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https://reachmd.com/programs/cme/emerging-data-in-the-management-of-intracranial-hemorrhage-in-the-anticoagulated-patient/18128/

Released: 02/27/2024
Valid until: 02/27/2025
Time needed to complete: 1h 08m

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Emerging Data in the Management of Intracranial Hemorrhage in the Anticoagulated Patient

Announcer:
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Dr. Gibler:
Our next speaker is Dr. Stuart Connolly. And he is Professor Emeritus at McMaster University, Senior Scientist for Population Health Research Institute in Hamilton, Ontario, Canada, which is essentially one of the birthplaces of anticoagulation in general. And Dr. Connolly is a cardiologist by training, in addition to having all this work in thrombosis, and he's going to talk about primarily ANNEXa-I. And this is important for the management of intracranial hemorrhage in the anticoagulated patient. Dr. Connolly, thank you for being here.

Dr. Connolly:
Thank you for the introduction. It's a pleasure to be here. And, as was just said, I'm going to talk about andexanet. And to get the ball rolling, I'm going to tell you a little bit what andexanet is. Of course, it's a drug that is designed to rapidly reverse factor Xa inhibitors, and it is actually a protein that is very similar to factor Xa itself, native factor Xa, as shown on the far left of the slide. But it has been modified to lack the catalytic activity and to prevent any anticoagulant effects, but it does maintain its ability to bind the factor Xa inhibitors, such as rivaroxaban, so it can bind it very avidly. And what it actually does, is it pulls it off of native factor Xa, where it's been inhibiting coagulation, and it allows the native factor Xa to do its job. So, it's a decoy that sucks up the factor Xa inhibitors like rivaroxaban. Now, this drug is a designer drug, was developed by Portola Pharma many, many years ago, and was tested initially in healthy volunteers. And it's, I think, useful to see the healthy volunteer data just to see how incredibly effective this drug is. So, these were patients – not patients, they were actually healthy elderly volunteers who were given factor Xa inhibitors, in this case I believe it is apixaban, but similar studies were done with all of the factor Xa inhibitors. These patients were dosed up to typical steady-state doses. And then they were either given placebo in black, or andexanet in red. And you can see that almost immediately the anticoagulant activity of these drugs is reduced back down to 0. So, we were no longer having any anticoagulation in these patients. And as long as the infusion is running, it remains very low. But once the infusion stops, it comes back up. The placebo patients on the other hand, have a very slow decay that is due to the renal excretion primarily of the factor Xa inhibitor.

We did the ANNEXA-4 study as shown at the very bottom of this slide, with this drug in patients for the first time, and it was published 2 or 3 years ago. And what we essentially showed in that study was that in patients with severe bleeding, mostly intracerebral hemorrhage, andexanet rapidly reversed anti-Xa activity, and we had a very good, excellent or good, hemostatic response in 80% of patients. We did, however, see thrombotic events in 10% of patients.

This led us to the randomized trial, the ANNEXa-I trial. It was a follow-up of the single arm of ANNEXA-4 that I just told you. And in this study, patients presenting with acute intracranial hemorrhage, primarily intracerebral hemorrhage, but a few patients with other intracranial hemorrhages at the early part of the study were enrolled. Patients, in addition, needed to be within 6 hours of symptom onset and within 15 hours of having taken their last dose of the oral factor Xa inhibitor. It was a simple 1:1 randomization. And patients

either received an andexanet bolus and infusion exactly like what I showed on the previous slide, or they received usual care, which essentially was no andexanet, and in many patients, prothrombin complex concentrate. And I'll show you more details on that in a moment.

Our primary endpoint was effective hemostasis, which we had used in the ANNEXA-4 study, and this will be explained in a couple of minutes as well. It was assessed by 12 hours with a follow-up CT or MRI. And then we had an external adjudication committee who reviewed all the findings, and they were blinded to whether the patients had received andexanet or usual care. We also studied the safety endpoints of thrombotic events and death. And this was a 30-day study, and patients that were no longer followed after 30 days.

