

Andexanet Alfa for Factor Xa Inhibitor–Associated Intracerebral Hemorrhage

Does a Specific Reversal Agent Justify Its Cost?

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Modeling the Clinical Implications of Andexanet Alfa in Factor Xa Inhibitor–Associated Intracerebral Hemorrhage

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Direct oral anticoagulants have been rapidly adopted for the prevention of acute ischemic stroke and the treatment of venous thromboembolism.¹ Despite direct oral anticoagulants being associated with less incidence of intracranial hemorrhage (ICH) than vitamin K antagonists, the risk is still present, up to 2% in some observational studies.² In 2015, the Food and Drug Administration granted accelerated approval to idarucizumab, a monoclonal antibody that binds to dabigatran, a direct thrombin inhibitor, and neutralizes its activity. At that time, factor Xa (fXa) inhibitors (rivaroxaban and apixaban) still did not have a specific reversal agent, and guidelines recommend the off-label use of 4-factor prothrombin complex concentrates (4F-PCCs) to treat patients taking these medications and presenting with major bleeding.³

Andexanet alfa, a recombinant human fXa decoy protein that binds directly to rivaroxaban and apixaban to reverse their anticoagulant effect, was granted accelerated approval by the Food and Drug Administration in 2018. This was based on the results of ANNEXA-4, an open-label, single-arm, prospective study examining the hemostatic effect of andexanet alfa on patients presenting with major bleeding after administration of an fXa inhibitor. Coprimary outcomes of change in anti-fXa activity and excellent/good hemostasis (defined as $\leq 35\%$ increase in hemorrhage volume) were investigated.⁴ A substudy of ANNEXA-4 examining patients with spontaneous ($n = 99$) and traumatic ($n = 70$) intracranial bleeding demonstrated excellent hemostasis in 79% of cases.⁵

Despite its accelerated approval, questions remain about the clinical efficacy, safety profile, and cost-effectiveness of andexanet alfa. ANNEXA-4 did not contain a comparator group, challenging valid inferences about its hemostatic efficacy. Moreover, patient-oriented outcomes were not examined. The patient population skewed toward those with smaller hemorrhages (median ICH volume 10 mL) with a high admission Glasgow Coma Scale score (median 15) who are at lower risk for hematoma expansion. While andexanet alfa has subsequently been incorporated into guidelines for the reversal of fXa inhibitors, the issues described above, along with its high cost (approximately \$24,750 per dose), make it difficult for hospital pharmacy and therapeutics committees to decide whether to incorporate the reversal agent in hospital formularies.⁶

This issue of *Neurology*® delivers a meticulously crafted study by Chuck et al.⁷ to explore some of the unknowns described above. The authors use a simulated dataset derived from a single-center ICH registry to model the potential hemostatic effects, patient-oriented outcomes, and costs associated with andexanet alfa in fXa inhibitor–associated ICH. They analyzed data from 603 patients admitted to their intensive care unit with ICH (55 with fXa inhibitor–associated ICH) to predict the probability of inadequate hemostasis, defined as hematoma expansion $>35\%$ of the initial ICH volume, akin to the ANNEXA-4 definition. They then simulated a larger cohort of patients with fXa inhibitor–associated ICH and modeled a range of potential effects of andexanet alfa on the reduction of inadequate hemostasis and 3-month unfavorable

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outcome, defined as a modified Rankin Scale score of 4 to 6. The authors' methodology allowed them to model outcomes for patients who were ineligible for ANNEXA-4. They conclude that andexanet alfa could be associated with an absolute risk reduction of 4.9% to 7.4% in 3-month unfavorable outcome with a number needed to treat of 14 to 21 with cumulative costs ranging from \$346,500 to \$519,750 for ANNEXA-4-eligible patients, if it improves hemostatic efficacy by 33% to 50% over 4F-PCCs. The absolute risk reduction for ANNEXA-4-ineligible patients (due to ICH volume >60 mL or Glasgow Coma Scale score <5) would be more modest (3.2%–5.0%) with a higher number needed to treat (20–31) at higher cumulative cost (\$495,000–\$767,250), if it improves hemostatic efficacy by similar margins.

