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Coagulation Factor Xa (Recombinant), Inactivated-Zhzo (Andexanet Alfa) Hemostatic Outcomes and Thrombotic Event Incidence at an Academic Medical Center

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Abstract

Andexanet alfa is approved for the reversal of factor Xa inhibitors in patients with major bleeding events. We aimed to review the incidence of effective hemostasis with andexanet alfa in a real-world environment. This retrospective cohort included patients hospitalized for a major bleed that resulted in andexanet alfa administration. The primary outcome was effective hemostasis at 12 hours after andexanet alfa treatment. Thromboembolic events and mortality within 30 days were also assessed. Over a 14-month period, 13 patients received andexanet alfa with a mean age of 69 $\pm$ 10 years, 54% male, 69% exposed to apixaban (31% rivaroxaban), and had intracranial (46%) and nonintracranial (54%) bleeding sites. Effective hemostasis was observed in 10 (77%) patients. Four (31%) patients experienced 5 thromboembolic events with a median time to event of 6.5 days (range: 0.5-29). Four thrombotic events occurred during the period in which anticoagulation (prophylaxis or therapeutic) was not restarted. Mortality rate was 15%. Andexanet alfa was effective in obtaining hemostasis in a majority of patients. However, the incidence of thromboembolic events was high and may be attributed to a delay in restarting anticoagulation.

Keywords

coagulation factor Xa (recombinant), inactivated-zhzo, andexanet, DOAC, bleed, rivaroxaban, apixaban, reversal

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Introduction

Use of oral factor Xa inhibitors such as apixaban and rivaroxaban has increased over the past decade.[1] Direct oral anticoagulants (DOACs) are recommended over warfarin for stroke prevention in patients with nonvalvular atrial fibrillation and for the treatment of venous thromboembolism (VTE).[2,3] Although variation exists among DOACs, they are generally associated with reduced incidence of major bleeding, equivalent or better efficacy, and provide a more simplified drug regimen when compared to warfarin.[4-7] As utilization of oral factor Xa inhibitors increases, management of consequential severe bleeding remains paramount, despite the decreased hemorrhagic risk compared to warfarin (relative risk 0.72, $P < .01$).[4,5] Significant morbidity and mortality associated with hemorrhagic events warrant timely and aggressive management to control the bleeding.[4,5,8] Until recently, there was no

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targeted reversal agent to treat patients on factor Xa inhibitors with an acute major bleeding episode.[9]

Coagulation factor Xa (recombinant), inactivated-zhzo (andexanet alfa) is a modified recombinant inactive form of human factor Xa developed to bind factor Xa inhibitor molecules.[9,10] By acting as a decoy protein, andexanet alfa allows for restoration of intrinsic factor Xa activity which then allows for normal hemostasis to occur.[9,10] Andexanet alfa was Food and Drug Administration approved under the Accelerated Approval Program in May 2018 and is indicated for the reversal of life-threatening or uncontrolled bleeding in patients receiving apixaban or rivaroxaban.[9,10]

The ANNEXA-4 trial assessed the efficacy and safety of andexanet alfa for patients who developed a major bleed while receiving factor Xa inhibitors or enoxaparin. Interim results of the trial were first released in 2016, and the full report was published in 2019.[9,10] Investigators reported 82% of 249 evaluable patients achieved excellent or good hemostatic efficacy at 12 hours after andexanet alfa.[9] Thrombotic event and mortality rates within 30 days were 10% and 14%, respectively.[9] Based on the results of the ANNEXA-4 trial, there have been recommendations by the American Society of Hematology and other guidance forums that suggest the use of andexanet alfa for patients with life-threatening bleeding during factor Xa inhibitor treatment.[4,5,8,11]

The ANNEXA-4 study provided important information regarding expected outcomes in a controlled study environment. While results from future trials are anticipated, it is important to review the utilization of this medication and resultant outcomes in the real-world environment. This retrospective cohort aimed to assess the hemostatic effectiveness and safety outcomes of andexanet alfa during clinical use at an academic medical center.

