Andexanet alfa vs. four-factor prothrombin complex concentrate

Andexanet alfa is FDA-approved to reverse rivaroxaban and apixaban, but my hospital does not stock it because it is so expensive. Is there an acceptable substitute?—HS, N.Y.

Autumn Koenig, PharmD; Jessica Offerle, PharmD; Tim Coppler, PharmD; and Dan Sheridan, MS, RPh, CPPS, respond—Andexanet alfa (Andexxa, AstraZeneca Pharmaceuticals) is a specific factor Xa reversal agent approved for life-threatening or uncontrolled bleeding associated with the factor Xa inhibitors, apixaban (Eliquis) and rivaroxaban (Xarelto). It works as a decoy molecule to bind factor Xa inhibitors with high affinity and sequester them.[1] Andexanet alfa has also been shown to increase tissue factor-initiated thrombin generation. These effects are observable within 2 minutes of administration, and it has a half-life of about 3 to 4 hours.[1]

The primary alternative to andexanet alfa is four-factor prothrombin complex concentrate (4F-PCC), a mixture of human coagulation factors (II, VII, IX, and X) in combination with the endogenous inhibitor proteins C and S. 4F-PCC (Kcentra, CSL Behring) is indicated for bleeding induced by vitamin K antagonists, such as warfarin. The American College of Cardiology recommends 4F-PCC as an acceptable alternative to andexanet alfa for its off-label indication for bleeding associated with factor Xa inhibitors.[2-4]

Although no head-to-head trials have compared andexanet alfa to 4F-PCC, trials performed for both drugs can offer more insight regarding each agent's role in therapy.[5,6]

Andexanet alfa – ANNEXA-4 trial

The Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors (ANNEXA-4) study was a multicenter, prospective study that evaluated 352 patients who were at least 18 years old and had experienced an acute major bleeding episode within 18 hours of receiving a factor Xa inhibitor.[5] All patients were included in the safety analysis; however, only patients with a baseline anti-factor Xa activity of 75 ng/mL or greater were included in the efficacy analysis. There were two primary outcomes: percentage change in anti-factor Xa activity and the rate of either excellent or good hemostatic efficacy. In the 134 patients receiving apixaban, the agent provided an immediate 92% decrease in anti-factor Xa activity. Four hours following the infusion, there was a 32% decrease from baseline. Over 82% of patients in the efficacy arm were found to have excellent (171) or good (33) hemostasis 12 hours after the infusion.[5]

While the ANNEXA-4 trial offers data to support the use of andexanet alfa for reversing factor Xa inhibitors in an acute bleeding episode, there are limitations to consider. The trial did not have a comparator group, so the amount of benefit andexanet alfa provides compared with placebo in achieving hemostasis is unclear. Additionally, decreases in anti-factor Xa activity may not directly correlate with positive clinical outcomes. Anti-factor Xa levels were utilized in this study to ensure patients have anti-factor Xa in circulation for study inclusion and to define reversal response numerically. However, anti-factor Xa level monitoring is not performed in typical clinical practice.

4F-PCC – UPRATE study

The Unactivated Prothrombin complex concentrates for the Reversal of Anti-factor TEn inhibitors (UPRATE) study is currently the largest to have evaluated 4F-PCC in managing major bleeding events. It evaluated the efficacy and safety of 4F-PCC in the reversal of apixaban and rivaroxaban for 92 patients in a multicenter, prospective setting in Sweden. Researchers evaluated a fixed-dose protocol of 1,500 or 2,000 units of 4F-PCC based on patient weight. Additional doses were allowed at the physician's discretion, and the protocol was based on approximating a 4F-PCC dose of 25 units/kg. Three patients in the study received an additional 4F-PCC dose due to inadequate response to the initial dosing.[6] Notably, administration of additional 4F-PCC doses varied from current dosing recommenda-

tions for factor Xa reversal of a one-time 2,000 unit dose or one-time 25-50 units/kg dose.[3,4,7] This study found that 4F-PCC was effective at achieving hemostasis in 58 patients and was ineffective in 26 patients (69.1% versus 30.9%). Similar to the ANNEXA-4 trial, the UPRATE study is limited by not having a comparator group.[6]

Discussion

The UPRATE study showed lower efficacy rates with 4F-PCC compared with the efficacy of andexanet alfa in the ANNEXA-4 trial (69.1% versus 82% respectively); however, inherent differences between the studies make it difficult to draw conclusions from comparison. For example, 61.5% of the patients who saw treatment failure in the UPRATE study also experienced an intracerebral hemorrhage (ICH). An ICH is generally associated with poor outcomes, with study mortality approaching 50%. The UPRATE trial included a higher percentage of patients with ICH overall than the ANNEXA-4 trial (70.2% versus 43%).[4] Additionally, the inclusion criteria for each study to determine factor Xa inhibitor association were unique, with ANNEXA-4 using baseline anti-factor Xa levels and the UPRATE trial requiring a dose of apixaban or rivaroxaban within the past 18 hours.

