Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/living-rheum/monitoring-gca-disease-activity-in-the-era-of-biologic-treatment/13344/

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

Monitoring GCA Disease Activity in the Era of Targeted Treatment

Announcer (Introduction):

You're listening to ReachMD. This episode of *Living Rheum*, titled "Monitoring GCA Disease Activity in the Era of Biologic Treatment" is sponsored by Novartis US Clinical Development and Medical Affairs. The host and speaker have been compensated for their time. This program is intended for health care professionals. Here's your host, Dr Anisha Dua.

Dr Dua:

As rheumatologists, we're always looking for the most effective and safest way to treat our patients, and control their disease. Glucocorticoids, also known as GCs, have historically been the cornerstone of therapy for giant cell arteritis (GCA). But, they do carry significant side effects. The elderly populations classically affected by GCA are especially vulnerable,[17] so the search for other, more targeted and effective, therapies is critical. This is ReachMD, and I'm Dr Anisha Dua. Joining me to discuss monitoring GCA disease activity is Dr Mike Putman. Dr Putman is an Assistant Professor of Medicine at the Medical College of Wisconsin. Dr Putman, thanks so much for being here to speak with me today.

Dr Putman:

Ah, thanks so much for having me. I'm very excited to be talking about therapies and therapeutics.

Dr Dua:

Absolutely. So, we know that GCA patients have been historically treated with a lot of glucocorticoids. Can you tell me a little bit about the side effects of this treatment option, as well as other treatment options that are available for GCA?

Dr Putman:

Yeah, that's a big topic. I'll focus on the glucocorticoids first, 'cause them alone – they deserve a little patch. So I always say glucocorticoids are our best worst drug. I think I saw a talk by Peter Merkl one time, and he said glucocorticoids are fantastic, except for the cardiovascular disease and cataracts and glaucoma and diabetes and… It just goes on and on and on, and the truth is that glucocorticoids cause a lot of side effects. So, there's weight gain, hypertension, diabetes, osteoporosis, cataracts, insomnia, mood changes,[19,34] and I actually read patients the list before I start them, because the patients will develop symptoms, and it's really important that they know what they're getting into when it comes to glucocorticoids.

Now, historically, haven't done a great job of monitoring for these. I think that's true in our own practice, where I feel like we could all be better about monitoring for osteoporosis –very low rates of screening for that – and a lot of observational data sets.

But then, just characterizing what's going wrong is really important. There's a new index, called the glucocorticoid toxicity index,[17,35] that I quite like, and I just think it's important to develop these metrics, for clinical trials and observational studies, but it's also important to take that forward into your practice, and actually screen for glucocorticoid-related side effects. Now, so, some of us try to prevent these side effects, and there's a lot of options for doing that. Things like proton pump inhibitors in people who are at high risk of GI bleeds, all the prophylactic medications.[17,36]

My overarching bias is to just try to give less steroids. I think that's the best prophylaxis against glucocorticoid toxicities, but it's hard. I mean, often they're necessary, and trying to just thread that needle is what makes rheumatology so challenging.

Dr Dua:

Yeah. No, absolutely. I think if we are able to get the disease under control, and then limiting the amount of steroids that we're giving people, is clearly the best option, 'cause as you mentioned, all those side effects are just rampant, and super toxic. But now we actually are able to do that a little bit, so let's talk about that. As we've developed our understanding of the pathophysiology of GCA, that's sort of led to some new therapeutic agents, so can you tell us a little bit about some of them?

Dr Putman:

Yeah, sure. The role of methotrexate in giant cell arteritis is remarkably controversial. There've been 3 trials. One of 'em was pretty well run, was a big failure, and then 2 were qualified success,[37] and if you meta-analyze them, it looks like there's a little bit of a benefit. So I think that the methotrexate has a role.[37,38] I do use it, but I think interleukin-6 inhibition has kind of taken over as the standard of care for most folks,[39] and that was certainly what was recommended in the recent guidelines that were produced, was to lead with interleukin-6 inhibition from the United States' side. And EULAR recommended it, in cases of relapse, for refractory disease, and for people who are at high risk of side effects, which I think is everybody.[39] So, I'd say that many of us, I think, are using less steroids and more interleukin-6 inhibition. But it's not perfect. We have a lot of people who will flare through that, still. And so, I think the search for a better molecule is very much under way.