While such high costs may seem prohibitive, back of the envelope calculations suggest that further study is warranted to investigate the effect on quality-adjusted life-years, which are valued between \$50,000 and \$100,000. Perhaps the high cost could be justified in those patients with the highest risk for hematoma expansion. Unfortunately, prior studies using imaging biomarkers predictive of hematoma expansion in non-fXa inhibitor-associated ICH have failed to show significant benefit for other hemostatic agents such as tranexamic acid and recombinant factor VIIa.^{8,9} Further research is necessary to determine which patients with fXa inhibitor-associated ICH are most likely to have meaningful hematoma expansion.

Of course, the authors' findings hinge on particularly optimistic assumptions of the hemostatic efficacy of andexanet alfa, which has not been directly compared to that of 4F-PCCs. In the authors' cohort, there was a 91% rate of hemostasis in fXa inhibitor-associated ICH when 4F-PCCs were used, comparing favorably to the ICH cohort in ANNEXA-4. This is further corroborated by a multicenter observational study demonstrating an 82% rate of hemostasis with 4F-PCC in a cohort of patients with fXa inhibitor-associated ICH.¹⁰ Thus, the superiority of andexanet alfa to 4F-PCCs remains in question. The study by Chuck et al. is further limited by a failure to account for adverse effects of andexanet alfa, including major cardiovascular events, which could alter the calculations.

Where does that leave us with andexanet alfa? Should it be incorporated as standard of care for reversal of fXa inhibitor-associated ICH? The answer is still unknown; there are no randomized controlled studies to properly assess the efficacy and safety of andexanet alfa. The ANNEXA-I study, comparing andexanet alfa to usual care (which should include 4F-PCC) in patients with fXa inhibitor-associated ICH, may provide some insight into these questions, but it is likely underpowered to detect differences in patient-centered outcomes. Thus, pharmacy and therapeutics committees will have to perform their own analyses like the one presented by Chuck et al., incorporating hemostatic efficacy comparisons from ANNEXA-4, to make their own informed decisions. The authors have graciously made their code publicly available to enable such analyses.

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Disclosure

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References

1. Wetmore JB, Roetker NS, Yan H, Reyes JL, Herzog CA. Direct-acting oral anticoagulants versus warfarin in Medicare patients with chronic kidney disease and atrial fibrillation. *Stroke*. 2020;51(8):2364-2373.
2. Kattoor AJ, Pothineni NV, Goel A, et al. Prescription patterns and outcomes of patients with atrial fibrillation treated with direct oral anticoagulants and warfarin: a real-world analysis. *J Cardiovasc Pharmacol Ther*. 2019;24(5):428-434.
3. Frontera JA, Lewin JJ III, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care*. 2016;24(1):6-46.
4. Connolly SJ, Milling TJ, Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2016;375:1131-1141.
5. Demchuk AM, Yue P, Zotova E, et al. Hemostatic efficacy and anti-FXa (factor Xa) reversal with andexanet alfa in intracranial hemorrhage: ANNEXA-4 substudy. *Stroke*. 2021;52(6):2096-2105.
6. Peled H, Dau NQ, Lau H. Key points to consider when evaluating andexanet alfa for formulary addition. *Neurocrit Care*. 2020;33(1):20-24.
7. Chuck CC, Kim D, Kalagara R, et al. Modeling the clinical implications of andexanet alfa in factor Xa inhibitor-associated intracerebral hemorrhage. *Neurology*. 2021;97(21):e2054-e2064.
8. Ovesen C, Jakobsen JC, Gluud C, et al. Tranexamic acid for prevention of hematoma expansion in intracerebral hemorrhage patients with or without spot sign. *Stroke*. 2021;52(suppl 1):2629-2636.
9. Gladstone DJ, Aviv RI, Demchuk AM, et al. Effect of recombinant activated coagulation factor VII on hemorrhage expansion among patients with spot sign-positive acute intracerebral hemorrhage: the SPOTLIGHT and STOP-IT randomized clinical trials. *JAMA Neurol*. 2019;76(12):1493.
10. Panos NG, Cook AM, John S, et al. Factor Xa inhibitor-related intracranial hemorrhage: results from a multicenter, observational cohort receiving prothrombin complex concentrates. *Circulation*. 2020;141(21):1681-1689.