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Evaluating First-Line Therapy for Acute Graft-Versus-Host Disease

Announcer:
You're listening to ReachMD. This medical industry feature, titled "Evaluating First-Line Therapy for Acute Graft-Versus-Host Disease," is sponsored by CSL Behring. This program is intended for physicians.

Here's your host, Dr Charles Turck.

Dr Charles Turck:
This is ReachMD, and I'm Dr Charles Turck. Joining me to discuss acute graft-versus-host disease, or acute GVHD (aGVHD) for short, treatment are Dr Yi-Bin Chen and Dr Olaf Penack. Dr Chen is Director of the Hematopoietic Cell Transplant and Cell Therapy Program at Massachusetts General Hospital, as well as the Allen B. Rogers, Jr. and Cara J. Rogers Endowed Chair and Professor of Medicine at Harvard Medical School.

Dr Chen, thanks for being here today.

Dr Yi-Bin Chen:
It's my pleasure, Dr Turck.

Dr Charles Turck:
And Dr Penack is a Senior Physician and PI within Hematology and Oncology at Charité Berlin. He also is part of the Working Parties for the European Society for Blood and Marrow Transplantation and the German Society of Hematology and Oncology.

Dr Penack, it's great to have you with us as well.

Dr Olaf Penack:
Thank you so much for having me and looking forward to our discussion.

Dr Charles Turck:
Well, it's great to have you both here to discuss aGVHD treatment. Let's start with the basics. What are the current options available for first-line treatment of aGVHD?

Dr Olaf Penack:
In Germany, current treatment options for aGVHD are all immunosuppressive. For low-grade aGVHD, such as Grade 1, treatment is typically with topical steroids only.[1,2] Higher grades aGVHD, like Grades 2 to 4, require systemic treatment of steroids.[1,2]

I usually start with 2 mg/kg of methylprednisolone or prednisolone, and I start that as early as when we do the diagnosis. In cases where a patient already has skin aGVHD, but then develops severe diarrhea, I prefer to start steroid treatment immediately and not delay until after the endoscopy of formal diagnosis. Ideally, I'm looking to achieve complete response. So typically, this is continued until complete response and not discontinued before then.

And most patients will respond to this first-line treatment. For most patients with aGVHD, I think steroids work pretty well. We have many patients who can be treated for relatively short amount of time with steroids and who then will be in complete remission. However, for severe cases, we need to move fast to a next line of treatment.

Dr Charles Turck:
Is it the same for you in the US, Dr Chen?

Dr Yi-Bin Chen:
Yes. We're following something pretty similar. When it's just a skin rash, we do aim for topical treatments in order to spare the patient systemic immunosuppression, but usually if a patient develops overall Grade 2 to Grade 4, certainly stage 3 skin or stage 2 gut and above, we do prescribe systemic therapy.[1,2]

Standard treatment for the last three to four decades, disappointingly, has remained systemic high-dose steroids. The therapies that we have traditionally used in the past, including steroids, were all immunosuppressive, anti–T–cell in mechanism.[3] Historically, we believe that for patients with severe aGVHD, we're able to fix it, or patients died from it. As we are now developing and using less toxic and less immunosuppressive therapies, there does appear to be a subset of patients who may keep a partial response for longer and not die of opportunistic infections or for other reasons.

Over the last few years, I've treated several patients with severe GI aGVHD, who unfortunately have had fibrotic or sclerosed bowels from a chronic partial response. I think we acknowledge that steroids, while essential in some ways to initially control aGVHD, are obviously not beneficial in the long run in terms of the toxicities associated with high cumulative doses. We have realized that we need to be more careful about how long patients are treated with steroids, and we've realized how slowly we traditionally tapered patients off of steroids.

With the approval of a second-line therapy in the US for steroid-refractory aGVHD, such as ruxolitinib, the trigger for the next line of therapy has moved closer, meaning we move much more quickly to second-line therapy.[4] For some patients, it's because they've had a response, but we're really concerned about the side effects of the steroids; so, we add ruxolitinib in order to taper steroids faster. For other patients, it's because they've had a partial response, but we need to improve that partial response in order to maximize quality of life. And yet, for other patients, it's because they're actually refractory to steroid use, and we need to capture a response to begin with.

Dr Charles Turck:
So how do you know when a patient with aGVHD isn't responding to steroids?

Dr Yi-Bin Chen:
Well, my standard definition of steroid-refractory aGVHD is that it gets worse after 3 days or it doesn't get better after 7 days of the standard dose of steroids that you started. But this definition doesn't really determine when we add second-line therapy, given the different reasons I stated previously.[5]

Dr Charles Turck:
And Dr Penack, can you tell us what you specifically look for when monitoring a patient's response to steroids?

Dr Olaf Penack:
Yes. We are very closely monitoring each patient individually for aGVHD onset before it develops to higher grades. Our aim is to get a response at the early stages so that we have a better chance of remission. I'm aligned with Dr Chen that the primary assessment of response needs to be very early. In our center, we will assess around Day 5, so a little bit later than Dr Chen's timing, but still early.