Methods

Study Design and Patients

This retrospective cohort study included all patients who were taking an oral factor Xa inhibitor and presented to a University of Colorado Health System Hospital (UCHealth) with a major bleed that resulted in andexanet alfa administration between June 2018 and August 2019. Patients were excluded if they were <18 years. This study was reviewed and approved by the institutional review board (IRB) at University of Colorado (protocol 19-1610). A waiver of patient consent was granted by the IRB.

Andexanet Alfa Use

At UCHealth, in accordance with the ANNEXA-4 trial and manufacturing recommendations, andexanet alfa is used for patients who received apixaban or rivaroxaban within the last 18 hours or at an unknown time and are in need of anticoagulation reversal due to a life-threatening or uncontrolled hemorrhage.[9,12] Institution-specific dosing recommendations mirror those recommended by the manufacturer and can be found in Supplementary Appendix A.[12] Requests for andexanet alfa use were approved by pharmacy or hematology to ensure use met aforementioned bleeding criteria. Anti-factor Xa (anti-Xa) levels or other laboratory test results indicated that factor Xa inhibitor presence was not required prior to administration of andexanet alfa.

Outcomes

The primary outcome was the percentage of patients who achieved excellent or good hemostatic outcomes within 12 hours after andexanet alfa administration. Hemostatic outcomes were classified as excellent, good, or poor based on the ANNEXA-4 study definitions.[9] Excellent and good outcomes were combined as "effective" hemostasis for the primary outcome. Briefly, effective hemostasis was considered for intracranial hemorrhage (ICH) if the hematoma volume did not increase by more than 35% on repeat imaging. An effective hemostatic outcome for nonintracranial bleeding was achieved if hemoglobin/hematocrit did not decrease by more than 20% within 12 hours. Hemoglobin and hematocrit were corrected for administered packed red blood cells.[9] If data were not available at 12 hours after infusion, then the next closest time point was used. Safety outcomes of interest were the rate of thrombotic events and all-cause mortality within 30 days of andexanet alfa administration. Patients discharged before 30 days were evaluated using clinic or readmission notes. If this information was not available, then the patient's last known outcomes were carried forward. The primary outcome was adjudicated by 2 independent reviewers who were blinded to the other's response. If there was a discrepancy, then a third author would individually review the case and be the deciding vote.

Data Collection

Retrospectively collected data included but was not limited to patient age, weight, past medical history, renal function at the time of andexanet alfa administration, factor Xa inhibitor drug and dose, coagulation studies such as anti-Xa levels, bleeding site, surgical interventions or procedures for bleeding control, thrombotic events, and reinitiation of anticoagulation. Additionally, as an extension of andexanet alfa efficacy and safety, data on administered blood products and other procoagulants were assessed.

Statistical Analysis

Categorical variables were expressed as values and percentages. Continuous variables were expressed as either mean $\pm$ standard deviation or median and interquartile range (IQR). Categorical associations were analyzed using a Fisher exact test. Statistical significance was defined as a P value of $<.05$. All patients who met criteria for study inclusion were assessed in the analysis.

Table 1. Baseline Characteristics.

Characteristic	Andexanet Alfa Patients, N = 13
Age, years	69 ± 10
Male	7 (54)
Body mass index, kg/m^2	32.5 ± 9.6
Estimated creatinine clearance	
< 30 mL/min	2 (15)
30-60 mL/min	4 (31)
> 60 mL/min	7 (54)
Primary indication for anticoagulation	
Atrial fibrillation	8 (62)
Venous thromboembolism	5 (38)
Past medical history	
Myocardial infarction	3 (23)
Stroke	0 (0)
Deep vein thrombosis	4 (31)
Pulmonary embolism	1 (8)
Heart failure	4 (31)
Diabetes mellitus	3 (23)
Factor Xa inhibitor	
Apixaban	9 (69)
Rivaroxaban	4 (31)
Site of bleeding	
Intracranial	6 (46)
Non-intracranial	7 (54)
Time since last factor Xa inhibitor dose	
< 8 hours	3 (23)
8-18 hours	6 (46)
Unknown	4 (31)
Hemodynamically unstable prior to andexanet alfa [b]	5 (38)
Andexanet alfa dosing	
High dose[c]	2 (15)
Low dose[d]	11 (85)

