Andexanet for Factor Xa Inhibitor-Associated Acute Intracerebral Hemorrhage

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SUMMARY

Andexanet alfa is a recombinant modified human factor Xa decoy protein designed to reverse the anticoagulant effects of factor Xa inhibitors, such as apixaban and rivaroxaban. Its role in treating factor Xa inhibitor-associated acute intracerebral hemorrhage (ICH) has been evaluated in several studies.

The ANNEXA-I trial demonstrated that andexanet alfa significantly improved hemostatic efficacy compared with usual care, with 67.0% of patients achieving hemostatic control versus 53.1% in the usual care group (adjusted difference, 13.4 percentage points; 95% CI, 4.6 to 22.2; $P = 0.003$).[1] This trial also showed a substantial reduction in antifactor Xa activity (94.5% with andexanet vs. 26.9% with usual care; $P < 0.001$).[1] However, the use of andexanet alfa was associated with a higher incidence of thrombotic events (TEs), including ischemic stroke (10.3% vs. 5.6%; $P = 0.048$).[1]

The ANNEXA-4 study, a single-arm trial, also reported high rates of hemostatic efficacy (78.6% in spontaneous ICH and 82.9% in traumatic ICH) and significant reductions in antifactor Xa activity (93.8% for apixaban and 92.6% for rivaroxaban).[2] TEs occurred in 9.3% of patients within 30 days.[2] Comparative studies have shown that andexanet alfa is associated with better hemostatic effectiveness and improved survival compared with 4-factor prothrombin complex concentrate (4F-PCC).[3]

The American College of Cardiology (ACC) recommends the use of andexanet alfa for the reversal of rivaroxaban- or apixaban-associated life-threatening bleeding, including ICH, when available.[4] In summary, andexanet alfa is effective in reversing the anticoagulant effects of factor Xa inhibitors and improving hemostatic outcomes in acute ICH, but it carries a notable risk of thrombotic events.

COMMENTARY

The anticoagulant reversal agent andexanet alfa has garnered significant interest as a potential antidote for life-threatening bleeds in patients treated with factor Xa inhibitors. The ANNEXA-I trial, published in the New England Journal of Medicine, provides the first randomized evaluation of andexanet's efficacy and safety specifically in the context of factor Xa inhibitor-associated intracerebral hemorrhage (ICH).[1] This multicenter study across 23 countries enrolled more than 500 patients with acute ICH who had recently received apixaban, rivaroxaban, or edoxaban, randomizing them to andexanet or usual care comprising primarily 4-factor prothrombin complex concentrate (PCC). The rigorous trial design, central adjudication of key end points, and pragmatic comparator make ANNEXA-I an important addition to the literature on anticoagulant-related ICH management.

From an efficacy stand point, the primary composite end point of "hemostatic efficacy" favored andexanet over usual care, driven by superior hematoma control. Hemostatic efficacy required meeting criteria for limited (≤35%) hematoma expansion at 12 hours, minimal neurologic deterioration, and no need for rescue hemostatic therapy. Andexanet achieved this end point in 67% of patients versus 53% of patients with usual care. Importantly, andexanet led to a marked 94.5% reduction in antifactor Xa activity by 1–2

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hours, consistent with its proposed mechanism of directly binding and sequestering factor Xa inhibitors.[5] This degree of rapid anticoagulation reversal provides a plausible mechanistic rationale for the observed reduction in hematoma expansion with andexanet.

These benefits must be weighed against the concerning 10.3% rate of TEs such as ischemic stroke in andexanet-treated patients, nearly double the 5.6% rate with usual care. This reflects the inherent double-edged nature of anticoagulation reversal in ICH.[6] Indeed, in the prior ANNEXA-4 study evaluating andexanet across all sites of major bleeding, a 10% thrombotic event rate was also reported, and higher andexanet doses increased this risk.[7]

Although ICH represents a potent prothrombotic stimulus where anticoagulation reversal could mitigate further bleeding, excessive procoagulant effects raise the opposite specter of recurrent ischemic events. The pathophysiologic drivers behind andexanet's thrombogenicity remain unclear but may relate to the rapid, excessive thrombin generation resulting from the complete reversal of factor Xa inhibition. Although necessary to control bleeding acutely, this proteolytic "rebound" state may precipitate clotting, particularly in patients with vascular risk factors such as atrial fibrillation (the predominant indication in this ICH population). An alternative hypothesis implicates andexanet's binding of tissue factor pathway inhibitor, triggering a transient procoagulant state.[8] Reassuringly, andexanet did not increase thrombotic risk in healthy volunteer studies, suggesting that the prothrombotic effects may be specific to acutely ill patient populations with ongoing vascular stressors such as ICH.[5]

