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What Future Studies Are Out There on the Meaningfulness of Reversal in ICH?

Announcer:
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Dr. Coleman:
Hello, my name is Craig Coleman, and I'm a Professor of Pharmacy Practice at the University of Connecticut School of Pharmacy. In this episode, I'd like to talk a little bit about future studies regarding reversal in patients with intracranial hemorrhage.

The first and by far the most important study that I wanted to review today is called the ANNEXA-I study. This is a trial of andexanet alfa in intracerebral hemorrhage patients receiving an oral factor Xa inhibitor. Now, this was a randomized, multicenter trial designed to determine the efficacy and safety of an andexanet alfa compared to usual-care therapy, whether that be PCC, 4-factor PPC or whatever a physician determined would be appropriate care in patients presenting with acute intracerebral bleeding episode defined as the as a intracerebral bleed of a volume of at least 0.5 mL, but no greater than 60 mL, within the 6 hours of symptom onset, and within 15 hours of taking an oral factor K inhibitor, unless local anti-factor Xa activity suggested that patients still had adequate anticoagulation on board that warranted reversal of anticoagulation.

Now, as I mentioned before, this was a prospective, randomized, open-label or what we call PROBE study design. And the primary efficacy outcome was adjudicated, effective hemostasis. Now, what's interesting about ANNEXA-I is their definition of effective hemostasis is a little different than what previous studies have used. It's a little more rigorous. And so it was defined as a change from baseline in NIH Stroke Severity score of +6 or less at a 12-hour time point, and having to have less than a 35% increase in hematoma volume compared to baseline at 12 hours, and no rescue therapy administered between 3 hours and 12 hours after randomization. So this is a very rigorous definition of effective hemostasis.

Now, the estimated enrollment of this study is now anticipated to be about 900 participants. And that's because the study was recently stopped early because of achievement of the prespecified efficacy criteria of hemostatic efficacy compared to usual care. And in order for that to occur, that was done by a independent review board, it demonstrates to us or what we can intuit from that is that andexanet alfa had at least a 10% absolute difference or benefit in the rate of hemostatic efficacy, compared to usual medical care therapy. So maybe more than 10%, but it had to be at least a 10% absolute difference of hemostatic efficacy in favor of andexanet alfa. So hopefully these results will be coming out fairly soon. And we're all going to look very forward to seeing what those results tell us.

Now another study that I wanted to briefly mention was called the ASTRO-DE study. And this was a non-interventional study in stroke units in Germany. It's a prospective, observational, non-interventional study, which actually in a lot of ways looks a lot like the ANNEXA-4 study. The aim of this study was to analyze under routine real-world conditions, whether the volume increase of intracranial hemorrhage in patients who had either rivaroxaban or apixaban-associated intracranial hemorrhage, was reduced when patients received andexanet alfa. The key outcome here was changed in size or volume of the hematoma computed by either a CT or MRI between 12 and 72 hours after the initial scan. Now, what's nice about the ASTRO-DE study is they have some very interesting

secondary objectives that will hopefully add a lot of interesting data to our discussion about reversal of factor Xa inhibitors.

Key secondary objectives in ASTRO-DE included functional status assessment using the modified Rankin score at discharge, at 30 days, as well as at 90 days, changes in stroke severity using the NIHSS score 72 hours after admission, and mortality rates at 7, 30, and 90 days following the hospital stay. Now in this study, the estimated enrollment is about 140 participants. And it's anticipated that this study will finish up sometime in December of 2024.

Now, the last study of interest that I wanted to quickly review is called the OCTAPLEX study or the study of OCTAPLEX in patients with acute major bleeding on DOAC therapy in patients with factor Xa inhibitors. Again, this is a multicenter, prospective, randomized, double-blind, phase 3 study to demonstrate the hemostatic efficacy and safety of 4-factor prothrombin complex concentrate, specifically OCTAPLEX, in patients with acute major bleeds due to factor Xa inhibitors. Now in this study the randomizing in a 1-to-1 fashion, low-dose versus high-dose 4-factor prothrombin complex concentrate in patients with acute major bleeds. This study is not going to tell us anything about the relative efficacy or safety of 4-factor PCC versus andexanet alfa, but rather low- versus high-dose 4-factor PCC.

Primary outcome is an adjudicated hemostatic efficacy outcome similar to what we see in other clinical trials, as well as 30-day mortality, and the risk of thrombotic events. Estimated enrollment is about 200 participants, and this study is projected to be completed in February 2024. But what again, this study is really going to hopefully tell us is if, in fact, other data like ANNEXA-I doesn't suggest that 4-factor PCC is no longer an appropriate therapy, that if we do need to use 4-factor PCC, what is the appropriate or optimal dosing? Some guidelines do suggest that we use high-dose 4-factor PCC, other guidelines, and in fact, real-world practice, often demonstrates that we're using lower doses of 4-factor PCC. So this study will hopefully answer a very important key clinical question.

Now taken together, all these studies will hopefully in the next year or two, help us advance the way that we treat severe or life-threatening major bleeds when patients do, in fact, bleed on factor Xa inhibitors.

Thank you very much.

Announcer:
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