There's GM-CSF inhibitors – there've been a couple of recent studies that were quite encouraging in that realm.[39] Interleukin-17 inhibitors are interesting.[39] Same thing: some data at ACR that was presented and hoping for some trial publications in the near future. And then, some of the small molecule inhibitors, in particular the Janus kinase inhibitors have had a lot of excitement lately.[39] Certainly there's some caution there, with the safety signals that we saw, especially in an older population, who will likely have many of the comorbidities that would make you worry about the Janus kinase inhibitor side effect profile.[40] But, I think all of these mechanisms have potential, and all of them have encouraging preliminary data. And so I'm hoping in the near future, we'll have more than just the interleukin-6s and maybe methotrexate, as treatment modalities.

Dr Dua:

Absolutely. It's definitely an exciting time though, just to see that we are discovering these new targets and possible ways, 'cause as you mentioned, while we're getting closer with IL-6 inhibition, there's still definitely a great need for this elderly population to try to minimize the toxicities, and get things under control, and keep them under control. So, with that in mind, how has the introduction of biologics impacted the way you monitor patients with GCA? We talked a little bit about different ways we try to monitor our patients – labs, clinically, imaging – how do biologics impact that for you?

Dr Putman:

Yeah, huh. In one sense, they make me do it more, because now you're adding toxicity that you need to monitor for. So, you need to know your agent. LFT abnormalities, lipid abnormalities – I screen more than I did otherwise. But beyond that, there's some really strange, idiosyncratic things that are very important.

So, with interleukin-6 inhibitors, in particular, the inflammatory markers tend to normalize, no matter how active disease is.[41] And a lot of those people can still have rip-roaring inflammation, despite normal labs, and so, that's one sign that we need more pathways, but also a sign that just putting someone on a drug means that you actually have to monitor them more closely, in my opinion, than if they weren't on it.

I think that a holistic exam, just listen to the story, paying very close attention to your patients. Checking the labs, even though they aren't as useful if people are taking those medications. And then, doing imaging modalities where necessary is very important. I think the thing that I see the most, is just overconfidence. Patients and providers often feel like, you're on a fancy medication and nothing could go wrong. But, the truth is that in clinical trials of all these agents, there've been a lot of patients who flared. And so, we're not eliminating this disease, we're getting away with less steroids, but still experiencing a fair number of people who will be active, despite our best treatments.

Dr Dua:

Dr Putman, let's take a look at the future. Tell me what you think about the future for GCA treatment, and monitoring, or biomarkers. Where are we headed in the field?

Dr Putman:

Yeah, I mean, I think some things are gonna stay the same. I think we're all going to be seeing these patients regularly, and a good clinical exam, and good diagnostic acumen will still be very important. But I'm actually pretty optimistic about opportunities for the future,

and just trying to really tailor therapies better.

A couple recent publications have been really interesting to me. One was the VEXAS study, and of course, we're all interested in finding VEXAS. But there was a patient with GCA, who had VEXAS, and so, I suspect that some of these patients have these somatic mutations, that are driving their disease. And I'm hopeful that actually trying to get pieces of the tissue could help, or we could be able to identify some of the disease in the near future. I mean, when you think about GCA, we talk about it as one disease, but it's probably dozens, if not hundreds of different little variants, that are driven by different pathways, and driven by different cell lines. And so, I think learning more about those drivers of disease will help us tailor therapy more appropriately.

And, another thing that people are doing to this direction is looking more at, specifically the RNA sequencing to see what's expressed, or proteomics to see what's coming from these cells, and trying to say, these patients have GCA, but they're more along this pathway. These are more IL-17 or IL-6 or GM-CSF, or one of these new modalities – CTLA-4 – there are patients who will be more likely to respond to this specific modality. And so, I think that in the future, we'll be doing a much better job than we are now. Where right now we say, you have GCA and this is our cookbook. But we should have many different options that are tailored more to the patient's specific cytokine or cell profile.

Dr Dua:

Yeah. No, that would be unbelievable, even in terms of figuring out what's going to work, and then also, how long do we need to keep patients on all these meds. That's like one of the biggest questions they ask us, and is there a signature, whether it be cytokine, RNA, whatever it is, that lets us know, hey, this person is actually gonna do okay after X amount of time on this drug, and you can stop it, or this is their signal you should look for that indicates they're gonna flare. All of that would be just pretty fantastic. We'll see what you can come up with.

Dr Putman:

Well, you have this conversation with patients all the time, right? They say, how long will I be on therapy? And my answer is like, aah, it's kind of up to you, because, I mean, there's some patients who really should probably be on some immunosuppression, long-term, indefinitely, but that's certainly not everybody. I mean, there are a lot of people who will go into durable drug-free remission for years, and you don't want to be giving them something toxic for the next 5, 10 years and you know, our time horizon, when it comes to clinical trials, is really short.