And aGVHD assessment is usually done using the MAGIC criteria.[6] For gut aGVHD, I monitor frequency and diarrhea, and ask the patient about symptoms of nausea and abdominal pain. For liver aGVHD, I will check how high bilirubin levels are and look for signs of jaundice in the eyes and skin. For skin aGVHD, it's important to not only visually check which body surfaces are affected, but also touch the skin. Sometimes the skin thickens and will feel differently from normal skin. So, in patients who are refractory to steroids, we'll see disease progression within those first days.

Dr Yi-Bin Chen:
We also try to have formal grading of aGVHD based on the MAGIC consensus criteria; we're following progress in these patients very similarly to what Dr Penack described. In patients with severe lower GI disease, I also like to look at the serum albumin and immunoglobulin levels because patients with severe GI GVHD will generally have a significant protein-losing enteropathy.[7]

Dr Charles Turck:
For those just tuning in, you're listening to ReachMD. I'm Dr Charles Turck, and today I'm speaking with Drs Chen and Penack about aGVHD first-line therapy. We spoke a bit earlier about patients with aGVHD who do not respond to first-line steroids, and how to assess their progress.

So then, how are you managing and treating these patients if steroids fail?

Dr Olaf Penack:
Ruxolitinib is an approved second-line standard of care in both the US and Europe.[4,8] This is also immunosuppressive. After that, we are in a situation where we have no standards. There are some options, but they're all, again, immunosuppressive. These patients who don't respond to steroids have extremely high mortality. When we look at why patients are dying, many patients are dying from infections because of the immunosuppressant.[9,10] So then you have to question yourself, do you really want to give a third immunosuppressive treatment or not? It would be important to have non-immunosuppressive or less toxic therapies. But the problem is, there's no established alternative therapy.

Dr Charles Turck:
What about you, Dr Chen, what approaches are you using when patients aren't responding to steroids?

Dr Yi-Bin Chen:
As I mentioned before, at our center, we're generally moving to second-line therapy quickly, even as soon as 3 days after starting steroids. With the initiation of ruxolitinib, we generally start to taper steroids at that point, because we've already become concerned about the cumulative exposure of steroids.

Over the last decade, less toxic therapies are being studied and have become available and are being implemented sooner and sooner.

I should mention there's also an important supportive care aspect to treating these patients. A key pillar of our program is the incorporation of supportive care and making outcomes better. Besides dealing with infections, these patients are not able to eat properly due to malnutrition and severe diarrhea, and thus, they often require IV nutritional support.[11] This and the low albumin levels from the protein-losing enteropathy often leads to significant lower extremity edema.[12] So not only will they need medical diuresis to attempt to get fluid out, but also physical therapy to prevent steroid-induced proximal muscle wasting and the natural deconditioning that happens in a prolonged hospital stay.[12] Ultimately, we want to prevent complications, such as falls from these issues, which can further impair their recovery. The use of steroids can also bring out hypertension and diabetes.[13] There's also the mental health support needed because steroids also frequently cause sleep disturbances, body dysmorphia, and mood disorders.[13] Again, I don't think it's the use of the initial high doses of steroids that leads to all of these side effects, but rather a consequence of the cumulative dose.

Dr Olaf Penack:
Furthermore, these negative side effects tend to leave a lasting impression on many patients, even long after steroid discontinuation. Patients remember the negative impact on their quality of life.[14,15] I have talked to patients several years after they have been treated with steroids, they are still kind of horrified by that. Their physical reactions when they enter the hospital building, such as sweating and tachycardia; aGVHD and immunosuppression have a massive influence on them.

Dr Charles Turck:
That’s very striking, Dr Penack. It really emphasizes the urgency to resolve aGVHD as quickly as possible. So what can be done moving forward to improve first-line steroid response and minimize cumulative steroid exposure?

Dr Olaf Penack:
In our situation, nearly all patients are cancer patients, and we're doing the allotransplant as an immunotherapy against the cancer.[16] So, we want the immune system to be very active after transplant, but we're mainly working with immunosuppressive agents for prophylaxis and treatment of aGVHD. So, this is totally contradictory to what we actually want. There's a big risk that not only are we inhibiting the anti-tumor effect with our current strategies, but also deteriorating the secondary immunodeficiency.[17] So, I'm not content with the overall approach of using immunosuppressants after allotransplant. I think the aim of translational research in this field should be get rid of steroids, especially for prolonged use.

