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Axatilimab for cGVHD: Assessing Organ-Specific Responses in AGAVE-201

Announcer:
You're listening to *Project Oncology* on ReachMD. And now, here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Today, we'll be taking an in-depth look at the analysis of the AGAVE-201 study that was presented at the European Hematology Association 2025 Congress. It examined organ-specific responses to axatilimab in patients with chronic graft-versus-host disease, or chronic GVHD for short. And joining me to discuss this analysis and its implications for clinical practice are Drs. Shernan Holtan and Alicia Lieberman.

Dr. Holtan is a Professor of Medicine and Chief of the Blood and Marrow Transplantation Section at Roswell Park Comprehensive Cancer Center in Buffalo, New York. Dr. Holtan, welcome to the program.

Dr. Holtan:
Thank you so much for having me. Happy to be here.

Dr. Turck:
Also joining us from Roswell Park is Dr. Lieberman, who's a rheumatologist specializing in GVHD and post-transplant immune dysregulation, as well as cellular therapies for refractory autoimmune disease. Dr. Lieberman, thank you for being here today.

Dr. Lieberman:
Thank you so much, Dr. Turck.

Dr. Turck:
So Dr. Holtan, I'd like to start with you. Would you walk us through the design of the AGAVE-201 trial, and why focusing on organ-specific responses in chronic GVHD is so important?

Dr. Holtan:
The AGAVE-201 trial was really unique in that it was a randomized study that looked at different doses of axatilimab and assessed overall response rate. This was not a design where it was compared to a placebo. We're really looking at different doses of the drug and seeing what happens within cohorts based upon these different doses.

And the thing that was fascinating to me at the conclusion of the study is that the lowest dose was actually the one that won out of the three arms. There was 0.3 milligrams per kilogram every two weeks, and then one milligram per kilogram every two weeks, and then three milligrams per kilogram every four weeks. And the lowest dose had an excellent response rate, but also had the best tolerability. Overall it's the winner of the three dose levels.

Dr. Turck:
Now turning to you, Dr. Lieberman, let's dive more into some of the data. The analysis found that across all axatilimab dose groups, the highest and most sustained organ responses were seen in the joints and fascia, esophagus, and liver. So what stands out to you about these findings? And how might they reflect underlying disease biology in those tissues?

Dr. Lieberman:
Well, I think what stands out is how refractory some of these tissues can be to our other and current immunomodulatory therapies—in particular, the fascia. That inflammation and fibrosis in the fascia is something that we also see in general rheumatology practice; it's

certainly a much more common manifestation in chronic GVHD and really refractory.

I think what's striking about this pattern—especially in the context of enrolling participants who have tried numerous other therapies with different mechanisms of action and presumably have had inadequate responses—it really speaks to an important subset at least, if not a more universal role for dysregulated tissue macrophages in driving the tissue ecosystem, inflammation, and impaired healing that we're seeing in some of these conditions. So I think that these particular conditions standing out as perhaps the best responses we're seeing and duration of responses in organs may also point to the role of the dysregulated tissue macrophage in driving the pathogenesis in these particular organ systems. I think it's very hypothesis generating and will lead to, really, a number of other studies going over time as we have more experience with axatilimab.

But it raises the question of which cells are really driving the inflammation and the healing, and there may be a different mix in different tissues, which will change the response rates that we're seeing.

Dr. Turck:
And staying with you for just another moment, Dr. Lieberman, the median response times for the skin, eyes, lungs, and mouth were longer, ranging from about 2.1 to 3.2 months. Why do you think these organ systems lagged behind?

Dr. Lieberman:
I think this is a very interesting question. And actually, my initial thoughts about this is to almost invert it, in that I'm also very intrigued that there are some organ systems showing responses at such a short time point in other chronic adaptive inflammatory conditions, such as many rheumatologic conditions and inflammatory bowel disease.

We really think about treatment efficacy assessments in three-month windows. And with most treatments, really, that are modulating immune responses or maybe altering how cells communicate with each other, over the past 20 years, we have really settled into an expectation of three to six months. And so the fact that we're seeing some improvements as early as one to two months, I think, is very encouraging that blocking the CSF-1 receptor signaling may be getting to the crux of what's driving some of this inflammation.

And similar to my prior statement, I think in different tissues the drivers there may be a different mix of inflammatory cells. So certainly we are getting to the tissue macrophages and the Kupffer cells in the liver. Interestingly, the Paneth cells in the GI tract are also known to express CSF-1 receptor. So we may be getting some further accelerated healing all along the GI tract. There may be some other mechanisms. We know there may be some neuromodulation, and certainly there's robust neural immune conversations happening in the fascia and in the GI tract.

