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

The Path Forward: What's On the Horizon?

Announcer:
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Dr. Patel:
I'm going to talk about the path forward and what's on the horizon for factor XI. So, our learning objectives for the next 15-20 minutes is to understand the mechanism of what's being thought of as these factor XI inhibitors. And we'll talk about factor XI and XIa, and understand the existing clinical data around these, and then understand that therapy and its promise for the future. Again, I apologize, I couldn't be there, but I'm looking forward to sharing with you all and answer some questions.

So, this is a good review, if you guys are looking for it, it's actually a review of the ongoing evaluation of factor XIa inhibitor drugs. It's actually not just stroke therapies, there's obviously VTE and some therapies in the ACS. So, we're thinking broadly about this this class, because we've heard importantly about the balance between bleeding and thrombosis prevention and what we're trying to do for our patients with stroke.

So, what is the promise of factor XI inhibition? And how did we get there? So, I wanted to just give you my simple understanding of our thrombotic system and our hemostasis system, and just to recognize that without an anticoagulant, usually we have a normal biologic process for hemostasis of which we know that X inhibitors are factor X inhibitors are central, as the factor X is central in the intrinsic and extrinsic pathway from tissue factor to get the thrombin. And then there's a thrombin amplification that propagates that thrombin. And when that's not well controlled, that can lead to a pathologic thrombus.

So, the idea with DOACs is that if you inhibit at least Xa or directly thrombin, you will prevent the thrombus from happening, which is good. We don't want thrombus extension of clotting or pathologic clotting. However, because of the central role of that, even though they're in many instances better than warfarin, they still will lead to some of the bleeding that we're trying to keep from happening, so that there's no free lunch, as we know, we're trying to get thrombus prevention, but sometimes that leads to the bleeding.

So, the idea with factor XI inhibition is that if you can get high enough levels of factor XI inhibition, and this is the hypothesis of hoping to uncouple hemostasis from thrombosis, that you'll see that you can prevent the pathologic thrombus. But you'll see that you may still be able to leave some of the hemostasis that occurs naturally through the factor pathway, therefore, tissue factor. So, fundamental to this hypothesis is that you have inhibition to the level which you can prevent the thrombosis but keep some level of hemostasis to have some at least preserved hemostasis and maybe less bleeding. So, that's a nice hypothesis.

Now, what are some of the reasons we're thinking about that? And so first, I'll go through the preclinical and observational data supporting factor XI as a therapy. And then we'll go into some of the early data. I know Ashkan going to follow me and he's going to share a lot of the direct, at least stroke prevention, non-atrial fibrillation stroke prevention, and I'll walk through some of the places where there's data action and trials ongoing.

So, one can imagine that there's some multiple lines of evidence before you get to human. So, you can have knockout mice where you have factor XI missing, and you can see that they're protected potentially for thrombosis. But there's a lot of things that work in animal models or mice that may not work in humans. The next level of interesting important information is factor XI inherited deficiency, which I'll go through in a second, in that there is a group of people that have a deficiency in factor XI, and they have reduced incidences of VTE and stroke that I'll walk through, and don't have hemorrhage unless it's actually occurring with trauma or surgery or a provocation. And then I'll walk through some of the phase 2 data, so then you can actually have clinical experience. We have ongoing phase 3 trials, which you likely all heard about, I'm involved with, others.

So, the genetic predisposition to having an absence of factor XI has been shown to be associated with reduced rates of ischemic stroke and VTE. In fact, when you look at this slide, you can see that there are differences and some important odds of having certain things. So, on the right, you can see that there's not a significant reduction, at least observed with myocardial infarction, it looks like that symbol and rate although one could postulate maybe there's a benefit. But there seems to be significantly less odds in these people, again observed to have ischemic stroke or VTE. And when we think about the stroke subtypes, certainly seems to be present for both small-vessel and large-vessel strokes and even potentially greater presence for cardioembolic. We'll see that in a second in the next slide.

So, you know, it not only is it the genetic predisposition, we actually have some observational data in people who have actually high plasma factor XI levels. And so, it's not just that you can not have it and have less risk, that when we see people that are actively, potentially have a risk of VTE in the future, that there's a relationship between the factor XI, that it should be factor XI level, and that's inversely related to the risk of thrombosis and that the more you have a factor XI concentration, the actual higher your rate of potentially having a VTE is. And the odds ratio for the thrombosis, as you can see in the middle, according to the quartiles goes up, is that as the rate goes up to the point that we think obviously that to be effective with factor XI deficient, you have to have greater than 90, ideally 95% of inhibition of factor XI to get potentially some of the benefits that we've seen, and you might see that genetically predisposed population.