Abbreviations: IV, intravenous; SD, standard deviation.
[a]Data presented as mean ± SD or n (%).
[b]Hemodynamically unstable defined as mean arterial pressure <65 mmHg and/or requiring vasopressor support.
[c]High-dose 800 mg IV bolus followed by 960 mg IV infusion over 2 hours.
[d]Low-dose 400 mg IV bolus followed by 480 mg IV infusion over 2 hours.

Results

From June 2018 through August 2019, 13 patients received andexanet alfa, and all were included in the study analysis. Per institutional criteria (Appendix A), 12 (92.3%) patients met initial appropriate criteria for use. The outlier patient received andexanet alfa after further discussion with the pharmacist and approval by the hematology attending. The majority (n = 11) of patients presented to the hospital due to a bleeding event, with only 2 patients having a bleed during admission for an alternate diagnosis. Baseline characteristics can be found in Table 1. Mean age was 69 ± 10 years, total body weight 95.3 ± 27.6 kg, and median length of hospital stay was 14 days (IQR: 7-22 days). Indications for factor Xa inhibitor use were atrial fibrillation (62%) and VTE (38%). Nine (69%) patients previously received apixaban at a median daily dose of 10 mg/d (5 mg twice daily), and 4 (31%) patients previously received rivaroxaban at a median daily dose of 20 mg/d. Intracranial bleeding occurred in 46% of patients. Nonintracranial severe bleeding (54%) included 2 patients with aortic dissection, a retroperitoneal bleed, an iliacus/psoas hematoma, a uterine hemorrhage, a flank hematoma, and a lower extremity muscular bleed. A total of 3 (23%) patients received 1 or more other procoagulants within 8 hours prior to or concurrently with andexanet alfa infusion. Adjunctive procoagulants included factor IV–prothrombin complex concentrate (4F-PCC; n = 2), recombinant factor VIIa (n = 2), and tranexamic acid (TXA; n = 3). One patient received desmopressin after andexanet alfa infusion. In the 11 patients who were admitted for bleeding, median time from patient admit to andexanet alfa order was 2.1 hours (IQR: 1.18-4.1 hours). Median time from andexanet alfa order entry to administration of the bolus dose was 46 minutes (IQR: 33-50 minutes).

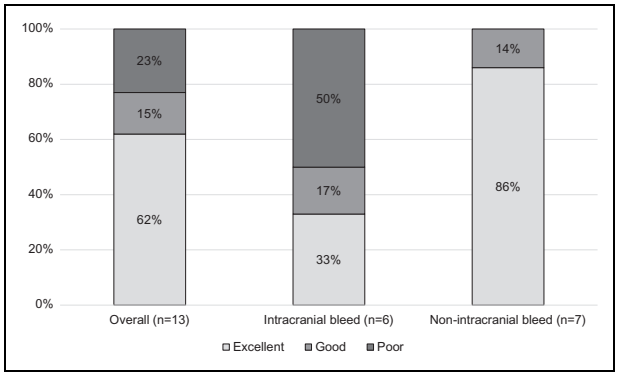

Figure 1. Hemostatic outcomes 12 hours after andexanet alfa infusion.

Effective hemostasis within 12 hours of andexanet alfa was reached by 10 (77%) patients (Figure 1). Of the 13 total patients, 8 (62%) patients were classified as having excellent hemostatic efficacy, and 2 (15%) patients were classified as achieving good hemostasis. The incidence of poor hemostatic efficacy was driven by patients with intracranial bleeding. Three of the 6 patients with an ICH had poor hemostasis at 12 hours compared to 0 of 7 patients with nonintracranial bleeds ($P = .07$). Five (38%) patients underwent a surgical intervention or procedure at the time of andexanet alfa infusion or within 12 hours after. All procedural bleeding was clinically judged as "normal or expected" for the procedure.

