been proven to be effective in 202 patients receiving dabigatran who required a surgery or a procedure that could not be delayed and required normal hemostasis [38].

Open questions

The preclinical data suggests that andexanet alfa is able to reverse at least partially the anticoagulant effect of LMWH and fondaparinux. In vitro, andexanet alfa was able to reverse the AT-dependent FXa inhibition of enoxaparin and pentasaccharide [21]. In one animal bleeding model (the rat tail transection), bleeding associated with the presence of enoxaparin or fondaparinux was stopped by andexanet alfa infusion [21]. Since andexanet alfa reverses FXa AT dependent inhibitor-mediated anticoagulation by sequestering the FXa inhibitor in a 1:1 molar ratio, the doses of andexanet needed to restore haemostasis may differ, depending on plasma levels of LMWH or fondaparinux. In the ANNEXA-4, four patients receiving LMWH were enrolled, but only one patient was included in the efficacy group. A reduction in anti-FXa activity from 0.61 to 0.15 IU/mL at the end of the bolus was observed; but the value returned to 0.46 IU/mL after 4 h [29]. To our knowledge, no human data are available for fondaparinux. More data are required to assess the impact of andexanet alfa for bleeding associated with LMWH and fondaparinux (e.g. venous thromboembolism initial treatment, bridging therapy with heparins) in clinical practice.

The impact of different doses of andexanet alfa for the various FXa inhibitors in clinical practice also needs to be considered. In fact, different doses of andexanet alfa are required to reverse the effects of the two direct FXa inhibitors apixaban and rivaroxaban, and it will be interesting to see the first results for edoxaban (Table 1). Due to the short half-life of andexanet alfa, some anticoagulant effects of the FXa inhibitor may return after stopping the infusion of andexanet alfa, raising concerns regarding the optimal duration of infusion and/or need for repeat administration [33]. It is also likely that different doses are needed for the FXa indirect inhibitors, such as fondaparinux and LMWHs, [29] and clinical data are lacking. This can make it more difficult to apply the appropriate doses under emergency conditions.

In a phase II cohort of patients who received apixaban and andexanet alfa, there were transient reductions in TFPI activity [37, 39]. TFPI inhibits the activity of the TF-factor/VIIa catalytic complex and can directly inhibit FXa [40]. A transient reduction of TFPI may lead, at least theoretically, to an increased risk of thrombosis. Moreover, being a modified clotting factor, andexanet alfa may theoretically stimulate an antibody response against its native counterpart FXa, potentially causing an iatrogenic clotting factor deficiency. A possible prothrombotic effect could be expected, as also shown by the ANNEXA-4 trial in which 18% of subjects had a thromboembolic event at 30-day follow-up [29]. The rate of thromboembolism was 10% in

Table 2 Comparison of clinical studies on management of DOACs-associated major bleeding

Study	RE-VERSE AD [38]	ANNEXA-4 [29]	UPRATE [8]
Antidote	Idarucizumab	Andexanet alfa	PCCs
Drugs	Dabigatran	Rivaroxaban Apixaban	Rivaroxaban Apixaban
N	301	67	84
Age, year	79	77	75
Female	42%	48%	43%
Intracranial bleeding	33%	42%	70%
Gastrointestinal bleeding	46%	49%	16%
Ineffective hemostasis	22%	21%	31%
30-day outcome:			
Death	14%	15%	32%
Thrombo-embolism	6%	18%	4%

PCCs prothrombin complex concentrate containing FII, FVII, FIX, FX

the preliminary report of RE-VERSE study with idarucizumab [41], and such figure seems in line with the rate of ANNEXA-4 study. Such high thromboembolic rates may be explained by the activation of the coagulation system during bleeding and/or by the higher baseline thromboembolic risk of the study populations (reduced mobility, trauma, intensive unit) and most of these events were in patients in which anticoagulation had not been restarted. However, in the final analysis of the RE-VERSE study [38], the thrombo-embolic events were lower (Table 2). As shown in Table 2, the rate of thromboembolism observed in the UPRATE study was low (3.6%) but mortality was high (32 vs. 15% of the ANNEXA-4 study), suggesting different risk profiles of the population enrolled in ANNEXA-4 study and in the UPRATE study [8].

In the Complete Response Letter (CRL) from the U.S. Food and Drug Administration (FDA) regarding its Biologics License Application (BLA) for AndexXa™ (andexanet alfa) in August 2016 FDA requested that Portola provide additional information primarily related to manufacturing, this being a complex molecule which requires a high degree of technical sophistication. The agency also asked for additional data to support inclusion of edoxaban and enoxaparin in the label, and indicated it needs to finalize its review of the clinical amendments to Portola's post-marketing commitments [42]. A new phase I A Healthy Volunteer PK/PD, Safety and Tolerability Study of Second Generation Andexanet Alfa is currently ongoing (ClinicalTrials.gov Identifier: NCT03083704). This is a randomized, double-blind, study in healthy volunteers dosed to steady state with FXa inhibitors, designed to (1) demonstrate PK/PD comparability between andexanet alfa manufactured by the Generation 1 and Generation 2 processes, (2) evaluate the degree to which the Generation 2 andexanet reverses FXa-inhibitor-induced anticoagulation in comparison to placebo, and (3) evaluate safety of Generation 2 andexanet alfa.

Conclusions

Major and minor bleedings still occur with oral FXa direct inhibitors. Andexanet alfa is able to reverse the anticoagulant effect of FXa direct inhibitors as well as that of LMWH and its efficacy has been demonstrated both in vitro and in vivo studies. Animal and human data have shown its potential efficacy and safety in case of major bleeding. However, clinical evidence is still preliminary. Additional studies are ongoing and andexanet alfa is expected to be launched in the market in the near future.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interests.

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