New Drug Reverses Anticoagulant Activity of Factor Xa Inhibitors

Andexanet alfa, a factor Xa-binding protein, reverses the anticoagulant activity of factor Xa inhibitors in phase 3 trials.

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January 11, 2016 – In healthy older volunteers taking factor Xa inhibitors, andexanet alfa (andexanet) rapidly reduced anti-factor Xa activity to a greater extent than placebo, according to the results of two randomized phase 3 trials.

Deborah M. Siegal, MD, with McMaster University in Hamilton, Ontario, and colleagues published their findings in the December 17, 2015 issue of the New England Journal of Medicine.

Andexanet is a factor Xa decoy protein that reduces anticoagulation activity and restores endogenous factor Xa activity by binding the active site of factor Xa inhibitors. Phase 2 studies have shown that andexanet reversed anticoagulation in a rapid and dose-dependent manner, without significant toxicity, in healthy volunteers taking factor Xa inhibitors. The current trials—Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors Apixaban (ANNEXA-A) and Rivaroxaban (ANNEXA-R)—were conducted in parallel to evaluate whether using andexanet to reverse anticoagulation with apixaban or rivaroxaban was safe and effective in healthy subjects.

In ANNEXA-A, 65 healthy older volunteers (aged 50 to 75 years) received apixaban 5 mg orally twice a day and were randomized to treatment with andexanet or placebo in a 3:1 ratio. In ANNEXA-R, 80 healthy older volunteers received rivaroxaban 20 mg orally once daily and were randomized to andexanet or placebo in a 2:1 ratio. Andexanet was administered as an intravenous bolus alone (400 mg in ANNEXA-A; 800 mg in ANNEXA-R) or as an intravenous bolus followed by a 120-minute infusion (4 mg per minute in ANNEXA-A; 8 mg per minute in ANNEXA-R).

Reversal of anticoagulation activity was measured using percent change in anti-factor Xa activity in the primary outcome for both studies. Anti-factor Xa activity was reduced to a significantly greater degree in those who received the andexanet bolus alone than in those who received placebo in ANNEXA-A (mean [±SD] reduction, 94±2% vs. 21±9%; P < .001) and ANNEXA-R (92±11% vs. 18±15%, P < .001). Similar results were sustained in the groups that received the andexanet bolus followed by an infusion in both studies.

Thrombin generation was restored in 100% and 96% of participants in the andexanet groups compared with 11% and 7% in the placebo groups in the apixaban and rivaroxaban studies, respectively (P < .001 for each comparison). The concentration of unbound apixaban or rivaroxaban was reduced by a significantly greater amount in participants who received andexanet versus placebo in both ANNEXA-A (by 9.3 ng/mL vs. 1.9 ng/mL, P < .001) and ANNEXA-R (by 23.4 ng/mL vs. 4.2 ng/mL, P < .001). Rapid reversal of anticoagulation activity, occurring within 2 to 5 minutes after the andexanet bolus was administered, was observed in all markers of anticoagulation in the andexanet groups.

Hives occurred in two participants who received andexanet, one of whom had a history of hives. All other adverse events were mild; no serious adverse events were reported. Although levels of D-dimer and prothrombin fragments were transiently elevated (24 to 72 hours in duration) in the andexanet treatment groups, no clinical thrombotic events occurred.

“The ability of andexanet to reverse anticoagulation markers in participants undergoing anticoagulation with apixaban, rivaroxaban, edoxaban, or enoxaparin makes it a potential universal antidote for both direct and indirect factor Xa inhibitors,” Dr. Siegal concluded in the New England Journal of Medicine. Dr. Siegal also indicated that efforts to study andexanet in patients taking factor Xa inhibitors are already underway: “The ongoing ANNEXA-4 phase 3b–4 study…is evaluating the efficacy and safety of andexanet in patients with factor Xa inhibitor-associated acute major bleeding.”
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