You know, we run trials over 1 year, and then we do a long-term extension study, which doesn't answer any questions usually. Not to be cynical, but… it's really hard, and the people are nonrandomized, and so it's just kind of a free-for-all. And then they analyze them based on the original groups. And so, you wind up not really knowing what to do after 1 or 2 years. And so, I think, for one, it's a big place for shared decision-making. You know, you need to assess the patient's values, how sick they were up front, how bad the side effects of therapy have been.

But then, two, you really just have to let them know that there's a lot of uncertainty, and that this is a decision that you make with them, and the decision that you can reassess over time, 'cause some people will need more, and some people will need a lot less.

Dr Dua:

Yeah. No, absolutely, you've brought up a lot of important points. Is there any final thoughts or takeaway messages you want to leave with our audience, before we wrap up?

Dr Putman:

Oh, absolutely, yeah. Just thinking back over the whole series that we've been discussing, I'm interested in the things that we're all doing and could probably be doing better. And, one of them is just that we need to be trying to find ways to use less glucocorticoids. I think that they're very harsh on our patients, and so, finding new treatment modalities, or personalized medicine, or whatever it takes, trying to make progress there is really important. And the next one is that you're probably not doing enough imaging, so think about imaging, and making sure you're using those to both diagnose people better, but also to screen for long-term complications.

And then, I mean, the last thing is just kind of a little vote for being collaborative. I mean, management of GCA – you need to know your radiologists, what are they good at, what's their favorite modality? You know your primary care doctors. You need to know the people who will be doing your temporal artery biopsies. 'Cause this is a disease that really requires many different specialists, to do right. And so, making sure that you have colleagues, and a system in place, to get your patients the care they deserve is really important for GCA.

Dr Dua:

Yeah. I completely agree. That's a great way to round out this discussion on this super important topic that is near and dear to definitely both of our hearts. I wanna thank you, Dr Michael Putman, for helping us better understand how we can monitor GCA disease activity in the era of biologic treatments. It was great speaking with you today, as always.

Dr Putman:

This was so much fun. Thank you again for having me, for the whole series, and hoping people enjoy it, so thanks for chatting.

Announcer (Close):

This industry podcast was sponsored by Novartis US Clinical Development and Medical Affairs. If you missed any part of this discussion or to find others in this series, visit reachmd.com/living-rheum. This is ReachMD. Be part of the knowledge.

References:

1. Ponte C, Rodrigues AF, O'Neill L, Luqmani RA. Giant cell arteritis: current treatment and management. *World J Clin Cases*. 2015;3(6):484-494. doi:10.12998/wjcc.v3.i6.484

2. Perrineau S, Ghesquière T, Charles P, et al. A French cohort of patients with giant cell arteritis: glucocorticoid treatment and its associated side effects. *Clin Exp Rheumatol*. 2021;39(2):S155-S160. doi:10.55563/clinexprheumatol/0nd4kk

3. Costello R, Patel R, Humphreys J, McBeth J, Dixon WG. Patient perceptions of glucocorticoid side effects: a cross-sectional survey of users in an online health community. *BMJ Open*. 2017;7(4):1-7. doi:10.1136/bmjopen-2016-014603

4. Stone JH, McDowell PJ, Jayne DRW, et al. The glucocorticoid toxicity index: measuring change in glucocorticoid toxicity over time. *Semin Arthritis Rheum*. 2022;55. doi:10.1016/j.semarthrit.2022.152010

5. Pujades-Rodriguez M, Morgan AW, Cubbon RM, Wu J. Dose-dependent oral glucocorticoid cardiovascular risks in people with immunemediated inflammatory diseases: a population-based cohort study. *PLoS Med*. 2020;17(12). doi:10.1371/journal.pmed.1003432

6. Hellmich B, Águeda AF, Monti S, Luqmani R. Treatment of giant cell arteritis and Takayasu arteritis—current and future. *Curr Rheumatol Rep*. 2020;22(84):1-13. doi:10.1007/s11926-020-00964-x

7. Deeming GMJ, Collingwood J, Pemberton MN. Methotrexate and oral ulceration. *Br Dent J*. 2005;198(2):83-85. doi:10.1038/sj.bdj.4811972

8. Harrington R, Al Nokhatha SA, Conway R. Biologic therapies for giant cell arteritis. *Biol Targets Ther*. 2021;15:17-29. doi:10.2147/BTT.S229662

9. Watanabe R, Hashimoto M. Perspectives of JAK Inhibitors for large vessel vasculitis. *Front Immunol*. 2022;13. doi:10.3389/fimmu.2022.881705

10. Ostrowski RA, Bussey MR, Tehrani R, Jay W. Biologic therapy for the treatment of giant cell arteritis. *Neuro-Ophthalmology*. 2014;38(3):107-112. doi:10.3109/01658107.2014.883635

194979 7/22