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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Optimizing Your Pharmacologic Approach to Reversing Anticoagulation for ICH

Announcer:
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Dr. Seiffge:
Hello, everybody from my side. So I now have the opportunity to discuss with you the Optimizing Your Pharmacologic Approach for Reversing Anticoagulation for ICH. And I will focus a bit more on these novel oral anticoagulants.

So we just discussed about the changing spectrum of anticoagulation-associated ICH. So roughly 20% of all ICH are on patients taking anticoagulant. This is data from Switzerland and Norway. And yes, you can see the blue parts of the bars are increasing over time, and now in these two countries, at least the vast majority of those ICH are actually DOAC-associated ICH, and because of the market share, they are actually factor Xa inhibitor-associated ICH. We should have this in mind. And I heard that it seems to be the same in several other countries as Australia, likely as well in the UK. So I think we have to, at least in Switzerland, VKA, ICH is an outlying feature.

What do we know about prothrombin complex concentrate in the setting of DOAC ICH? I don't want to go into detail of the specifications you just heard from Natalie, but there are two studies who actually assessed whether prothrombin complex concentrate has an effect in patients with direct oral anticoagulant-associated ICH, one from Germany on the left, one from Hong Kong on the right. The majority of those patients were actually taking factors Xa inhibitors, and as you can see, there was at least in observation data, no effect, neither in the German study, over here you see it's neutral, or here you see no effect, good neurological recovery, mortality in hospital, mortality or hematoma expansion. So at least from observational data, we don't have any hint that PCC should do anything to our patients actually.

Now coming to andexanet alfa, which was specifically designed as a reversal agent for Xa inhibitors, and it acts actually as a decoy binding molecule to target and inhibit the factor Xa inhibitors. It was first tested in a single arm cohort study called ANNEXA-4. And the main outcome, or the main primary outcome, was actually the change in anti-Xa activity after infusion. As you can see over here, this is a bit small, likely, but this is for apixaban, this is for rivaroxaban, and this is for edoxaban. So for all the other three Xa inhibitors, you have an instant decrease in the active factor Xa activity over here, reversing it quickly. But the study didn't have a comparison group at that time point, and that's why we matched last year, the clinical outcomes of patients enrolled in ANNEXA-I with patients enrolled in a Swiss perspective study called TICH-NOAC. And the outcomes were actually then in favor for those who received andexanet alfa compared to patients who received non-specific treatments, including PCC and tranexamic acid.

But we are happy that we don't have to rely anymore on these kind of matched comparisons, which are good in the absence of randomized controlled trials. But now we have randomized control trials. And the ANNEXA-I trial was a randomized controlled trial enrolling patients with acute ICH within 6 hours of onset and within 15 hours of last intake of Xa inhibitor. And those of you who are who have probably looked up in their mailbox, and you might have seen that the main trial results have just been published, so you can look it up now in *New England Journal*. And patients were randomized to andexanet alfa and unusual care, with the main outcome being hemostatic efficacy. And of course, the secondary outcomes were anti-Xa activity change and safety outcomes.

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The trial was stopped early after an interim analysis before reaching its predefined hemostatic efficacy endpoint. That's why you will likely see two different populations. The primary efficacy population being the population which was available for the time point of the interim analysis. And then there was an extended population which included all patients who actually received – were enrolled in the study until the study was stopped.

This was the change in factor Xa activity – anti-factor Xa activity. It doesn't come to a surprise to see that we also see this significant reduction of the factor Xa activity with andexanet alfa compared to usual care. And this is now the main outcome of hemostatic efficacy. On the left side you see the efficacy population. On the right side, the extended population. But you see that in those populations, there was an increase of 13.4 or 11% of the hemostatic efficacy in patients receiving andexanet alfa compared to usual care.

I would like to highlight your attention to some of the details of this outcome, because hemostatic efficacy was further defined in excellent or good. And the difference between andexanet alfa and usual care was actually mainly in those patients who had excellent outcome. So the absolute percentage was 10% difference here in excellent hemostasis. And further down, you see more the definition of hematoma increase of more than 12.5 mL from baseline to follow-ups of those patients who had actually a very extensive hematoma expansion on follow-up imaging. And you see that here, the absolute difference is 7% between andexanet alfa and usual care. So those patients with really impressive hematoma expansion.

Coming up to safety endpoints, there was an increase in thrombotic events in patients who received andexanet alfa - oops, sorry, it was a bit too quick – with a difference of 4.6% mainly in ischemic strokes, which there was a difference of 5%.

And finally, I looked up the rate of thrombotic events in different other studies, because this is now a kind of discussion that we have. And so the first one is the INCH trial. You have heard about it before, comparing fresh frozen plasma and PCC and vitamin K antagonists to ICH. This one is a TICH-NOAC study, a study from Switzerland, comparing tranexamic acid is add-on treatment on top of usual care for factor Xa inhibitor-associated ICH. In this ANNEXA-I population, and you see these two studies actually assessed at 90 days, a bit later than at here 30 days. But you see, in all these studies, we see quite an extensive risk of thrombotic events,

likely reflecting that this is a very high-risk population having a lot of thrombotic events.

Dr. Kreitzer:
Everybody, you know, has a lot of questions about the thromboembolic complications from the ANNEXA-I trial. I know yesterday you presented a secondary analysis looking at that and comparing that to hematoma expansion. Could you speak a little bit about that?

Dr. Seiffge:
Yeah, of course. So likely a few people were in a room yesterday, so you already saw the data, but what we actually did is we compared the clinical – or we assessed the clinical consequences of hematoma expansion on the one hand, and thrombotic events on the other hand, in patients enrolling in ANNEXA-I study, because at the moment, we are now left with two competing events. And I think for us as clinicians, it's important to know what these events actually mean for our patients.

And I think the main outcome from me, from this analysis, was that it really, really defines how bad hematoma expansion is. It was increased. It was associated with a threefold increase in mortality, and also associated with poor outcomes, a poor functional outcome, defined as a modified ranking scale of 4 to 6 with a twofold increase. We also realized that the association with thrombotic - between thrombotic events and mortality was also significant. I think this reflects a bit the care that we provide to these patients in terms of treatment restrictions, which might have been in place for some of these patients. But this is a speculation, of course. And yeah, these were mainly the results from the study.

Dr. Gibler:
Excellent.

Dr. Seiffge:
Thank you.

Dr. Gibler:
Thank you very much. Dr. Seiffge.

Announcer:
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