So, this is important because I think we're going to be thinking through both AF and non-AF. But there are patients that seem to get benefits of both. It's just that the rates and risk of that might vary in populations. And certainly, it's interesting that inherently, people with a genetically lower level of factor XI tend to actually also have long lives. And as you'd have long lives, you have a higher rate, as we've already heard, of afibrillated stroke, but also stroke from the epidemiologic question that I think Mike Sharma asked at the start of this conversation.

So, what are the clinical data with factor XI therapies? And maybe I'll make a comment on at least where we would some of the other programs, again that Ashkan is going to be talking about, where are the trials for our patients who are at risk with stroke not related or secondary stroke prevention, who haven't had an atrial fibrillation or cardioembolic stroke, what I'll call a large and an unmet need.

So, the first proof of concept I'll just sort of say are important trial data we have here from people with antisense, an ASO, an antisense oligonucleotide for the prevention of venous thrombosis. And Harry Buller and Peter Verhamme, and others published in the *New England Journal*, initially, it's important observation that these patients, in fact, did have less thrombosis for VTE in people who are going through knee surgery, and it's compared to an enoxaparin, and you can see that there's our first evidence of some efficacy signal. And you can see that, in fact, it raises the aPTT 1.5- to two-fold. And that was the first evidence that factor XI inhibition might prevent venous thrombosis in this TKA study.

And so, you know, that was an oligo sense nucleotide. This is abelacimab, which is an antibody to the catalytic portion of factor XI; in the conversion of factor XI, did factor XIa, and so preventing activation of factor XI into an activated compound by giving an antibody and using different doses of the antibody and comparing it, again, in patients undergoing unilateral total knee to see if they have a venous thrombotic event. I wish we had a great, you know, biomarker or at least a model for stroke, but we don't; we have these venous thrombosis ones and then we extrapolate into atrial fibrillation and stroke based on some of the dosing. And so, you don't see that this study, which was published in the *New England Journal,* actually showed two really important findings. I'll just have you look towards the right of this slide where you'll see the effect of enoxaparin, standard therapy for patients at risk of venous thromboembolism, and seeing that increasing doses of abelacimab reduced the rate of venous thromboembolism to the point where at the 150 dose, you have about 75 or 80% less composite of either subclinical symptomatic or imaging-related VTE. So, at least an efficacy signal on thrombus propagation in the venous system, as we would imagine with factor XI.

On the left side, you can see the readout of major or clinically relevant non-major bleeding. And again, very infrequent rates, but seeing again, no increase, or at least a similar or small ring of bleeding. It's hard to make when there's a 0 rate in the 150 in the enoxaparin, but reassuring again that there wasn't a higher rate of bleeding and really no bleeding sort of gradient as much as you might imagine.

Well, with that, you know, we talked about an ASO and then we talked about an antibody, well then in another more compounded space is milvexian, which is a small molecule. And this AXIOMATIC-TKR was a study again looking across multiple doses in patients

undergoing a total knee surgery. And you're going to see the dosing from that.

And so, I'll again have you look to the right where you will see I think this slide is a little bit short on showing you the actual dosing but it's enoxaparin, and then it's 25, 50, 100, 200 once a day, and then it's 25, 50, 200 twice a day on the right. And so, you can see that there's, again, a dose relationship as you go up in dose, 100 twice a day or 200 once a day, you can see has a significant reduction compared to an enoxaparin. And then those doses again to the left, once and twice daily, again, show you that you can see significant evidence that they have similar, if not lower rates of bleeding, but often similar rates of bleeding compared to enoxaparin. So again, evidence of some efficacy with similar bleeding rates, if not better.

This is a study I was involved with Jonathan Piccini. And this is a study in patients with asundexian, now another compound that you're going to hear more about in a second, a small molecule at 50 and 20 mg compared to apixaban in patients with atrial fibrillation. This was a study where we're trying to learn a little bit about dose across a broad program, but also trying to understand adult bleeding. And the primary endpoint was ISTH major clinically relevant non-major bleeding. And then of course, we also looked at both an assay for factor XI and looked for efficacy endpoints, although we knew that would be limited. And so, at least on the activity level, you could see that the 50-mg and the 20-mg dosing, at least biologically in these patients that have atrial fibrillation, were able to get towards almost total inhibition with both peak and trough being near the level of what you can actually detect for factor XI, at least believing you were over 90% maybe at the 50-mg dose, at least close to 95% and would be having significant inhibition.