Dr Yi-Bin Chen:
I'm always concerned as well about adding immunosuppression after transplant, given the risks of opportunistic infection and disease relapse that Dr Penack mentioned. I think one way to move forward in treating patients with aGVHD is that we need to be able to accurately risk stratify patients at diagnosis—be it with biomarkers, clinical risk, or a combination of the two.
In the US, the BMT CTN conducted a clinical trial using sirolimus, and the MAGIC consortium used itacitinib in a clinical trial as well, both as single-agent therapy for low-risk aGVHD without steroids.[18,19] Both trials showed that for a majority of patients with low-risk disease, you likely do not need to use systemic steroids, certainly not at the doses we consider to be standard.[18,19]

Moving forward, we should continue to refine how we define low-risk patients and what agents could be used to treat them instead of steroids. For higher-risk patients, we probably still need steroids, but likely with an additional agent. Now, I don't know ideally what this

agent should be, but the field is gradually moving away from added global immunosuppression.

In the past, based on the convention that aGVHD is a result of a Th1 T-cell immunological response, we just hammered away at that pathway. We gave anti–T-cell agents, like anti–T-cell antibodies, even treatments like alemtuzumab,[3] or we hit major pathways like IL-2 or TNF alpha to try to really knock out that T-cell response.[20,21] For some of these patients, given the therapies they received, you just couldn't believe there are any active T cells left, and they clearly still had the whole clinical picture of active aGVHD.

So, I think the way to move forward would be studying treatments targeted to alternative pathways that are active in aGVHD but are not totally T cell driven.

Dr Charles Turck:
What are some specific strategies in research or development to improve the first-line treatment of aGVHD? Do you both have any clinical trials of interest?

Dr Olaf Penack:
We have several drugs which are late in pipeline and may come out onto the market in the next 2 to 5 years. I think we can also look forward to biomarkers to stratify the patients and predict steroid responsiveness. Perhaps, if we can identify these patients that do not benefit from prolonged steroid use, we can do something differently to prevent steroid-refractory aGVHD in the first place. This may mean giving interventions, pre- or para-transplant, or even rethinking the value of transplant to the patient in the first place. If you know this patient is going to get steroid-refractory aGVHD, maybe we question the transplant indication, because do you want to expose the patient to such a high risk?

Dr Yi-Bin Chen:
I mean, it's a good question. Right now, we have well studied and validated biomarkers measured at the diagnosis of aGVHD that are a surrogate for predicting if the patient will develop steroid-refractory aGVHD. These biomarkers can potentially risk stratify patients into high-risk and low-risk groups.[22] Traditionally, that definition of high risk or low risk has been different risks for non-relapse mortality, and most of those non-relapse mortality deaths are from acute GVHD.[23] However, I have not yet seen any clinical trials that have demonstrated different outcomes if we treat high-risk patients differently.

Dr Olaf Penack:
Yes. Response and mortality really go hand in hand. It's very complicated. We'll need to design prospective clinical trials to use these biomarkers for earlier intervention and for making clinical decisions. This will take much longer to develop. But what I'm most excited about is the potential of non-immunosuppressive treatment options. For instance, cellular therapies like mesenchymal stromal cells, and how we can increase protection of regularization of tissues like the epithelium and endothelium, as opposed to further escalating immunosuppression.[24,25] If we had better drugs that were not immunosuppressive, or just better drugs with better efficacy and safety, it would be easier to discontinue steroids and to switch to these other agents to avoid the risk of toxicity from steroids.

Dr Yi-Bin Chen:
I agree. With access to more agents that work better or are less toxic, or better yet both, I would be motivated to use them faster and to taper steroids faster.

Olaf, I'm also very interested in trying to enhance and improve organ resiliency and healing, particularly measures that protect the intestinal stem cells. There are recent mouse studies in aGVHD showing that the early attack by donor T cells is in the crypt base, where all your intestinal stem cells are located.[26] So even if systemic steroids are able to stop the immune response that initially drove that damage, you still have no intestinal stem cells left, so you can't heal your gut.

So what are some ways to promote organ resiliency? Agents proposed to have included IL-22 and alpha-1 antitrypsin, which have already been studied in trials. Urinary-derived human chorionic gonadotropin with epidermal growth factor has also been studied by our colleagues at the University of Minnesota to try and exploit this strategy as well.[27-29] This is one approach that I'm really excited about because I definitely think we have harmed patients at times from continually hammering away at their immune system.

Dr Olaf Penack:
Yeah, I agree that we're in quite exciting times right now with the potential for non-immunosuppressive options in the future. I think we had several decades of trying steroids, and now we should move on to newer strategies.

Dr Charles Turck:
Those are great, forward-looking insights for us to think on as we come to the end of today's program. And I want to thank my guests for helping us better understand the negative consequences of immunosuppression for aGVHD. Dr Chen, Dr Penack, it was great speaking

with you both today.

Dr Olaf Penack:
Yeah. Thank you so much for having us and for the good moderation for the discussion.

Dr Yi-Bin Chen:
It was my pleasure to be a part of this discussion today, and hope we shed some insight on acute graft-versus-host disease.

Announcer:
This program was brought to you by CSL Behring. If you missed any part of this discussion, visit Industry Features on ReachMD.com, where you can Be Part of the Knowledge.

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