Importantly, not all patients with ICH face equivalent thrombotic risk that would contraindicate andexanet. Those without an underlying prothrombotic indication such as atrial fibrillation could theoretically derive greater net benefit from hemorrhage control with lower competing ischemic event risk. Similarly, patients already harboring a sizeable completed infarct volume may tolerate further thrombotic complications less consequentially than ongoing hematoma expansion.[9] Individual stratification of thrombotic and hemorrhagic hazards is paramount when considering andexanet's overall harm–benefit ratio.[10] In addition, it would have been beneficial if the trial had better stratified the high-dose versus low-dose andexanet groups elucidating how many TEs occurred in each group; this would guide a determination if such events are dose dependent. Although the trial was not powered to draw conclusions about subgroups, the subgroup analysis table suggests that patients who received a low dose of andexanet fared better than those who received high dose of andexanet.

The ANNEXA-I trial had several limitations worth noting. The primary end point was a nontraditional composite lacking insight into key clinical outcomes such as mortality and functional status. Although limited exploratory analyses suggested no difference in 30-day mortality or poor functional outcome between groups, the open-label design introduces potential ascertainment bias on subjective elements such as NIHSS scoring. Importantly, there was no central assessment of final infarct volumes to quantify the balance between reduced hematoma growth and paradoxical ischemic injury with andexanet. Future studies should prioritize patient-centered efficacy outcomes such as functional status and quality-of-life metrics, capturing the net impacts of hemorrhagic and thrombotic complications. In addition, the secondary end point of the trial was to measure the percentage change in antifactor Xa activity from baseline to nadir within the first 2 hours after randomization.

Subgroup analyses were limited, obscuring potential effect heterogeneity across specific clinical phenotypes that could inform patient selection for andexanet. Did benefits persist across the entire spectrum of ICH severity and hematoma sizes, or only in the largest, most catastrophic bleeds? Did certain factor Xa inhibitors derive greater relative efficacy from reversal? Can we leverage biomarkers or clinical–radiographic prediction models to enrich the likelihood of hematoma expansion and identify those most likely to benefit? Granular characterization of such effect modifiers is an unmet need.

Ultimately, although imperfect, the ANNEXA-I data argue for a role for andexanet in selected ICH patients with factor Xa inhibitor-related coagulopathy, particularly those with actively expanding bleeds causing neurologic devastation. However, its use should be judicious given the concerning thrombotic event signal, carefully weighing the risks and benefits in each case. In lower hemorrhagic risk scenarios where hematoma expansion has plateaued, andexanet may carry excessive ischemic hazards that outweigh its utility. Rather than a one-size-fits-all approach, anticoagulant reversal likely necessitates a nuanced, individualized strategy balancing hemorrhagic and thrombotic risks based on the clinical presentation.[11] From the neurosurgical perspective, andexanet is particularly useful in patients with acute intracerebral hemorrhage who are destined for emergent OR intervention. In operative patients with ICH prescribed and treated with factor Xa inhibitors, achieving thrombosis before surgical intervention is paramount and potentially life saving, thus the appropriate reversal agent ought to be selected. This decision is guided by choosing the most potent and efficacious option, which is no doubt andexanet for patients who are therapeutic on rivaroxaban or apixaban.

The ANNEXA-I results reinforce the pressing need for continued research into more refined reversal strategies that can decouple control of acute hemorrhage from downstream thrombotic complications. Novel investigational agents such as the antifactor Xa monoclonal antibody ciraparantag offer theoretical advantages in providing targeted reversal of factor Xa inhibitors without generalized upregulation of thrombin generation.[12] Future trials incorporating advanced neuroimaging, coagulation biomarkers, and genetic determinants of hemostasis may allow enrichment for likely hematoma expanders and better delineation of andexanet's benefits.[13] The ANNEXA-I study represents an important step toward addressing the clinical conundrum of safe and effective anticoagulation reversal after ICH. But the quest continues for optimized, personalized reversal strategies to definitively tip the scales in favor of protecting the brain without promoting unwanted clots.

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