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ANNEXa-I: Recent Advances in the Treatment of Intracranial Hemorrhage (ICH)

Announcer:
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Dr. Kreitzer:
Hi, my name is Natalie Kreitzer. I'm an Associate Professor of Emergency Medicine in Neurocritical Care, and I'm part of the UC Stroke Team at the University of Cincinnati in Cincinnati, Ohio. And I'm going to speak about ANNEXa-I and some recent results as well as the trial design, as we talk about the treatment of patients with intracerebral hemorrhage.

The first thing I want to discuss is the concept of hematoma expansion in intracerebral hemorrhage. And we know that this is a critical target of treatment in patients who have an ICH. I've got a couple of images here of CT scans that demonstrate what happens when hematoma expansion. Now, hematoma expansion happens, unfortunately not uncommonly, in patients with intracerebral hemorrhage. But those patients who are anticoagulated have a much higher risk compared to those patients who are not anticoagulated.

So, as we think about the background and some of the work that went into planning the ANNEXa-I study, the primary endpoint was looking predominantly at that hematoma expansion. Now, I have a table here from a study below that looks at factors that are associated with outcome after ICH. And you can see going through several of these, they have a lot to do with ICH volume, as well as change in volume. And you'll see a couple of these, for example, the percent change in ICH volume at 24 hours, as well as the absolute change in ICH volume at 24 hours are both statistically significantly associated with long-term modified Rankin Scale outcomes in patients with ICH. Now unfortunately, baseline ICH volume in cc's is also highly correlated. However, that's not something that really can be targeted for intervention; that primary event has already taken place.

Now, as we think through what the ANNEXa-I study did, here's a figure of the study design. So, these were adult patients who presented with an intracerebral hemorrhage within 6 hours of symptom onset or their last seen well time, they had to be within 15 hours of taking a factor Xa inhibitor or presumed to have been within 15 hours. They were randomized to either receiving andexanet alfa or usual care, the majority of which received prothrombin complex concentrates. These patients all had a baseline head CT, they got labs, including an anti-Xa activity level, as well as clinical assessments. And they were followed for the next 30 days for both efficacy, as well as safety endpoints.

Now patients were included if they were 18, if they had ICH volume that was 0.5 cc to 60 cc's, they had to have their imaging done within 2 hours prior to randomization. This needed to be done quickly in order for it to work well. And as I mentioned before, a treatment with a factor Xa inhibitor within 15 hours or in those centers that were able to obtain this lab draw of the factor Xa activity of 100 ng/mL. They needed to have an NIH Stroke Scale less than or equal to 35. And their last seen well, as I mentioned, was less than 6 hours prior to that first imaging.

Patients were excluded if they were pregnant, lactating, if they had a planned surgery within 12 hours, although there were a number of procedures that were allowed in the study, a GCS less than 7, thromboembolic events within 2 weeks, if they were not expected to

survive, or if they received any type of anticoagulation reversal agent or blood products, or if they were in a different trial, they thought that the ICH is related to a tumor, or if they had received andexanet alfa in the past, or if they had already received the drug and couldn't be randomized, or a known allergy or hypersensitivity reaction.

Now the primary endpoint was that effective hemostasis, as I've mentioned before, because that's such a critical component of our patients' outcome in ICH. This was deemed by a second group of independent adjudicators who looked at the head CTs, and this is similar to previous studies and definitions of hematoma expansion.

Less than 20% hematoma expansion at 12 hours was considered excellent, and less than or equal to 35% at 12 hours was considered good. But not only did they need to have this as an imaging endpoint, but the patients also had to have a change in NIH Stroke Scale of 7 or less, and no rescue therapy administered over the past –sorry, over the next 3 to 12 hours post randomization. So, all three of these had to be met in order for a patient to meet that primary endpoint.

There were a number of secondary endpoints that I'm not going to get into extensively. But these are certainly things that, as this data comes out over the coming months and we see the manuscript, that we will be hearing a lot more about.

Now, safety endpoints for this study were very important. The big one was looking at thromboembolic risks as - or sorry, thromboembolic events, as well as mortality over the next 30 days post randomization. All vital signs and adverse events were recorded. All mortality, both in hospital over the next 30 days were recorded, hospital length of stay, ICU length of stay, rehospitalizations, performance of any necessary procedures in order to manage ICH, such as an external ventricular drain, or patients who formed any antibodies to andexanet alfa, native factor X, or factor Xa.

Now, looking through some of the results of this study, the patients with their baseline characteristics in the two groups are shown in this table. And I want to point out that the mean age in both of these groups was 79.4 in the andexanet alfa, and 78.7 in the usual care. Otherwise, the groups were quite well balanced in terms of their medical history, hematoma volume, and even the timing of treatments was very similar in both groups in terms of the median door-to-needle time.

Now, most importantly, that primary endpoint of this study was met. And not only that, but it was met early and the trial was actually stopped early because of this. Now, as we look at this table, those patients who were in the andexanet alfa group met that primary endpoint 63.9%, and then those in the usual care met that primary endpoint 52.4%. Remember, that primary endpoint required three separate things, that was that excellent or good hemostatic efficacy, and then patients could not decline in their NIH Stroke Scale by 7 or more, and they also could not receive any blood products or additional reversal agents after they had received either andexanet alfa or usual care. And this resulted in an absolute increase in the andexanet alfa group in the primary endpoint of hemostatic efficacy overall of 11%. And it was statistically significantly different between the two groups.

Now, not surprisingly, in some of those additional endpoints that we have information for thus far, the change in anti-factor Xa activity mirrored previous studies, with a drop of 94% in the apixaban group, rivaroxaban group was 96%. Interestingly, edoxaban was not quite as high, although that is quite a small number of patients in both of the groups who were on edoxaban in this study, and then the hematoma volume and modified Rankin Score are included below as well. The modified Rankin Score was not statistically significant at 30 days. However, this was not a study which was powered to detect a big change in modified Rankin Score.

And lastly, the safety endpoints are going to be informative as we learn more information about this study. This again mirrored the previous study demonstrating that that all-percent thromboembolic risk was about 10.4% in both the andexanet alfa group, and then 5.6% in the usual care group.

So, in summary, these patients with ICH warrant early and aggressive management because of that hematoma expansion. ANNEXa-I is the only randomized controlled trial that's looked at andexanet alfa compared to the usual care of these patients. And achievement of effective hemostasis was significantly higher in those patients with andexanet alfa. And again, this is the only FDA approved specific reversal agent for apixaban or rivaroxaban in patients with factor Xa inhibitor-related life-threatening or uncontrolled bleeding.

Thank you.

Announcer:
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