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Review of Andexanet Alfa: New Reversal Agent for the New Oral Anticoagulants

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Abstract

Background: The use of Factor Xa (FXa) inhibitors for patients with Non-Valvular Atrial Fibrillation (NVAF) and Venous Thromboembolism (VTE) management continues to increase as clinicians become more familiar with their safety and efficacy profiles. For patients who experience clinically significant bleeding, andexanet alfa is a newly FDA approved agent to reverse the anticoagulant effects of apixaban and rivaroxaban.

Methods: A comprehensive, systematic review was conducted using EMBASE (1980-2019 Week 14) and MEDLINE (1966- March week 5 2019) for trials evaluating the efficacy and safety of andexanet alfa for reversing the anticoagulant effects of FXa inhibitors. The search was limited to clinical trials that were conducted in humans and published in English. These searches yielded 23 articles and abstracts. After excluding reviews and commentaries, and cross-referencing key articles for additional trials, ten articles and abstracts were chosen for this review.

Results: ANNEXA-A and ANNEXA-R evaluated the reduction in anti-Xa activity of andexanet alfa in apixaban and rivaroxaban, respectively. Statistically significant reduction in anti-Xa activity was found in apixaban and rivaroxaban groups compared to placebo in both studies. Similar results were reported in the ANNEXA-4 study, which evaluated the efficacy and safety of andexanet alfa in patients who experienced major bleeding while on apixaban, rivaroxaban, edoxaban or enoxaparin.

Conclusion: Evidence supports the use of andexanet alfa to reverse the anticoagulant effects of FXa inhibitors. Institutions will need to establish guidelines or protocols to guide prescribing and use. Current approval is for apixaban and rivaroxaban, though, off label use for reversal of these agents will likely occur and would be supported by the current data.

Keywords: Venous thromboembolism; Oral anticoagulants

Introduction

Several Direct Acting Oral Anticoagulants (DOACs) have been approved for the management of Venous Thromboembolism (VTE) as well as for secondary prevention of stroke in patients with Non-Valvular Atrial Fibrillation (NVAF). The use of these agents continues to increase as clinicians develop familiarity and comfort with their place in therapy. Factor Xa (FXa) inhibitors, including apixaban, rivaroxaban, edoxaban, and betrixaban, are DOACs which exert their therapeutic effects by binding to FXa [1-4]. Despite their established efficacy, there remains a concern for bleeding risk with their use, particularly in special populations, such as severe renal disease and advanced age. Unlike vitamin K antagonists, there is lack of reliable laboratory monitoring parameters and a specific reversal agent for FXa inhibitors. Therefore, challenges exist when monitoring their anticoagulant effects especially when a need arises to reverse therapy due to emergent surgeries or life-threatening bleeding. Until recently, limited data suggest the use of Prothrombin Complex Concentrate (PCC), activated Prothrombin Complex Concentrate (aPCC), and recombinant activated factor VII as reversal agents. Andexanet alfa is a recombinant, modified human FXa decoy protein that has been shown to work as a reversal agent for both direct and indirect FXa inhibitors [5-9]. Although catalytically inactive, this modified protein binds FXa inhibitors in the active site with high affinity. As a result, the activity of endogenous FXa is restored, leading to reduction in anticoagulation activity. The protein also prevents the activity of Tissue Factor Pathway Inhibitor, which leads to increasing factor-initiated thrombin generation.

Portola Pharmaceuticals was granted the United States Orphan Drug and FDA Breakthrough Therapy designations for andexanet alfa, and in May 2018, received approval for andexanet alfa, or Andexxa®, for the reversal of anticoagulation activity secondary to apixaban or rivaroxaban therapy. Shortly thereafter, in December 2018, the approval was expanded upon the FDA acceptance of the prior approval supplement, opening the door for increased availability of the agent in the United States [10].