So again, I think there may be a lot of information coming out of studies going forward.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Drs. Shernan Holtan and Alicia Lieberman about response patterns to axatilimab in patients with chronic graft-versus-host disease, or chronic GVHD.

Coming back to you, Dr. Holtan, let's shift gears and discuss how we can think about these data in clinical practice. When you look at the timing of response by organ—some taking just one month while others take three or more—how might that influence our clinical decision-making, especially when it comes to escalating or changing therapy?

Dr. Holtan:
It is absolutely critical to think about these different patterns of response based upon organ involvement and really have patience to assess response over time. I think what Dr. Lieberman was just stating is so important, and I really value her insight in this. In the rheumatology world, looking at responses at three to six months is the norm.

Let's not forget that in chronic graft-versus-host disease, some of our previous clinical trials had us assessing response at eight weeks at the very soonest. And even that was considered a very early response. With this chronic disease, we really do have to have patience. And so this gives us that little piece of information that we need to reassure ourselves that we can give time to see an effect without changing therapy too quickly.

As long as the therapy isn't fraught with side effects or too difficult to give, and we're not dealing with other toxicities that would lead us to have to make a treatment change, this really shows us how important that patience is, and we're just waiting to see what happens over time with our responses.

Dr. Turck:
Now, before we wrap up our program, I'd like to ask each of you one more question. Starting with you, Dr. Holtan, given that some patients show deep and sustained responses in select organ systems, do you think there's a role for using organ-level data to guide

dose reductions or treatment holidays down the line?

Dr. Holtan:
I absolutely do. As we get more real-world experience with this drug, I imagine that we're going to see some studies coming out that can help to guide us with this. Right now, we are really doing this empirically. I can recall when I treated patients on the original clinical trial for this, we saw a lot of toxicities, and we had to hold treatments or delay treatments. This was at the higher dose levels, but it showed us that we didn't have to stick to an every-two-week infusion for some patients; it was completely safe and even more tolerable sometimes to space out infusions. Maybe that's something that we will be looking at in the future. Perhaps even a lower dose would work for some patients.

So even though the AGAVE-201 study studied those three dose levels, I'm not sure that we actually know truly what the right dose interval and duration is for every patient. Something that I always tell my fellows is that if you've seen one patient with chronic graft-versus-host disease, you've seen one patient with chronic graft-versus-host disease. And this does have to be watched carefully and individualized.

One other comment I would like to make with my experience with this drug in the clinical trial setting is that we can look at the data in terms of the response rate, but we still need more patient-reported outcomes. I can recall a specific patient I had with very severe skin chronic GVHD with hidebound changes and deep ulcerations. And this patient had technically no response to the drug by the stated criteria. He still had hidebound skin, he still had ulcerations, but they were much improved.

And so I think we do have to take these responses with a little bit of recognition that these are arbitrary human-defined responses and not what's actually happening biologically. So in the future, perhaps we'll have some biomarkers to help guide us with our dosing and personalization of care.

Dr. Turck:
And Dr. Lieberman, in a disease as diverse as chronic GVHD, how might this type of organ-specific data change the way we think about and implement team-based care?

Dr. Lieberman:
Well, as a rheumatologist who, in a way, has jumped silos and has now joined the transplant and cellular therapy team, I may be a bit biased. But, firstly, there's tremendous opportunity for interdisciplinary collaboration and learning, leading to improved patient outcomes, efficacious treatments, modification of our disease activity scoring tools, and maybe understanding of the chronic damage that could be seen and how best to characterize and index this.

But for heterogeneous inflammatory conditions like chronic GVHD and other conditions such as systemic lupus, we know that although there is a pervasive adaptive immune dysregulation, how that manifests and causes tissue damage in different parts of the body varies. We also know, certainly in rheumatology practice, that different clinical manifestations respond differently to drugs.

And so it really makes sense to tease these out a little bit, score them individually, and look at specific biomarkers, or any other biomarkers, imaging, or tissue that's available, along with patient outcomes, to really get a little more granular and refine our disease monitoring.

And I think that there's often the analogy of the blind men meeting an elephant and trying to describe what they see. And we all look at these things from our own perspectives, what we have been trained in and cultured in, and describe what we're seeing. And I think it's just such a more accurate and richer picture by widening the silo and including an interdisciplinary approach.

Dr. Turck:
Well, as those final comments bring us to the end of today's program, I want to thank my guests, Drs. Shernan Holtan and Alicia Lieberman, for joining me to discuss the AGAVE-201 trial's findings on organ-specific responses to axatilimab in patients with chronic graft-versus-host disease. Dr. Holtan, Dr. Lieberman, it was great having you both on the program.

Dr. Holtan:
Thank you so much, Dr. Turck.

Dr. Lieberman:
Thank you. It was my sincere pleasure.

Announcer:
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