CLINICAL STUDY REPORT SYNOPSIS

Acute major bleed chart audit

Andexanet alfa and 4F-PCC use in patients hospitalised with an anticoagulant-related major bleed

Milestones:	Study protocol approved: 04 July 2022 Study protocol amendment approved: 16 November 2022 Final analytic dataset: 20 December 2022 Final CSR: 28 June 2023
Phase of development:	Marketed
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Clinicaltrials.gov registration:	NCT05548777

This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

Background/rationale:

Oral Factor Xa inhibitors have been shown to be safe and effective for the treatment and prevention of venous thromboembolism and for stroke prevention in patients with atrial fibrillation. However, oral Factor Xa inhibitors are associated with an increased risk of major and fatal bleeding events. Historically, options for reversing the anticoagulant effect of Factor Xa inhibitors in patients with major bleeding have been limited, and were often treated with non-specific indirect reversal or factor replacement strategies, such as 4-Factor Prothrombin Complex Concentrates (4F-PCC).

In May 2018, the US FDA approved a specific reversal agent, andexanet alfa, which binds specifically to Factor Xa inhibitors and rapidly reverse their anticoagulant effect. Andexanet alfa is the first FDA-approved management for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Research is

needed to better understand how andexanet alfa is used in routine clinical practice and how it compares to usual care agents such as 4F-PCC in terms of outcomes such as mortality.

Objectives:

The primary objective was to describe characteristics, treatments and outcomes in adult patients treated with andexanet alfa or 4F-PCC during a hospitalization for an anticoagulation-related major bleed.

The secondary objectives included to compare the risk of in-hospital mortality in patients treated with andexanet alfa versus 4F-PCC overall and within patient subgroups, pending feasibility.

Study design:

This was an observational study based on secondary data collected via chart audit.

Data source:

Chart audit of electronic medical charts from selected hospitals in the United States that had either andexanet alfa or 4F-PCC (or both) on formulary.

Study population:

The study population included adult US patients treated with andexanet alfa or 4F-PCC during a hospitalization for an anticoagulation-related major bleed, with discharge dates between May 2018 and September 2022.

Inclusion criteria:

- ICD-10-CM diagnosis code of D68.32 (Hemorrhagic disorder due to extrinsic circulating anticoagulants) as part of an inpatient admission
- Taking either an oral FXa inhibitor or enoxaparin at the time of hospitalization for their bleeding event
- Treated with either andexanet alfa or 4F-PCC during the hospitalization for their bleeding event
- Had documented discharge disposition (i.e. the hospitalization was completed and discharge disposition was reported)

Exclusion criteria:

- Less than 18 years old
- Treated with both andexanet alfa and 4F-PCC during the hospitalization for their bleeding event

Statistical methods:

Descriptive statistics were used to summarize baseline demographic and clinical characteristics.

Complete-case multivariable logistic regression analysis was used as the primary analysis method to compare odds of mortality in patients treated with andexanet alfa versus 4F-PCC; propensity-score weighted logistic regression analyses using multiple imputations for missing baseline covariate data was used as the secondary analysis method.

Subgroup analyses were performed in patients with intracranial hemorrhage (ICH) and with gastrointestinal (GI) bleeds.

Results:

As part of the assessment of feasibility for comparative analyses, potential differences in patient characteristics over time and between patients treated with andexanet alfa versus 4F-PCC were assessed. To align with the US FDA approval, and due to observed differences over time in characteristics of patients categorized as taking enoxaparin at the time of their bleeding event hospitalization, these analyses were performed in patients taking either apixaban or rivoraxoban at the time of their hospitalization for their bleeding event.

A total of 354 hospital institutions participated in the study, representing 42 states. The study population included 4395 patients, of which 2122 had been treated with andexanet alfa and 2273 with 4F-PCC. Mean age was 65.6 and 66.6 years, respectively, and 57.2% and 60.5% were men. Most patients had GI bleeds (andexanet alfa, 56.8%; 4F-PCC, 59.9%), and just under one-third had ICH (andexanet alfa, 31.4%; 4F-PCC, 29.1%). Do-not-resuscitate (DNR) orders were present in 18.3% of andexanet alfa-treated and 19.8% of 4F-PCC-treated patients. Approximately 1 in 3 patients in both groups had impaired mental status upon admission.

Time since last anticoagulant dose was similar between the andexanet alfa and 4F-PCC cohorts, with more than 80% of patients in both groups having <18 hours in between their last dose of oral FXa inhibitor and hospital admission. The median time from hospital arrival to administration of andexanet alfa or 4F-PCC was 2.5 and 2.3 hours, respectively.

Other treatment strategies, such as intravenous fluids, packed red blood cells, or fresh frozen plasma, were administered to a lower proportion of patients treated with andexanet alfa than with 4F-PCC (44.8% vs 71.6%).

In-hospital mortality occurred in 6.0% of patients treated with andexanet alfa and in 10.6% of the 4F-PCC cohort.

In the multivariable logistic regression analysis, the odds of in-hospital mortality was 50% lower in patients treated with andexanet alfa compared with patients treated with 4F-PCC (adjusted odds ratio [aOR]: 0.50; 95% confidence interval [CI]: 0.39-0.65; p <0.01); similar results were obtained from the propensity score-weighted logistic regression analysis (OR: 0.59; 95% CI: 0.46-0.74; p<0.01). Other factors associated with higher odds of death included ICH and critical compartment bleeds (vs GI bleed), increasing age, liver disease, chronic kidney disease, heart failure, impaired mental status, and a DNR order.

Among patients with ICH, in-hospital mortality occurred in 12.6% of patients in the andexanet alfa cohort compared with 23.3% of patients in the 4F-PCC cohort, and the adjusted odds of in-hospital mortality were 45% lower with andexanet alfa compared with 4F-PCC (aOR: 0.55; 95% CI: 0.39-0.76; p<0.01).

In patients with GI bleeds, in-hospital mortality occurred in 2.5% of patients treated with andexanet alfa versus in 4.3% of patients treated with 4F-PCC. The adjusted odds of in-hospital mortality were 51% lower (aOR: 0.49; 95% CI: 0.29-0.81; p=0.01).

Conclusion:

This observational study describes the use of andexanet alfa among patients hospitalized with rivaroxaban- or apixaban-related major bleeding in routine clinical practice, and how it compares to 4F-PCC in terms of in-hospital mortality. Treatment with andexanet alfa was associated with 50% lower odds of in-hospital mortality compared to 4F-PCC, and the magnitude of the risk reduction was similar in ICH (45%) and GI bleeds (51%).

Publications:

- Dobesh PP, Fermann GJ, Christoph MJ, Koch B, Lesén E, Chen H, Lovelace B, Dettling T, Danese M, Ulloa J, Danese S, Coleman CI. Lower mortality with andexanet alfa vs 4-factor prothrombin complex concentrate for factor Xa inhibitor-related major bleeding in a U.S. hospital-based observational study. Res Pract Thromb Haemost. 2023 Aug 30;7(6):102192. doi: 10.1016/j.rpth.2023.102192.