Six patients had baseline anti-Xa levels collected, and the median level was >1.70 IU/mL using a previously reported heparin calibrated assay.[13] Two patients had a baseline anti-Xa level and a follow-up level after andexanet alfa administration. One patient had anti-Xa levels at 1 hour and 2.5 hours after andexanet alfa infusion had completed which were both >1.70 IU/mL. The other patient had an anti-Xa level at 8 hours after andexanet alfa infusion which was also >1.70 IU/mL. One patient achieved excellent hemostasis, while the other had a poor hemostatic outcome.

Four (31%) patients experienced 5 thrombotic events within 30 days after andexanet alfa (Table 2). The median time to

Table 2. Safety Outcomes.[a]

Variable	Patients, N = 13
≥ 1 Thrombotic event within 30 days	4 (31)
Myocardial infarction	1 (8)
Ischemic stroke	1 (8)
Deep vein thrombosis	1 (8)
Pulmonary embolism	1 (8)
Superficial venous thrombosis	1 (8)
Death within 30 days	2 (15)
Restart of any anticoagulation (AC)	8 (62)
Prophylactic AC	5 (38)
Therapeutic AC	3 (23)
Thrombotic event after AC restarted	1 (8)

[a]Data are presented as n (%).

event was 6.5 days (IQR: 1-26 days). Events included deep vein thrombosis, ischemic stroke, pulmonary embolism, myocardial infarction, and superficial venous thrombosis. A total of 5 patients were not restarted on either prophylactic or therapeutic anticoagulation during their hospital admission. For those patients who were restarted on any form of anticoagulation, the median time to initiation after bleed was 4.5 days (IQR: 2-5.5 days). Of the 5 thrombotic events, 4 occurred before prophylactic or therapeutic anticoagulation was restarted. Notably, 2 of the 4 patients who experienced a thrombotic event also received factor VIIa and/or 4F-PCC.

Mortality rate within 30 days after andexanet alfa was 15% (n = 2). Median time to event was 2 days (range: 1.5-2.5). Both patients had an ICH with a Glasgow Coma Score (GCS) of 8 and 4, respectively. No patients in the non-ICH group died. No patients were lost to follow-up prior to day 30 post-andexanet alfa administration.

Discussion

In this retrospective cohort of patients administered andexanet alfa for reversal of factor Xa inhibitor activity in the setting of acute hemorrhage, 77% of patients achieved excellent or good hemostatic efficacy. This is comparable to the 82% effective hemostasis reported in the ANNEXA-4 trial.[9] One difference that should be noted in the ANNEXA-4 trial is that 80% of patients with intracranial bleeding had excellent or good outcomes compared to only 50% in this present cohort. One possible reason for this difference is the exclusion criteria of the ANNEXA-4 trial. Patients with an expected survival of less than 1 month as well as patients with intracranial bleeding and a GCS of <7 were excluded. Lower GCS scores in the setting of an ICH are a known independent predictor of mortality.[14,15] There were 2 patients with ICH included in our retrospective review who had a GCS of <7, one of which had ineffective hemostasis at 12 hours while the other died within 30 days. Although the use of andexanet alfa in severely neurologically injured ICH will likely occur in real-world use, the clinical benefit remains undefined in those with a low GCS and requires further research to fully elucidate.