The purpose of the review is to summarize published data on the use of andexanet alfa as a reversal agent for direct acting oral anticoagulants that exert their effects through FXa inhibition. Although there have been studies assessing the efficacy of andexanet alfa for reversal of other FXa inhibitors, two major studies leading to

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its approval were focused on rivaroxaban and apixaban, and therefore will be the primary focus of this review.

Methods

A comprehensive, systematic review was conducted using EMBASE (1980-2019 Week 14) and MEDLINE (1966- March week 5 2019) for trials evaluating the efficacy and safety of andexanet alfa for reversing the anticoagulant effects of FXa inhibitors. Key terms included *andexanet alfa*. The search was limited to clinical trials that were conducted in humans and published in English. These searches yielded 23 articles and abstracts. After excluding reviews and commentaries, and cross-referencing key articles for additional trials, five articles and abstracts were chosen for this review (Table 1).

Results and Discussion

Studies in healthy volunteers

The results of the ANNEXA- A and ANNEXA-R trials were reported together as both were phase 3, randomized, placebo controlled, dose range studies [11]. The ANNEXA- A evaluated the safety and efficacy of andexanet alfa in healthy volunteers anticoagulated with apixaban. In ANNEXA-R, healthy volunteers were anticoagulated with rivaroxaban. In both trials, volunteers were administered FXa inhibitors until steady state was achieved. Specifically, apixaban was dosed at 5 mg twice daily for 3.5 days, while rivaroxaban was dosed at 20 mg once daily for 4 days. In both studies, the treatment group was administered a bolus of andexanet alfa (Part 1) followed by a 2-hour continuous infusion (Part 2). The 2-hour infusion time resembled twice the half-life of andexanet alfa in order to extend the duration of FXa inhibitor reversal. In Part 1, 24 patients were on apixaban, 27 patients were on rivaroxaban, and 23 patients received placebo (9 in the apixaban group and 14 in the rivaroxaban group). In Part 2, 24 patients were on apixaban, 26 patients were on rivaroxaban, and 21 patients received placebo (8 in the apixaban group and 13 in the rivaroxaban group). Andexanet alfa doses in the ANNEXA-R study were twice that of the ANNEXA-A based on results from previous studies: 800 mg bolus followed by an 8 mg per minute infusion compared to 400 mg bolus followed by a 4 mg per minute infusion [11-13].

In total, 145 patients were included in the modified intention to treat analysis for the final results, of which 39% were women [11]. The average patient age was 57.9 years old (range 50-75 years), which is reflective of the population typically prescribed apixaban and rivaroxaban in practice. Of the 101 volunteers who received andexanet alfa, 53 were enrolled in ANNEXA-R and 48 in ANNEXA-A. In total, 44 volunteers were randomized to placebo (ANNEXA-R=27 and ANNEXA-A = 17). The primary efficacy endpoint for Part 1 was percent change in FXa enzymatic activity from baseline to nadir, defined as the value of anti-Factor Xa (anti-FXa) activity at 2 or 5 minutes (the lower result) after the bolus. In Part 2, the primary efficacy endpoint was defined as the lowest value between 10 minutes before and 5 minutes after the end of the infusion. Results for the primary endpoint of both studies indicate that the andexanet alfa group had significantly more patients achieving an 80% or greater reduction in anti-FXa activity compared to no patients in the placebo group ($p<0.0001$). There was one patient in the treatment group who did not receive the full andexanet alfa dose and therefore, did not achieve this endpoint. Investigators also measured mean plasma concentrations and found less than clinically significant levels for anticoagulant effect for both apixaban (< 3.5 ng per mL) and rivaroxaban (< 4 ng per mL). In Part 1, 100% of patients (n=24) in ANNEXA-A treatment group achieved normal Thrombin Generation (TG) time within 2-10 minutes of the bolus dose compared to 11% (n=1) of patients taking placebo ($p<0.001$). Similarly, 96% of patients (n=26) in the treatment group in ANNEXA-R achieved the same outcome, compared to 7% (n=1) in the placebo group ($p<0.001$). Overall, the mean change in TG for both ANNEXA-A and ANNEXA-R treatment groups was significantly greater than the placebo groups. For some patients, the mean TG exceeded baseline levels by more than 1 standard deviation (22%) and by more than 2 standard deviations (7%) of the treatment groups. In the latter, TG returned to less than 2 standard deviations within 30 minutes of treatment with andexanet alfa. Although seemingly transient, this leads to a concern for overcorrecting and increased risk of thrombosis. Regarding the aforementioned efficacy outcomes, the effects persisted 1-3 hours after the bolus or infusion was completed, as anticipated given the half-life of the treatment. No significant adverse effects were reported in either Part of each study, though one patient experienced hives. In all, 17 patients (17%) in the andexanet alfa group developed non-neutralizing antibodies, compared to only one patient in the placebo group (2%). This suggests that there is little immunogenicity associated with andexanet alfa administration. The positive results of these trials set the foundation for trials in patients requiring urgent or emergent reversal of apixaban and rivaroxaban anticoagulation therapy. Similar results were found in a study evaluating andexanet alfa in patients receiving betrixaban [14].

