Adventures With Andexanet Alfa in Efficacy, Effectiveness, and One-Armed Studies

May 2019 Annals of Emergency Medicine Journal Club

Guest Contributors
Ryan P. Radecki, MD, MS; Rory J. Spiegel, MD

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2019.03.015

Editor's Note: *You are reading the 70th installment of* Annals of Emergency Medicine *Journal Club. As the Journal Club enters its second decade of publication, the format has been revised and will focus on a monthly succinct review of high-impact articles from this journal and other premier medical journals relevant to emergency medicine. The reviews are followed by questions demonstrating principles by which readers—be they clinicians, academics, residents, or medical students—may critically appraise the literature. We are interested in receiving feedback about this feature. Please e-mail journalclub@acep.org with your comments.*

ARTICLE IN REVIEW

Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2019; http://doi.org/10.1056/NEJMoa1814051.

What Question Did This Investigation Aim to Answer?

In adult patients currently treated with a factor Xa inhibitor and experiencing major bleeding, is andexanet alfa effective at achieving hemostasis?

What Study Design Did the Authors Choose?

Design: Prospective, multicenter, open-label, single-group, clinical trial. ANNEXA-4 ClinicalTrials.gov identifier: NCT02329327.

Setting: Sixty-three hospitals in North America and Europe.

Population: Three hundred fifty-two adult patients with acute major bleeding who had received a dose of apixaban, rivaroxaban, edoxaban, or enoxaparin within 18 hours of presentation. Substantive changes to enrollment criteria occurred throughout the 3-year study period.

Intervention: Protocolized treatment with andexanet alfa, a variable initial bolus followed by a 2-hour infusion.

Primary and Secondary Outcomes: Coprimary efficacy outcomes described as percentage change from baseline in anti-factor Xa activity after andexanet treatment, and percentage of patients with excellent or good hemostatic efficacy as assessed 12 hours after andexanet infusion. Important safety outcomes were death and thrombotic events.

Sponsor: Portola Pharmaceuticals, South San Francisco, United States.

How Did the Authors Interpret the Results?

In 254 patients eligible for the primary efficacy analyses, andexanet alfa bolus and infusion reduced anti-factor Xa activity by a median of 92% (interquartile range 91% to 93%), 90% (interquartile range 87% to 93%), and 73% (interquartile range 67% to 77%) for apixaban, rivaroxaban, and enoxaparin, respectively. Hemostatic efficacy was good or excellent in 204 patients (82%). The remaining patients were excluded from the efficacy analysis for failing to meet criteria for bleeding severity or sufficient anti-factor Xa activity. All 352 patients were included in 30-day safety analyses, and thrombotic events occurred in 34 (10%), including 7 myocardial infarctions and 14 ischemic strokes. Anti-factor Xa activity during andexanet therapy was not associated with overall adjudicated assessments of hemostatic efficacy, as evaluated by means of receiver operating curves (area under the curve 0.53 [95% confidence interval 0.44 to 0.62]).

Conclusion: Treatment of factor Xa inhibitor–associated acute major bleeding with andexanet alfa was efficacious, as adjudicated according to prespecified criteria.

How Might This Study Affect Your Clinical Practice in the Emergency Department?

This single-arm clinical trial lacked a control or comparator group and therefore may not provide adequate evidence to inform practice. An ongoing clinical trial (ClinicalTrials.gov number NCT03661528) is comparing andexanet alfa with standard care. Costs of andexanet alfa approach $50,000 for the high-dose protocol,[1] far more than current treatment protocols using 4-factor prothrombin concentrate complexes.[2] Absent data

demonstrating superiority over current strategies, the clinical role of andexanet remains unclear.

DISCUSSION POINTS

1. The Prospective, Open-Label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor Who Have Acute Major Bleeding (ANNEXA-4) enrolled 352 patients, but only 254 were included in the primary efficacy analysis. How does this affect the primary outcomes? Should a similar exclusion be applied to an efficacy analysis in the follow-up randomized controlled clinical trial?

An efficacy analysis describes the clinical benefit associated with a treatment under ideal circumstances. It is reasonable for the authors to restrict their observations, as they have done here, to patients verified to have therapeutic anti-Xa levels or clinically meaningful bleeding. An effectiveness analysis assesses an intervention under actual conditions. In the latter case, it is important to retain all subjects who would potentially receive the drug in clinical application.