All-cause, 30-day mortality was similar between the current cohort and ANNEXA-4 (15% [2/13] vs 14% [49/352], respectively). A higher percentage of patients developed a thrombotic event in this cohort compared to ANNEXA-4 (31% [4/13] vs 10% [34/352], respectively). This difference could be explained by several possible factors, first being low patient numbers in our cohort which amplifies the percentage of each event. Additionally, our cohort had a higher proportion of patients with a baseline VTE indication for DOAC use compared to ANNEXA-4 (38% [5/13] vs 17% [61/352], respectively). In those on a DOAC for a VTE indication versus a stroke prevention indication, the rates of thrombotic development after andexanet alfa were 40% (2/5) compared to 25% (2/8), respectively. Another possible factor for the higher thrombotic rate in this cohort is that 2 of 4 patients who had a thrombotic event received 4F-PCC and/or factor VIIa in addition to andexanet alfa. Patients who received these factors within 7 days of screening were excluded from the ANNEXA-4 trial as well as those anticipated to receive procoagulants within 12 hours following andexanet alfa administration. Both factor VIIa and 4F-PCC carry an independent thrombotic risk and might explain the higher incidence of thrombotic events noted here with andexanet alfa use in a real-world environment.[16,17] One of the patients refused all blood products but agreed to receive 4F-PCC. Adequate bleeding control was not achieved in this patient; therefore, andexanet alfa was given 8 hours later. The 2 patients who received both factor VIIa and TXA had a type A aortic dissection. It is common practice at our hospital to administer TXA when coming off cardiac bypass pump. Factor VIIa is given when there are complications coming off bypass, and its use is occasionally guided by thromboelastography or other coagulation test results assessed in the operating room. One of the aortic dissection patients received 4F-PCC in addition to andexanet alfa likely due to extensive injury and bleeding. Both patients who received 4F-PCC went on to develop some form of a VTE. The combination of adding clotting factors while reversing DOAC effects is a double-hit scenario for clot development. Our institution does not advise the use of andexanet alfa with other procoagulants due to the thrombotic risk. Institutional wide efforts to reeducate health-care providers about the risks of providing additional procoagulants while acutely reversing an anticoagulant using these data are ongoing.

Both ANNEXA-4 and this retrospective cohort found that about two-thirds of the thrombotic events occurred ≥6 days after andexanet alfa administration. In both studies, 62% of patients were restarted on either prophylactic or therapeutic anticoagulation. The incidence of a thrombotic event after prophylactic or therapeutic anticoagulation was restarted was low in both the current cohort and ANNEXA-4 (13% [1/8] vs 2% [8/220], respectively).

Taken together, this information indicates the need for a risk assessment of provisional procoagulant prior to, during, or following andexanet alfa treatment. Additionally, the reinitiation of prophylactic or therapeutic anticoagulation following andexanet alfa administration for a major bleeding event should be

pursued as soon as clinically appropriate. A goal of restarting anticoagulation or antithrombotic prophylaxis within a 6-day period may be achievable for stable patients and might decrease the incidence of thrombotic events.

The ANNEXA-4 investigators hypothesized a correlation between reduction in anti-Xa levels and hemostatic efficacy outcomes. However, they were unable to find an association between the two. In the present cohort, there were 2 patients with anti-Xa levels above the detectable limit of our assay within the 8 hours after andexanet alfa administration. One patient had an excellent hemostatic outcome, while the other had a poor hemostatic outcome. While the population size is too small to draw meaningful conclusions from, this may still support the notion made by the ANNEXA-4 trial that change in anti-Xa levels is unlikely to be useful for predicting effective hemostasis. Furthermore, currently available commercial anti-Xa assays will provide falsely elevated anti-Xa levels in the presence of a factor Xa inhibitor and andexanet alfa. A modified anti-Xa activity assay is required to accurately assess andexanet alfa effect.[18] Although we advise providers to consider obtaining baseline anti-Xa levels, particularly for patients with unknown DOAC exposure to inform subsequent decisions, we strongly caution interpretation of follow-up anti-Xa values after andexanet alfa exposure. Importantly, andexanet alfa administration should not be delayed to obtain and assess a baseline anti-Xa.

Conclusions

Andexanet alfa achieved effective hemostasis in a majority of patients. However, about one-third of patients experienced a thromboembolic event. The high incidence may be in part attributed to use of other procoagulants as well as a delay in the reinitiation of anticoagulation. The use of andexanet alfa for patients with an ICH and a low GCS will occur in clinical practice; however, the benefit of its use in this patient population requires further exploration.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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