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(866) 423-7849

Interpreting and Applying cGVHD Clinical Trial Data

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and here with me today is Dr. Christopher Graham, an Assistant Professor in the Division of Hematology, Oncology, and Transplantation at the University of Minnesota. Together, we'll be looking at how we can interpret and apply clinical trial data in chronic graft-versus-host disease, or chronic GVHD for short. Dr. Graham, thanks so much for being here today.

Dr. Graham:
Thanks so much for inviting me, Dr. Turck.

Dr. Turck:
Well, let's start with the big picture, Dr. Graham. When you evaluate a trial, what baseline patient characteristics do you focus on first and why?

Dr. Graham:
I think the big thing for me is the organs that are involved, particularly patients with lung involvement, also called bronchiolitis obliterans syndrome. Those patients typically have pretty resistant disease with high comorbidities, morbidity, and mortality associated with their lung involvement, which can lead to death in that case. So seeing activity in that population of patients is very important to me as a clinician.

Additionally, other organ-specific factors like sclerosis or liver involvement also play into things along with prior lines of therapies, like how many previous lines of therapies before the trial they allow.

Dr. Turck:
And if we zero in on prior therapy exposure, how does that patient-specific variable shape your interpretation of efficacy and safety outcomes?

Dr. Graham:
So when we looked at some of the early data for chronic GVHD clinical trials, predominantly with ibrutinib, they allowed early lines of therapy—around one to three lines prior to ibrutinib. Whereas some of the later studies, such as the AGAVE-201 study of axatilimab and the ROCKstar study with belumosudil, they had subsequent lines of therapy—up to as many as seven or more lines of therapy.

So when we look at response rates, we know that the fewer lines of therapy, the more likely the patient is to have a higher rate of response. Whereas in some of the newer studies, the response rates might be muted because of previous lines of therapy.

The only caveat is the ruxolitinib study of REACH3, which compared ruxolitinib versus the best available therapy, and they allowed a crossover from those receiving best available therapy. And they had the same amount of response rates after switching over to ruxolitinib compared to the patients who only received ruxolitinib as part of the initial part of the trial. So that's the only time where we have actual clinical trial data where there's been a crossover from previous lines of therapy.

Dr. Turck:
So switching gears now to the impact of study designs, many chronic GVHD trials allow ongoing corticosteroids or concurrent immunosuppression. But how can that complicate our assessment of treatment benefit?

Dr. Graham:
So typically as a physician, we like to get patients off steroids or try to reduce their concurrent immunosuppressive therapies. However,

in two of the most recent studies, both the AGAVE-201 with axatilimab and the ROCKstar trial with belumosudil, most of the patients were on concurrent immunosuppressives—99 percent of the time for the ROCKstar trial and around 70 percent of the time with the AGAVE-201 study.

And so for those patients that want to get off steroids earlier, it might be difficult to decide how fast to taper for getting on these agents. So that impacts our clinical decision-making about therapies.

Dr. Turck:
For those just tuning in, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Christopher Graham about how patient characteristics, study design, and endpoint selection can shape our interpretation of trial data in chronic graft-versus-host disease or chronic GVHD.

Now, Dr. Graham, randomized controlled trials remain relatively uncommon in chronic GVHD. So what are the strengths and limitations of the single-arm studies that often make up the evidence base?

Dr. Graham:
So a lot of the time, the single-arm studies are closer in line with what we see in real life. Even though we try to have strict criteria for inclusion, with chronic GVHD, it's hard to have strict criteria for inclusion. And sometimes, we run into the issue where if we have a feeling that one drug is stronger than the other, we wouldn't want to randomize a patient to an inferior drug.

So a lot of times, we do a single arm both for efficacy and safety, especially in these heavily pretreated populations. And especially if they have significant chronic GVHD, particularly moderate to severe, we can't really compare to a placebo arm in that case because of the increased morbidity or mortality associated with it. So a lot of times what we have are these single-arm studies.

Dr. Turck:
Before we move on, let's examine one more key aspect of chronic GVHD trials. When it comes to endpoint selection, why is it no longer enough to rely solely on clinician-assessed response rates in defining clinical benefit?

Dr. Graham:
Yes, so we do have a lot of optimism when it comes to patients responding because we want patients to respond. I think incorporating how patients feel in the form of patient-reported outcome, or PRO, data is very helpful for chronic GVHD because we've seen with multiple other studies—both the AGAVE-201 study with axatilimab and the ROCKstar study with belumosudil—that patients actually feel better before we see a clinical improvement based on the NIH criteria for response.

And so because the NIH criteria has a lot of variability with going from a partial response to a complete response and a whole lot of time between each response assessment based on the degree of skin involvement, for instance, we need to have some patient-reported outcomes so that patients can start to feel the benefits, even if we don't objectively see a benefit based off of our current NIH reporting.

Dr. Turck:
And do you have anything else to add about how the endpoints of patient-reported outcomes and prospective measurement of immunosuppression reduction are changing the way we think about meaningful benefit? What are some of the trends you're seeing?

Dr. Graham:
Yeah, so I think one of the big benefits we're seeing with some of these newer agents is that the side effect profile is a lot better than with previously used corticosteroids or immunosuppressives. We're seeing more immune reconstitution happening and less infectious complications with some of these newer agents compared to what we'd previously seen with tacrolimus, sirolimus, or corticosteroids. So these newer agents have a better side effect profile, and patients are tolerating them better.

And I think with chronic GVHD—because outside of BOS, most of this is a morbid condition—having improved responses, both with reducing infectious risk and tapering corticosteroids or other immunosuppressives, is more meaningful for patients because they are able to be in the hospital less because of infectious complications. They're able to do more. They're not needing as much transfusion support, or they're not needing as many medications to support the side effects that they're having from their GVHD medications.

Dr. Turck:
Now, given everything we've discussed today, Dr. Graham, what are your key takeaways for interpreting chronic GVHD trial data and applying them to personalizing patient care?

Dr. Graham:
I think we should really harp on adding PROs to all of our data in trials in the future. Because as I mentioned before, there's a huge discrepancy between what patients feel and what we see as clinicians. And again, chronic GVHD affects patients' lives, first and

foremost. There's some increased risk for mortality for some subtypes of chronic GVHD, particularly lung chronic GVHD. So I think if trials do not incorporate PRO going forward, it's not allowing patients to have a seat at the table for their care. So I think that's a big deal.

Additionally, we need to try to find a safer drug that's targeted to certain pathways, especially with some of the other agents that target particular pathways that are less infectious and come with less immunosuppression. And one of the things that we see with totality of immunosuppression is a potential increased risk for relapse. If we add on more immunosuppression, that can potentially increase the risk of relapse in those patients. So I think identifying the safest drug to treat their chronic GVHD that doesn't increase the risk of relapse but also controls their disease without increasing their infections or other comorbid conditions is something that as a group we're actively trying to identify.

Dr. Turck:
Well, with those key takeaways in mind, I want to thank my guest, Dr. Christopher Graham, for joining me to evaluate the key aspects of chronic graft-versus-host disease that influence our interpretation and application of clinical trial data. Dr. Graham, it was great having you on the program.

Dr. Graham:
It was great to be here.

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