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Poster Pearl: Axatilimab's Impact on Fibrosis-Dominant Organs in cGVHD

Dr. Turck:
This is *Project Oncology* on ReachMD. I'm your host, Dr. Charles Turck, and today I'm joined by Dr. Daniel Wolff to discuss his research on axatilimab for chronic graft versus host disease, which we'll refer to as cGVHD, and responses in fibrosis-dominant organs in the AGAVE201 trial. He's a Professor in the Department of Internal Medicine at the University Hospital Regensburg in Germany, and the findings of his study were published in September of 2024 in the *New England Journal of Medicine*. Dr. Wolff, thanks so much for being here today.

Dr. Wolff:
Yeah. Thank you very much for giving me the opportunity to share some results from the AGAVE201 trial.

Dr. Turck:
Absolutely. Well, beginning with some background, Dr. Wolff, would you tell us about axatilimab and its mechanism of action in treating cGVHD?

Dr. Wolff:
Yeah. Axatilimab is an interesting concept of treatment; it targets the CSF1 receptor. The CSF1 receptors express mainly on M2 macrophages and monocytes and regulate the production of profibrotic and proinflammatory signals.

Dr. Turck:
And would you tell us a little bit more about the trial design of AGAVE201 and your findings concerning the safety and efficacy of axatilimab?

Dr. Wolff:
Yeah. The AGAVE201 trial was a large, randomized trial comparing three different doses and two different schedules, acknowledging that within a Phase 1-2a trial, the number of patients treated with different doses would not be sufficient to identify the optimal dosing. It was a global trial running across different continents. A lot of countries contributed patients, and there was a fairly significant number of patients treated—241—which is, for a rare disease like chronic graft versus host disease, a fairly high number of patients.

Patients were randomized to one of those three arms and were included in case we had advanced chronic graft versus host disease failing at least two prior treatment lines or for a significant number of patients who failed more than two treatment lines. We had to have active chronic graft versus host disease.

But an age above 2 years was required without higher limit, and the patients were allowed to continue the standard treatment—being corticosteroids, calcineurin inhibitors, or mTOR inhibitors. That was not required, but that was the only concomitant agent allowed, or our agent had to be stopped. And the primary endpoint was overall response rate at 6 cycles, and secondary endpoints were toxicity rate and the symptom load, which improved organ-specific response rates.

Dr. Turck:
And can you give us some highlights concerning the safety and efficacy of axatilimab? What did you find?

Dr. Wolff:
The AGAVE201 trial came with two big surprises. One is, given that those patients failed multiple lines, there was a surprisingly high response rate being significantly above 50 percent. So 75 percent of patients responded. They responded fairly quickly, which was also

a surprise. And the biggest surprise was that the lower doses were best. There was an observed inverse response dose relationship. Although the trial was never powered for that purpose, it was obvious that the patient didn't need the high dose to respond. But there was a clear association of toxicity with higher doses and the lowest dose being very well-tolerated and leading even to the highest response rate. And that also identified this low dose as the optimal dose, which is now also approved for treatment of advanced chronic graft versus host disease.

There was no increase in infectious complications, at least in the low-dose arm, and there is a specific side effect, which I wouldn't really call side effect, but it's a lab phenomenon because axatilimab also depletes Kupffer cells in the liver. It reduces the clearance of liver enzymes and pancreatic enzymes in the serum, so it goes somewhat up during treatment, which is not a damage signal; it's just the signal of decreased clearing. But that was fairly low in the low-dose axatilimab arm. There's another specific side effect, which was also very infrequent in the low-dose arm, which is periorbital edema. It looks funny but isn't dangerous, and it has only been observed in very few patients in the low-dose arm.

Dr. Turck:
And turning to a sub-analysis you conducted, why did you decide to focus on fibrosis-dominant organ specific responses?

Dr. Wolff:
For a very simple reason: this agent was used in a very advanced population who failed multiple treatment lines, and those patients suffered a lot from fibrotic manifestations or situations where you would basically regard their changes as nonreversible. And to our big surprise, nonreversible applied to conventional immunosuppressive agents, but not to the CSF1 receptor pathway targeting.

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 Dr. Daniel Wolff about axatilimab for chronic graft versus host disease, or cGVHD, and the responses to it by fibrosis-dominant organs.

So, Dr. Wolff, let's dive deeper now into each organ response, starting with the esophagus. What results did you find specifically with respect to swallowing?

Dr. Wolff:
The majority of the patients showed a response. 80 percent showed response in the low-dose arm by at least one-point improvement on the symptom scale, which is an incredibly high response rate we didn't expect when we designed the trial.

Dr. Turck:
Now, how did the lungs respond and what did patients report about their shortness of breath?

Dr. Wolff:
Shortness of breath was also improved. And the very interesting finding with the improved shortness of breath was that the lung function was getting only slightly better—the FEV1, so the volume of air you can exhale within one second. But the function of the lung got better in that the patients were less short on breath and had a better capability to exercise, which was recognized in a number of patients. And given, again, that there was a significant proportion of patients with severe lung GVH disease included, that was something which convinced us that axatilimab is of value.

And there's another aspect to that. Axatilimab does not increase, or seems not to increase, the infectious rate. And given that lung involvement is usually associated with frequent infectious complications, axatilimab does not increase infectious complications but makes the function of the lung better in a way that patients have less symptoms. This is just a perfect match.

Dr. Turck:
And finally, you analyzed responses in the joints, fascia, and skin. What results did you see there?

Dr. Wolff:
With joints, there was a nice response rate. In the P-ROM scale, there was a nice response rate also with skin and joint tightening and skin thickening. There was some disappointment in that partial and complete responses were hardly seen in skin assessed by the physician. But that's not because patients do not get better. They do. They get significantly better. The point is the NIH grading requires a complete resolution of deep sclerosis to call that a partial remission. And even if you had a 90 percent reduction of the surface with deep sclerosis, if you're left with 10 percent, you didn't even have a partial response, and that's explaining the low response rate in terms of NIH response assessment, but a significant response rate within the symptom load.

Dr. Turck:
Well, Dr. Wolff, before we close, do you have any insights you'd like to share on how these findings might impact the future of C-GVHD treatment?

Dr. Wolff:
Yeah, I have a couple of thoughts. First of all, this trial is a perfect example of how preclinical findings turn into success in clinics. Second, it shows that nonreversible organ manifestations are just nonreversible to a specific mechanism of action. Having said that, axatilimab results in high response rate, but fails in some patients, indicating that it's not the end of the play and the way to target chronic graft versus host. And we are now in the fortunate situation of having more than one agent. We have a couple of agents approved for the disease, and the challenge now is to identify in advance who would benefit from which agent and in each individual patient, which pathway is driving the disease to be targeted to gain success.

Dr. Turck:
Well, with those final thoughts in mind, we come to the end of our program. And I want to thank my guest, Dr. Daniel Wolff, for joining me to discuss his research on axatilimab in chronic graft versus host disease and its effect on fibrosis-dominant organs. Dr. Wolff, it was great to have you with us.

Dr. Wolff:
Yeah, you're highly welcome.

Dr. Turck:
For ReachMD, I'm your host, Dr. Charles Turck. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.