These data then when we looked at the primary bleeding classification, and remember we were looking for ISTH major bleeds, there were no ISTH major bleeds in any of the treatment arms, it's a 3-month safety study to understand it, but there was, when we looked at ISTH major, but then also clinically relevant non-major, if you look across multiple doses there, you can see that asundexian has less bleeding than apixaban in these patients. And of course, the bigger question would be how we can compare inactive comparator or placebo-controlled trials for different indications.

There was an exploratory part of that study to see about efficacy, and again, very small numbers, similar in rate between asundexian and apixaban. But again, 3 months of exposure, and one or two of that number is so hard to make it more data to be really hard to draw any conclusions, but the data was at least presented here for you all to see.

And this, I think Ashkan is going to go over everything in the phase 3 in a second. But this is sort of the landscape of where we were in what I've described for phase 2, which is to show that VTE prophylaxis now has several trials, AFib has had a few phase 2 studies, I showed you PACIFIC. AZALEA was presented at AHA, where the antibody, again, significantly reduced bleeding, at least numerically had similar, if not a little bit higher strokes than rivaroxaban. But again, full study is not done yet. And then we're going to hear about AXIOMATIC-STROKE and PACIFIC-STROKE here in a second as we think about the phase 3 programs. And there was an AMI study done with asundexian, again, no increase in bleeding but no real efficacy at least going forward in that space with asundexian, although milvexian, I think, is going to be going forward in an acute coronary syndrome indication.

So, you can see there's multiple comparators, multiple indications, and multiple types of mechanisms, whether it's small molecule, an antibody, or an ASO.

So, with that, let's think about phase 3 studies and then I'll ask a question and see if you can scan your cookie, etc., although it may not see your results.

So, here's the landscape of the phase 3 studies. So, milvexian is doing three large outcome studies with these factor XI inhibitors, that small molecule, a 15,000-patient study in stroke, a 16,000-patient study in patients with cardiovascular disease MI, and then a 15,000-patient study in patients with stroke who had atrial fibrillation, so to prevent not just AF stroke, but also a secondary stroke. I told you about AZALEA; that's going to be - that compound is going to be studied. LILAC, which is a comparative study against atrial fibrillation, but in patients who aren't on treatment, so against placebo. You're going to hear a little bit about OCEANIC STROKE here in a second. I've been involved in OCEANIC AF, and I'll talk about that in a second. But it's important to recognize those are two large outcome studies also.

So, there's a lot of emerging data. And the field I think is going to be somewhat complicated and we're going to be working on that. So, the ASO antibody and small molecules are being tested against factor XI. As of November, in the last 3 months, OCEANIC AF was actually stopped by the DSMB for inferior efficacy, which is always disappointing, though we're getting all the data in and we're going to be presenting those data as soon as we can, maybe in an upcoming meeting. Valeria and others have been involved with that. And that is in active comparator against apixaban, often on patients who've been on DOACs. So, there's a variety of complexities to doing that study, but we enrolled quite a few number of patients, and that, I think, speaks to maybe the importance of atrial fibrillation in active comparator therapies and how complicated it is to potentially be better there. I think that doesn't relate to secondary stroke where there's a large unmet need, and the dose might be different and might be importantly captured here by the OCEANIC group and the

milvexian groups. So, I think the keys to maximizing these compounds will be the strengths, maximizing the strengths of the compounds in the patients, identifying the right comparators, and the right, obviously, indication with the dose. I also think understanding patients' preferences as Valeria highlighted about net benefits, bleeding and thrombosis, and how we get those patients that have those into the studies will be important and to understand them. And then we're going to need broad inputs, bleeding and thrombotic inputs are important. And then patient perspectives and certainly patient tolerability will be important because that's, I think, how some of these therapies will win.

So, a complicated field. It's exciting. It's great to have other therapies. But thank you guys for letting me present that I'll kick it back to Ashkan to talk to you guys about the emerging data for acute ischemic stroke. And again, thank you guys for letting me present. I'm sorry I couldn't be there.

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