Lacking a head-to-head trial, the decision for utilizing andexanet alfa versus 4F-PCC for factor Xa reversal often comes down to price and logistics. Andexanet alfa is more expensive, with the typical cost of therapy nearing $29,000 for low-dose therapy and $58,000 for high-dose therapy.[8] The typical cost of therapy for 4F-PCC is approximately $6,000, with a maximum dose costing $16,300.[9] Additionally, andexanet alfa requires an I.V. bolus followed by an I.V. infusion for 2 hours, while 4F-PCC only requires a one-time dose over 15-30 minutes. For factor Xa reversal, 4F-PCC is given either as a flat or weight-based dose, while andexanet alfa is dosed based on several factors including which factor Xa inhibitor the patient is taking, the dose of the factor Xa inhibitor, and the time since the patient's last dose.[1-4]

Due to the simple administration and affordability of 4F-PCC compared with andexanet alfa, 4F-PCC is often the only reversal agent available at community hospitals. Without access to andexanet alfa, 4F-PCC is an acceptable alternative for the reversal of apixaban or rivaroxaban for most patients. However, 4F-PCC contains heparin and is contraindicated in patients with a history of heparin-induced thrombocytopenia (HIT).[2] HIT occurs in up to 5% of patients who receive heparin products.[10] For patients with HIT and life-threatening bleeding from apixaban or rivaroxaban, local access to andexanet alfa is critical, making it an important factor for hospitals to consider before omitting the drug from the formulary.

In the event of life-threatening bleeding associated with apixaban or rivaroxaban, only andexanet alfa has a labeled indication; however, 4F-PCC provides an acceptable alternative. The ultimate decision for whether one or both agents are on the formulary depends on a hospital's budget, size, and local availability of andexanet alfa. ■

REFERENCES

1. Andexxa (andexanet alfa) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; February 2023.
2. Kcentra (prothrombin complex concentrate human) [prescribing information]. Kankakee, IL: CSL Behring; October 2018.
3. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2020;76(5):594-622. doi:10.1016/j.jacc.2020.04.053.
4. Baugh CW, Levine M, Cornutt D, et al. Anticoagulant reversal strategies in the emergency department setting: recommendations of a multidisciplinary expert panel. *Ann Emerg Med*. 2020;76(4):470-485. doi:10.1016/j.annemergmed.2019.09.001.
5. Connolly SJ, Crowther M, Eikelboom JW, et al. ANNEXA-4 Investigators. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2019;380(14):1326-1335. doi:10.1056/NEJMoa1814051.
6. Majeed A, Ågren A, Holmström M, et al. Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood*. 2017;130(15):1706-1712. doi:10.1182/blood-2017-05-782060.
7. Frontera JA, Lewin JJ 3rd, 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. doi:10.1007/s12028-015-0222-x.
8. Carpenter E, Singh D, Dietrich E, Gums J. Andexanet alfa for reversal of factor Xa inhibitor-associated anticoagulation. *Ther Adv Drug Saf*. 2019;10. doi:10.1177/2042098619888133.
9. Fanikos J, Goldstein JN, Lovelace B, Beaubrun AC, Blissett RS, Aragão F. Cost-effectiveness of andexanet alfa versus four-factor prothrombin complex concentrate for the treatment of oral factor Xa inhibitor-related intracranial hemorrhage in the US. *J Med Econ*. 2022;25(1):309-320. doi:10.1080/13696998.2022.2042106.
10. Solanki J, Shenoy S, Downs E, Palkimas S, Goldman S, Sharma AM. Heparin-induced thrombocytopenia and cardiac surgery. *Semin Thorac Cardiovasc Surg*. 2019;31(3):335-344. doi:10.1053/j.semtcvs.2018.10.011.

Autumn Koenig is a pharmacist at Cleveland Clinic, Jessica Offerle is a pharmacy practice resident at Parkview Health in Fort Wayne, Ind., Tim Coppler is a pharmacist at Institutional Care Pharmacy in Tiffin, Ohio. Dan Sheridan is a medication safety pharmacist at OhioHealth Marion General Hospital and a member of the *Nursing*2023 editorial board.

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