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Clinical Implications of ANNEXa-I on the Management of ICH for Neurointensivists and Emergency Physicians

Announcer:
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Dr. Gibler:
Hello, everyone. My name is Brian Gibler. I'm Professor of Emergency Medicine at the University of Cincinnati College of Medicine. And I have with me today three experts in anticoagulation and reversal of anticoagulation as it relates to three different fields. Dr. Gregory Fermann, also from the University of Cincinnati, is an Emergency Physician, Dr. Natalie Kreitzer is a Neurointensivist as well as being an Emergency Physician, and then Dr. Paul Dobesh, who is from the University of Nebraska, and he's Pharmacist. And all three of these individuals, I think, can provide very interesting perspective on this whole area of ANNEXa-I, which was just recently - it was stopped early in the summer for efficacy of the comparator arm of andexanet alfa, and then was recently presented at the World Stroke Conference in Toronto in mid-October.

So, I will ask you, all three of you, and I want to start with you, Greg, because you see patients coming into the emergency department, what do you see as a potential impact of an ANNEXa-I, now a randomized controlled trial with data? What is that going to do, do you think, to the practice of Emergency Medicine?

Dr. Fermann:
So, I believe that more often than not, the decision to reverse a patient with - who is identified to have an ICH is often left up to the emergency physician, because these folks will present with stroke-like symptoms to the emergency department. And it's a time-dependent condition, so oftentimes, it comes to the emergency physician to make a decision to whether or not to reverse a patient or not. And yet - and a lot of factors go into that decision.

And prior to ANNEXa-I, we didn't have much guidance on how to do that. ANNEXA-4 was a – it did not have a comparator group, so we were waiting for a comparator group, because a lot of us were stuck in the middle of deciding whether or not we were going to use andexanet alfa versus 4-factor PCCs in patient selection. And this gives us a lot more data to make those decisions.

Dr. Gibler:
Alright, thank you, Greg. Natalie, from your perspective, you work in the neurointensive care unit with fellowship training in this area. How do you see this impacting your routine care of these patients with intracranial hemorrhage?

Dr. Kreitzer:
I agree with Dr. Fermann and what he said about these patients being cared for in the emergency department. We know that ICH expansion happens really in the first few hours. And ideally, if patients can receive anticoagulation reversal in those first couple hours, as soon as possible, that's going to impact their outcomes far better, you know, than anything we could do later that same day in the neuroscience ICU. So, I really agree with his point that this is truly in the realm of emergency physicians.

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Dr. Gibler:
Excellent. And, Paul, you come to – you're a colleague from pharmacy coming to the table, how do you see this impacting the world of pharmacy as it relates to reversal agents? And also, because you all are - obviously you're a clinical pharmacist, you're somebody that interacts with - and are a clinician from that perspective, how do you see that impacting the pharmacy in hospitals across the country, and the world for that matter?

Dr. Dobesh:
Sure, you know, because I think sometimes the pharmacy seems to be the kind of the stumbling block to using andexa. And my hope here is that these data are able to get those pharmacies or those hospitals that have not yet added andexa to formulary, or put significant restrictions on its use, hopefully, to kind of open up the gates to where that can happen. You know, and I think that the data is very telling in the fact that this is really what we see. You know, we've - everyone says, well, there's, like Dr. Fermann said, 'Oh, we needed a comparator.' Well, now, okay, we've done that study, and the outcome that was selected as the primary outcome was met. And so, it really should hopefully, kind of bring down some of those barriers that others - that some would use to kind of maybe withhold the use of andexa or having andexa within the institution.

Dr. Gibler:
Well, that - and that's very helpful, Paul, because we have to, you know, our colleagues in pharmacy, our colleagues in all areas of medicine, you know, have to be on board, if you will, with the emergency physician's decision to take care of these patients through, in this case, reversal if they're on a factor Xa inhibitor.

And I wanted to talk a little bit if we could, and Natalie, you have within this series, this third wave of the real-world evidence series, you presented the study that was just ANNEXa-I, which was just presented at the World Stroke Conference. Can you talk a little bit about those three aspects of what were used to identify these patients? And then what the findings were from a standpoint of the patients that -with intracranial hemorrhage in this group?