Studies in acute major bleeds

Interim results of ANNEXA- 4 were published in 2016, leading to the initial FDA approval of andexanet alfa in May 2018. The final ANNEXA- 4 results were published in early 2019 [15]. ANNEXA-4 is an open-label, single arm study evaluating the safety and efficacy of andexanet alfa for the reversal of apixaban, rivaroxaban, edoxaban, or enoxaparin in patients with acute major bleeding. Patients at least 18 years old taking therapeutic doses of an anticoagulant within 18 hours of presentation were included in the analysis. Exclusion criteria included scheduled surgery (excluding minimally invasive surgery or procedures) within 12 hours of presentation, Intracranial Hemorrhage (ICH) with a Glasgow Coma Scale score less than 7 or with an ICH volume greater than 60mL, less than 6 month expected survival, major thrombotic event within 2 weeks prior, or receipt of anti-or pro-coagulant products that may confound results within 7 days of presentation (e.g., vitamin K antagonist, dabigatran, PCC, whole blood, or plasma). Based on results from previous trials, the dosing of the study drug was determined by the anticoagulant utilized and time since last dose. Patients who had taken apixaban or rivaroxaban greater than 7 hours before andexanet alfa received a 400 mg bolus followed by 480 mg infused over 2 hours. A bolus dose of 800 mg followed by a 960 mg infusion was administered to patients who had been taking enoxaparin, rivaroxaban, or edoxaban within 7 hours or at an unknown time prior to andexanet alfa. The safety outcomes, including thrombotic events, 30 day mortality, adverse reactions, and antibody formation, were evaluated in all patients who received the study drug. However, the primary efficacy outcomes

Table 1: Summary of Studies.