Just to go over the patient eligibility. Of course, there was a long list of inclusion and exclusion, but the key issues were an acute intracerebral bleeding episode documented by brain imaging showing the intracranial bleeding. And that had to be done within 2 hours of randomization. The hematoma volume needed to be greater than 0.5 and less than 60 mL. As I said before, the oral factor Xa had to be used, the last dose within 15 hours, and the symptom onset had to be less than 6 hours prior to the baseline scan. And patients had to be in reasonably good shape from point of view of their Glasgow Coma Scale, had to be greater than 7, as you'll see, it was in most patients, much greater.

The primary endpoint, as I told you, was excellent or good hemostatic efficacy. And this basically was relying on hematoma expansion of less than 35%. We called it excellent if it was less than 20%. But a patient was considered to have had a good result if it was less than 35%. But in addition to this, we would not call a patient a good result if the NIHSS score was 7 points or greater. And the patients couldn't receive a rescue therapy of either surgery or an additional thrombotic agent between 3 and 12 hours post-randomization.

So, that's the background. The statistics are worth mentioning very briefly, which was we planned a 900-patient study, but we did decide that we would do an interim analysis at 450 patients to see whether the drug was working even better than we had perhaps hoped for. And we said we would stop the trial if the P value was less than 0.03. And we actually did this interim analysis last May, and that criterion was met, which then led to study close out. And the final results are now presented. Now, we did enroll some more patients between 450, and we ended up with 530 patients, because there was some delays between the data freeze and the actual interim analysis.

So, I'm going to show you the results on the 530 patients today. This slide has a lot of data on it, so we're not going to go over every single bit. But it's an elderly population, as you well know from clinical practice. And there's a significant burden of cardiovascular disease in these patients, including myocardial infarction, stroke, and venous thrombosis in a significant percentage of patients. Baseline hematoma volume was close to 10 cc. And the baseline NIHSS was 9 in both groups. Most patients received the low clinical dose of andexanet, but you can see that it was about 75% of patients. Median time from symptoms to baseline scan was 2.2 hours.

This shows the reduction in the anti-Xa activity with andexanet compared to usual care. And very similar to what I showed you in that almost first slide, there's a very sharp and rapid reduction. We show it at 1 hour, but in fact, we know it was down within a few minutes, as soon as the bolus was given, but we didn't measure it at that time, so we're showing the 1-hour values. I'm not going to go into the details of each of the factor Xa inhibitors, but the reduction is greater for apixaban and rivaroxaban than it is for edoxaban.

This is the money slide, as they say; this is our primary efficacy outcome. We had a good or excellent result in 63.9% of andexanet patients compared to 52.4% of the usual care patients. And that's the percentage increase of 11.0, and that was highly statistically significant. I'm going to draw your attention to the hematoma increase of 12.5 mL or greater, or death, as is mentioned in the footnote. This occurred in more patients on usual care, 19%, than on andexanet 11.6%, a percentage improvement with andexanet of 7.4%. I show at the bottom, the Modified Rankin Score at 30 days, which was essentially the same for both groups.

Thrombotic events and death were carefully tracked, as they were the primary safety outcomes. And as shown in the first line, there were 27 patients with one of these on andexanet compared to 15 on usual care. That’s a percentage increase of 4.6%, and is statistically significant. Ischemic stroke was increased on andexanet, as was myocardial infarction. Interestingly, deep vein thrombosis and pulmonary embolism, venous thromboembolic disease, was actually higher with usual care than with andexanet. Mortality rate, at the bottom, is 27.8% and 25.5%, no significant difference between the two treatment arms.

The next slides are subgroups, and I'm not going to expect you to try and decipher these very small prints. And as would be expected, there were no major differences in the treatment benefit for hemostatic efficacy according to any of the subgroups that we looked at. So, andexanet worked equally well in all of these groups. Some of them were higher risk, and some of them were lower risk, but the treatment effect was the same.

For thrombotic events, subgroup analysis is extremely limited by the relatively small size of the trial and the relatively small number of thrombotic events. But the same holds true, as I mentioned, for hemostatic efficacy, we don't see any subgroups at this point in our analysis that had a particularly high or low risk of thrombotic events.

This brings me to my concluding slide, which has to be covered in – oh, I'm overdue by 15 seconds. So, it's pretty obvious that andexanet rapidly reduced anti-Xa activity as expected. But what had never been seen before and clearly proven in this study was that it increases the rate of hemostatic efficacy by a significant amount. Andexanet, however, did increase the rate of thrombotic events compared to usual care. Andexanet should be considered, in my opinion, for patients with acute intracerebral hemorrhage associated with factor Xa inhibitor therapy. And I'd be glad to answer any questions.