Dr. Kreitzer:
Yeah, absolutely. So, the trial was stopped early. The DSMB stopped the trial much sooner than expected because that primary endpoint was met. And that primary endpoint of hemostasis consisted of patients having to meet three requirements. So, the first was simply a head CT requirement, and that was whether or not patients had good or excellent hemostatic efficacy based on the percent of hematoma expansion that occurred in serial head CTs. That's a great endpoint because it's very objective and it's adjudicated by independent people who look at those serial head CTs. And it's also a great intermediate endpoint when thinking about the pathway of these patients, because it is the one endpoint that is directly impacted by anticoagulation reversal. The second component was the patients could not worsen by NIH Stroke Scale of 7 or more. So, there was that clinical piece as well. And then the third was that they could not receive additional anticoagulation reversal or resuscitative products after reversal. So that was statistically significantly different between the two groups, of course, with the andexanet alfa group having met that endpoint more so than the usual care, which was, in most cases, 4-factor prothrombin complex concentrates.

Dr. Gibler:
Thank you, Natalie. And that gives a really nice perspective with this. I think one of the things that was found in the two groups was there were more thrombotic events in the group treated with andexanet alfa than the usual care group. But that probably isn't a surprise to the three of you all. And I wanted to first ask you, Greg, and then Natalie, and then Paul, to put some touches on this because you are obviously actively treating a patient with a reversal agent. And I want Natalie to really hone in on when can you restart, if you will, anticoagulation in these patients that just came in with an intracranial hemorrhage? Greg, do you want to talk about that a little bit?

Dr. Fermann:
Yeah, ever since we've started having this conversation, what often gets lost is the reason why patients are on the DOACs to begin with. And they're on it because they have a thrombotic disorder, they're either on it for a-fib most commonly or for a DVT/PE. So, once you reverse a patient, if you do so effectively, you're going to expose that patient to their baseline thrombotic risk. And if it's most commonly a-fib, you're going to see some strokes, some thrombotic strokes. And so, it's not a surprise to any of us that once you do that, that you're going to see some ischemic strokes.

I guess the question is, is when you embark on this therapy, the risk-benefit analysis has to come into play and it's a clinical decision. It really should be made by clinicians, in combination with the patients and the patient's families.

Dr. Gibler:
Well, you make a great point, that patient with intracranial hemorrhage that, before you know that if you don't reverse that, that the expansion of that hemorrhage could well be lethal, that's an important point. And Natalie, talk about it from your perspective, not just that, but also how difficult it is to restart, if you will, anticoagulation for those individuals.

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Dr. Kreitzer:
Yeah, I think with some of these thromboembolic events, I'm personally very excited to see the full dataset once the paper is published to really get a sense of which subgroup of patients that it may have been seen the most in, as well as whether or not it was impacted by, for example, DVT prophylaxis, things like that, which we had seen in previous studies. And then lastly, just the severity of some of those events, I will be certainly very interested in seeing.

And then in terms of restarting anticoagulation, in our patients with - certainly with like a spontaneous ICH, it's not an easy decision to make. It should be multidisciplinary. It should, you know, things like weigh in such as fall risk, things like that, we use HAS-BLED scores, different pieces of data to really determine whether or not it's going to be safe or even beneficial for a patient to be restarted on their anticoagulation after an ICH. It's not certainly a one-size-fits-all decision. It really never should be.

Dr. Gibler:
Excellent, Natalie, thank you. Paul, you want to put a finishing touch on this roundtable discussion from the perspective of pharmacy when you're treating these patients, and you potentially do expose the patient to a thrombotic risk?

Dr. Dobesh:
Yeah, I think it's very much kind of what Greg was mentioning, it, you know, it's the pathophysiology of the patient, right? They are a propensity to clot, we take that protective anticoagulant away because we need to and we expose that underlying pathophysiology. We also have to remember these patients are actively bleeding, your body's natural response to bleeding is to activate the clotting cascade and try to stop the bleed. So, you have these two things coming together. And so, I would argue, right, that the event rates we see, you know, this is what happens when you reverse somebody, when you actively go in and try and reverse the anticoagulant effect of the drug that's there. And that while the number is lower with 4-factor PCC, one could argue that since it's not reversing anything and not really treating the bleed, per se, well, no, you're not exposing the underlying pathobiology, but you're also not getting any efficacy with that. And so, I think it's important to kind of think about just what the - who these patients really are. And then when we give agents, kind of what the, you know, how they work and what that can lead to.

And I think Natalie's comment about looking at the severity of these events and when they occurred and things like that, I think will also be extremely helpful in really teasing out, you know, what this all may mean.

Dr. Gibler:
Excellent. Doctors Kreitzer, Fermann, and Dobesh, thank you all very much. It's been a very entertaining roundtable. And thanks, everyone, for watching and listening.

Announcer:
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