An important consideration when proving effectiveness is to analyze the primary outcomes by intention to treat. The core feature of a randomized controlled trial is the randomization, which is intended to distribute variation between treatment arms. Breaking randomization introduces bias to the analysis. Under the principle of intention to treat, the patient remains in the assigned treatment group regardless of whether he or she received the intervention.

Some trials may present per-protocol and as-treated analyses. Per-protocol analysis omits subjects with protocol violations, and as-treated analysis moves subjects receiving the wrong intervention to the arm of treatment they received. Although per-protocol and as-treated analyses are important tools for assessing the internal and external validity of a trial, they are no longer truly random, introducing potential bias to the results. For example, if patients randomized to the experimental group died before receiving andexanet alfa, they would be excluded from the per-protocol analysis. This would obviously bias the results in favor of andexanet alfa because it would systematically reduce the number of the sickest patients in the intervention group.

In most cases, an intention-to-treat analysis observes a smaller effect size than a per-protocol or as-treated analysis. This dilution of efficacy by an intention-to-treat analysis may result in type II error, the inability to demonstrate a true treatment effect when one exists. In these cases, the per-protocol and as-treated analyses become important in identifying procedures and subgroup populations for hypotheses for future study. For example, in ANNEXA-4, even though no overall correlation between anti-Xa levels and hemostasis was observed, there was correlation observed in the subgroup of patients with intracranial hemorrhage. This may enable further hypothesis testing translatable to actual effectiveness.

2. The authors state that "[a]t the time of study initiation, it was determined that a randomized, controlled trial would have logistic and ethical challenges, given the perceived risks of placebo assignment in this highly vulnerable population." Why might this argument be made, and is it valid?

The use of placebo in clinical trials is advised by the Declaration of Helsinki, section 33, which states that "…patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention."[3] This statement produces an understandably controversial gray area in regard to the ethical use of placeboes or active comparators when new treatments are evaluated. The issue hinges on whether, in this case, andexanet alfa qualifies as the "best proven intervention" on the basis of preclinical studies.[4]

An oft-cited illustrative example involves whether parachutes to prevent death or major trauma could be tested in a randomized controlled trial.[5] Although parachutes have never been tested against placebo, it is not ethical to randomize individuals to a control arm of almost certain harm. Competing viewpoints argue most medical treatments are not parachutes,[6] but the underlying concept remains valid for consideration.

For comparison, the Study of the RE-VERSal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) is a similar single-arm trial of idarucizumab for the emergency reversal of dabigatran.[7] The trial's approach and evaluation of efficacy are similar, and it also lacks a control arm for comparison. Therefore, these data also provide inherently limited information about the true clinical utility of idarucizumab. However, a reasonable argument may be made that the preclinical work describing idarucizumab is sufficient to make it unethical to randomize patients to placebo, given the potential for serious harm. In contrast, there are valid alternatives to andexanet for the treatment of factor Xa inhibitor–related major bleeding in the form of prothrombin concentrate complexes. Not only is it likely ethical to perform a randomized controlled trial of andexanet alfa versus prothrombin concentrate complexes, as is currently planned, but also it could easily be argued it was unethical to conduct ANNEXA-4 as a single-arm trial in the first place. Ethical exposure of patients to the risk of an experimental treatment requires production of clinically meaningful data to justify their inclusion in a study.

Section editor: Tyler W. Barrett, MD, MSCI
Guest editor: Henry E. Wang, MD, MS

Dr. Barrett recused himself from the editing of this journal club due to his role as a clinical trial site investigator for Portola.

Author affiliations: From Northwest Permanente, Portland, OR, and The University of Texas Health Science Center at Houston, Houston, TX (Radecki); and the University of Maryland, Baltimore, MD (Spiegel).

Authorship: All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Andexxa: an antidote for apixaban and rivaroxaban. *Med Lett Drugs Ther*. 2018;60:99-100.
2. 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;24:6-46.
3. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310:2191-2194.
4. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med*. 2015;373:2413-2424.
5. Smith GC, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *BMJ*. 2003;327:1459-1461.
6. Hayes MJ, Kaestner V, Mailankody S, et al. Most medical practices are not parachutes: a citation analysis of practices felt by biomedical authors to be analogous to parachutes. *CMAJ Open*. 2018;6:E31-E38.
7. Pollack CV, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal: full cohort analysis. *N Engl J Med*. 2017;377:431-441.