Dr. Gibler:
Thank you very much.

Dr. Connolly:
My pleasure.

Dr. Gibler:
That was excellent. You know, can we open it to the group here? And then – great.

Dr. Cadena:
I have a question for you. You said after the treatment, that you did not allow any surgical procedures 3 to 12 hours after the administration, the completion of the drug. Correct?

Dr. Connolly:
Correct.

Dr. Cadena:
So, what about patients –

Dr. Connolly:
I didn't quite – we didn't disallow them.

Dr. Cadena:
Yeah, that's what I wondered. If you had a patient that needed surgery.

Dr. Connolly:
Oh no, we didn't disallow them. If a surgical procedure was required between 3 and 12 hours, that was considered to be a failure of therapy, no matter what else happened.

Dr. Cadena:
Okay. Okay. Did you happen to analyze those patients to see if they had an increased risk of hemorrhage with the procedures, whether it's an EBD or surgery?

Dr. Connolly:
We have not done so. Yeah, that's something that remains to be done. Good question.

Dr. Gibler:
Dr. Albers?

Dr. Albers:
So, the door-to-needle time was a little over 2 hours, it's a bit longer than we would usually think for a thrombolytic administration. But you didn't show any difference in efficacy with the earlier versus later treatment. Do you think earlier treatment is needed, and we should do things to try to get this drug in faster?

Dr. Connolly:
Yeah, so I mean, patients in a clinical trial are going to get delays. Unfortunately, that's how clinical trials are. So, there is a whole consent process. And so, I think that in real-life practice, we would have shorter door-to-needle times. Now, there's two factors here: andexanet seems to work equally well in patients with short and long door-to-needle times in terms of reducing hematoma expansion. But patients with - who come in very early, tend to have a greater risk of hematoma expansion, just like patients with larger hematomas. So, the underlying risk is higher, and they have more potentially to benefit. I mean, if they don't come in for 6 or 8 hours, they're probably not going to benefit from andexanet, compared to if they come in very early, I think is the message. But the actual effect of andexanet appears to be the same in both groups as a relative effect.

Dr. Albers:
So, your Rankin Scores didn't differ much. I'm sure you were underpowered for that. Were you expecting to see more of a clinical

change in the 30-day Rankin or 90-day Rankin?

Dr. Connolly:
No. No, we really weren't. I mean, it was terribly underpowered for that.

Dr. Gibler:
You would expect for the thrombotic events, the fact that you saw virtually the same thing in ANNEXA-4 that you did in ANNEXa-I, it tells you that you, you know, that your findings, even though it didn't have a comparator arm, in ANNEXA-4, were correct.

Dr. Connolly:
Yeah, exactly. That's a good point that you're making, which I didn't point out. So, in ANNEXA-4 – or I didn't make a strong point. In ANNEXA-4, the rate of thrombotic events was 10%. That's exactly what we saw here. So, the difference here is we had a control arm that only had 5 and a bit percent.

Dr. Albers:
And the morbidity from those thrombotic events. Did you –

Dr. Connolly:
We're still working on that. It's a difficult question to answer, as we were just discussing it in the lobby tonight and we're trying to work on a secondary paper that we're hoping to present at ESOC, almost surely will be. I mean, the question, you know, we want to compare the clinical impact of a reducing hematoma expansion, which is going to be good on clinical outcomes, against the clinical impact of having an ischemic stroke primarily. Those are the thrombotic events we're really worried about. And you know, the thrombotic events occurred during the treatment, they didn't all occur on day 1. So, you have to have some very clever statistics to come up with a real accurate estimate of what are the relative impacts of these two phenomenon; the good one and the bad one? And we're still working on that, so I can't give you any clear answer at all. I suspect that, I mean, one thing to note is that the reduction – the increase in hemostatic efficacy is quite a lot larger than the effect on ischemic stroke. So, but just purely numerically, I think that's what we're going to end up being able to say in our paper, that hopefully will be coming out quite soon, is that numerically at least it looks like there's an advantage for andexanet. But you know, it all depends on the clinical impact of these events, which is always tough, right?

Dr. Albers:
Yeah.

Dr. Gibler:
Dr. Connolly, thank you very much.

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