




Andexanet alfa — Recommendations for clinical use. Multidisciplinary experts' standpoint

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Treatment with direct-acting oral anticoagulants is associated with an increased risk of bleeding [1]. A 1-year (2016) retrospective analysis of the United States Nationwide Readmissions Database identified 196,878 index bleeding-related hospitalizations in the cohort of patients with atrial fibrillation. The overall incidences of in-hospital mortality, need for post-discharge out-of-home care, and 30-day readmission were 4.9%, 50.8%, and 18.2%, respectively. Gastrointestinal bleeding was the most frequent cause of bleeding-related hospitalizations followed by traumatic and non-traumatic intracranial hemorrhage (ICH) and genitourinary bleeding [2]. The clinical burden of bleeding-related hospitalizations is mainly driven by relatively rare but severe and life-threatening ICH and less morbid gastrointestinal bleeding and

genitourinary bleeding. ICH related to treatment with oral anticoagulants resulted in the highest in-hospital mortality rates of 29% in nontraumatic and 12% in traumatic cases [2]. Treatment with direct-acting oral anticoagulants inhibiting factor Xa (FXa) apixaban and rivaroxaban has been shown to be associated with a lower risk of bleeding compared to vitamin K antagonists. Nevertheless, the American Heart Association registry also revealed a high in-hospital mortality rate of 27% for patients with nontraumatic ICH treated with FXa inhibitors. The odds of mortality were significantly higher as compared to patients not receiving anticoagulants but significantly lower compared to those taking warfarin [3].

Andexanet alfa (AA) is a recently developed recombinant, inactive FXa protein designed as

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Table 1. The recommended andexanet alfa (AA) dosing regimen.

Factor Xa inhibitor	Last dose	Time from the last dose to AA administration	
		< 8 hours/unknown	≥ 8 hours
Apixaban	≤ 5 mg	Bolus of 400 mg + infusion 4 mg/min	Bolus of 400 mg + infusion 4 mg/min
	> 5 mg/unknown	Bolus of 800 mg + infusion 8 mg/min	
Rivaroxaban	≤ 5 mg	Bolus of 400 mg + infusion 4 mg/min	Bolus of 400 mg + infusion 4 mg/min
	> 5 mg/unknown	Bolus of 800 mg + infusion 8 mg/min	

a universal antidote for the anticoagulant effects of direct and indirect FXa inhibitors. AA acts as a decoy protein that binds to FXa inhibitors, neutralizing their anticoagulant effects by preventing the inhibitors from binding to endogenous FXa [4–7]. The report of real-world data on utility and outcomes associated with reversal or replacement agents (fresh frozen plasma [FFP], four-factor prothrombin complex concentrate [PCC], or AA) used in the management of bleedings related to the use of FXa inhibitors showed the lowest mortality rate across all types of bleedings and shorter hospitalization in an intensive care unit for AA compared with other agents [8]. Based on the experience gained so far, AA is expected to provide the greatest clinical benefit in severely ill and very vulnerable populations [8–16].

The specific reversal agent for another direct-acting oral anticoagulant — the competitive thrombin inhibitor — dabigatran, is also available. In contrast to AA, idarucizumab is a humanized monoclonal antibody fragment that binds dabigatran with high affinity and specificity and rapidly reverses its anticoagulant activity [17].

Time from onset of bleeding is the variable that determines the clinical outcome of AA administration; therefore, pre-hospital logistics procedures ensuring quick transport of high-risk patients with life-threatening bleeding to centers with the possibility of effective therapy with AA should be developed similarly to acute coronary syndromes [18–20].

The ANNEXA-4 trial assessed the clinical outcome in 352 patients on treatment with FXa inhibitor, who received a bolus of AA, followed by a 2-hour infusion due to acute major bleeding. In subjects on apixaban or rivaroxaban, the median anti-FXa activity decreased equally by 92%. This laboratory effect was associated with excellent or good hemostasis obtained in 82% of patients. However, reduction in anti-FXa activity was not predictive of hemostatic efficacy overall, but it was modestly predictive in patients with intracranial hemorrhage [12].

The results of randomized trials, observational studies, and meta-analyses suggest that the high anticoagulatory effectiveness of AA resulting in mortality reduction is accompanied by an increased risk of thrombotic complications [1, 7–16]. The recommended dosing regimen is a single intravenous bolus at a target rate of approximately 30 mg/min for 15 min (low dose of 400 mg) or 30 min (high dose of 800 mg) followed by a continuous infusion for up to 120 min (low dose of 4 mg/min or high dose of 8 mg/min); the dosage depends upon the last dose of rivaroxaban or apixaban, and the time of the last dose (Table 1) [4].

However, a study evaluating the effects of AA at 2 concentrations (50 or 100 µg/mL) with thromboelastography showed “over-neutralization” — a relative hypercoagulable state in some cases at higher concentration, suggesting the possibility of overdosage, potentially leading to adverse effects. On the other hand, only a partial neutralization effect was seen with different anti-FXa agents when a lower concentration of AA was administered. Because the neutralization of various FXa inhibitors is dose- and donor-dependent, dose adjustment of AA is warranted for optimal results [5]. Thromboelastography represents a whole blood assay where the blood, plasma, and its components contribute to the biological effect of both FXa inhibitors and AA. Therefore, this method is likely to represent the endogenous effects observed in clinical conditions [5]. In another study, thromboelastography showed AA to be capable of neutralizing *in vitro* anticoagulant effects of unfractionated heparin and enoxaparin, but not fondaparinux [21].

Andexanet alfa has been approved by the United States Food and Drug Administration and European Medicines Agency for patients treated with rivaroxaban or apixaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. However, AA is not suitable for initial treatment in emergency surgery [22, 23]. The Summary of Product Characteristics is avail-

able on the European Medicines Agency website [24]. It is expected that AA will be available also in Poland in the second half of 2023.

Taking into account the available data, in particular the higher efficacy of AA compared to FFP and PCC, AA should be considered the therapy of choice in patients with uncontrollable, life-threatening bleeding on treatment with FXa inhibitors.

Recommendations

- AA should be considered in all patients treated with FXa inhibitors who experience life-threatening bleeding and for whom local hemostasis is not possible, regardless of the bleeding site.
- AA should be available in all stroke centers, trauma centers and in centers providing endoscopic treatment of gastrointestinal bleeding.
- To optimize the effectiveness and minimize the risk of AA use, each of these centers should develop a local protocol for the management of patients on oral anticoagulants, or with reasonable suspicion of taking them, who experience acute, serious bleeding.
- Due to the possibility of thrombotic complications after AA administration, the causal relationship between treatment with FXa inhibitors and the bleeding should be confirmed by anti-FXa activity tests or by FXa inhibitor concentration assessment. This, however, should not delay the administration of AA.
- AA should not be used in patients who are expected to require heparin in the acute phase of treatment.
- Logistical limitations resulting from the specific indication for AA determine the need to develop pre-hospital procedures for the proper transfer of patients.
- Due to limited experience with the use of AA and the expected low frequency of use, all administrations of this drug should be documented in a dedicated national registry.
- The application of thromboelastography to monitor the effects of AA should be considered because it could provide data allowing future dosage adjustments in order to improve the efficacy and safety of therapy.

Summing up, AA offers an opportunity for effective therapy of patients with uncontrollable, life-threatening bleeding on treatment with FXa inhibitors. Nevertheless, the risk of complications and high therapy costs require special care when using AA.

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