Study	Study Design	FXa Inhibitor	Andexanet Dose	Efficacy Results
[11] (ANNEXA-A)[3]	Randomized double blind placebo controlled	apixaban 5 mg twice daily for 3.5 days	Part 1: 400 mg IV bolus (30 mg per minute)	Part 1: Anti-FXa activity was reduced in andexanet alfa (94+2%) vs. placebo (21+9%) [P<0.001]
			Part 2: 400 mg IV bolus followed by 4 mg per minute continuous infusion for 120 minutes (total dose of 480 mg)	Part 2: andexanet alfa (92+3%) vs. placebo (33+6%) [P<0.001]
[11] (ANNEXA-R)[3]	Randomized double blind placebo controlled	rivaroxaban 20 mg PO daily for 4 days	Part 1: 800 mg IV bolus (30 mg per minute)	Part 1: Anti-FXa activity was reduced in andexanet alfa (92+11%) vs. placebo (18+15%) [P<0.001]
			Part 2: 800 mg IV bolus followed by 8 mg per minute continuous infusion for 120 minutes (total dose of 960 mg)	Part 2: andexanet alfa (97+2%) vs. placebo (45+12%) [P<0.001]
[15] (ANNEXA-4)[6]	Prospective, open-label, single-arm study	apixaban, rivaroxaban, edoxaban, enoxaparin	-Last dose^ > 7 hours: 400 mg IV bolus followed by 4 mg per minute continuous infusion for 120 minutes (total dose of 480 mg) -Last dose^^ ≤ 7 hours: 800 mg IV bolus followed by 8 mg per minute continuous infusion for 120 minutes (total dose of 960 mg)	Patients with good of excellent hemostasis: 204 (82%) [95% CI 77-87%] Anti-FXa activity reduction at end of bolus: apixaban 92% (95% CI 92-93) rivaroxban 92% (95% CI 88-94) enoxaparin 75% (95% CI 66-79)
[14]	Randomized double blind placebo controlled	betrixaban 80 mg daily for 7 days	Cohort 1: 800 mg IV bolus	Cohort 1: Anti-FXa activity was reduced in andexanet alfa (6.5+4.5) vs. placebo (43+37.7)
			-Cohort 2: 800 mg IV bolus followed by 8 mg per min continuous infusion for 120 minutes	Cohort 2: Similar results

^apixaban and rivaroxaban
^^enoxaparin, edoxaban, or rivaroxaban

(percent change in baseline anti-FXa activity and rating of excellent/good hemostatic efficacy 12 hour post-infusion) were only assessed in patients with a baseline anti-FXa activity of 75 ng per mL or greater (or 0.5 international units or greater for patients on enoxaparin) and in patients with acute major bleeding who met the study criteria. Both requirements were adjudicated at a later time. Hemostatic efficacy requirements were consistent with those used in similar studies regarding the efficacy of PCC and determined by an independent adjudication committee.

Of the 352 patients enrolled in the study, 55% of patients (n=194) were on apixaban, and 36% (n=128) were on rivaroxaban. Average daily doses were 7.7 mg, and 19.3 mg respectively [15,16]. The mean time from hospitalization to andexanet alfa dose was 4.5-5.8 hours and from last anticoagulant dose to andexanet alfa was 9.5-13.1 hours. The independent committee adjudicated 254 patients to include in the efficacy analysis. The average age of patients was 77 years, 53% were male, and 80% were anticoagulated for NVAF. Over 86% had a creatinine clearance greater than 30mL per minute, which is expected given the renal dosing recommendations of the FXa inhibitors. In the total population, 20% of the patients had a history of stroke and 14% had a history of myocardial infarction. In the efficacy population, 67% of patients reported with ICH and 24% had gastrointestinal bleeding. For the 100 patients on rivaroxaban in the efficacy population, anti-FXa activity had decreased significantly by 92% at the end of the bolus (95% CI 88-94), and by 62% 12 hours after the infusion (95% CI 58-65). Interestingly, the 134 patients on apixaban also experienced a 92% reduction at the end of the bolus (95% CI 91-93), but only a 38% reduction 12 hours later (95% CI 38-41). Of the 249 patients who were evaluated for hemostatic efficacy, 82% patients achieved excellent/good hemostasis (95% CI 77-87). Achievement of hemostasis appears independent of change in anti-FXa activity. Of note, there appears to be a link with hemostasis and degree of anti-FXa activity in patients with ICH. Concerning safety, at 30 days, 220 patients (62%) had restarted anticoagulation (e.g., at least 1 dose), and of these only 8 patients (2%) had a thrombotic event. In total, at 30 days, 34 patients (10%) had a thrombotic event, of which 11 occurred within 5 days. Of the 49 deaths reported within 30 days of the study drug administration, 35 were due to cardiovascular reasons. There were no infusion reactions nor antibody formation identified.

Dosing, reconstitution, and storage considerations

Andexanet alfa is available in single-use vials of 100 mg of recombinant FXa [5]. Two dosing regimens can be utilized depending on the dose of the FXa inhibitor as well as the time of last ingestion. The low dose (an initial IV bolus of 400 mg followed by 4 mg per minute IV infusion) is used when apixaban and rivaroxaban are dosed at or less than 5mg and 10mg, respectively. The high dose strategy, an initial IV bolus of 400mg followed by 4 mg per minute IV infusion, is used when apixaban and rivaroxaban are dosed higher than 5mg and 10mg, respectively. The bolus dose in both regimens is administered at a target rate of 30 mg per minute, while the IV infusion is administered for up to 2 hours. The time of last ingestion for both dosing regimens should be less than 8 hours. If the time of last ingestion exceeds 8 hours or is unknown, then the low dose regimen is recommended.

Each vial is reconstituted with 10mL sterile water for injection, which can take up to 5 minutes per vial, to a final concentration 10 mg per mL. The reconstituted vials and IV bags are stable at room temperature for up to 8 hours, or may be stored at 2°C to 8°C for up to 24 hours for vials and 16 hours for IV bags.

Conclusion

Evidence supports the use of andexanet alfa to reverse the

anticoagulant effects of FXa inhibitors. Institutions will need to establish guidelines or protocols to guide prescribing and use. Potential challenges associated with the use of andexanet alfa include time for preparation and lack of experience with use compared to PCC and aPCC. Even though PCC and aPCC provide additional clotting factors rather than reversing the effect of FXa inhibitors, head-to-head studies on clinical outcomes may provide additional information to direct practice. It is important for practitioners to remember that most patients will still have an underlying indication for anticoagulation therapy after reversal. The decision to resume anticoagulation and the timeline should be determined by providers based on patient specific risk factors. Although current approval for andexanet alfa is specific to apixaban and rivaroxaban, the approved indication may be expanded to include other anticoagulants as studies get published. In the interim, off label use for reversal of these agents will likely occur and would be supported by the aforementioned data.

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References

1. Eliquis. Bristol Meyers Squibb Company. Princetone, NJ. 2016.
2. Xarelto. Janssen Pharmaceuticals. Inc, Titusville, NJ. January 2019.
3. Savyasa. Daiichi Sankyo. Inc. Basking Ridge, NJ. 2017.
4. Bevyxxa. Portola Pharmaceuticals. Inc. South San Francisco, CA. 2017.
5. Andexxa. Portola Pharmaceuticals. Inc. South San Francisco, CA. 2018.
6. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011; 365: 981-992.
7. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013; 369: 799-808.
8. The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010; 363: 2499-2510.
9. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011; 365: 883-891.
10. News release. Portola Pharmaceuticals. 2018.
11. Siegal DM, Curenutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, et al. Andexanet for the reversal of factor Xa inhibitor activity. N Engl J Med. 2015; 373: 2413-2424.
12. 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. Blood 2013; 122: 3636.
13. Crowther M, Levy GG, Lu G, Leeds J, Lin J, Pratikhya P, et al. A phase 2 randomized, double-blind, placebo-controlled trial demonstrating reversal of edoxaban-induced anticoagulation in healthy subjects by andexanet alfa (PRT064445), a universal antidote for factor Xa (fXa) inhibitors. Blood. 2014; 124: 4269.
14. Crowther M, Lu G, Leeds J, Lin J, Conley P, Curnutte J. Andexanet alfa reverses anticoagulation induced by betrixaban in healthy volunteers. Crit Care Med. 2017; 46.
15. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, et al. Full study report of andexanet alfa for bleeding associated with Factor Xa inhibitors. N Engl J Med. 2019; 380:1326-1335.
16. Andexanet alfa in factor Xa inhibitor associate major bleeding. American College of Cardiology 67th Annual Scientific Session and Expo. 2018.

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