Transcript Details

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Incorporating Targeted Therapies in Treatment Planning for AAV

Announcer:
Welcome to CME on ReachMD. This episode is part of the Global Kidney Academy and is brought to you by Medtelligence.

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Dr. Jayne:
Have you ever wondered about the role of the complement pathway in the pathogenesis of ANCA [anti-neutrophil cytoplasmic antibody]-associated vasculitis, or AAV? Stay with us as we explore this crucial aspect and dive into the efficacy and safety of induction and maintenance therapies. We'll also look at how best to incorporate novel treatments into the care of patients with AAV.

This is CME on ReachMD, and I'm Dr. David Jayne.

Dr. Hellmich:
And I'm Dr. Bernhard Hellmich.

David, can you give us some background on the role of the alternative complement pathway in the pathogenesis of AAV?

Dr. Jayne:
ANCA-associated vasculitis, AAV, is a neutrophil-predominant vasculitis, and complement factor 5a, C5a, is the key activator of neutrophils. This makes the C5a receptor a prime therapeutic target, as it demonstrated, at least in the animal model, that this targeted therapy could completely stop the effects of vasculitis from occurring, and it's provided a mode of action for C5a receptor antagonists to move in the clinic in ANCA-associated vasculitis, and here we're particularly considering avacopan.

We have an animation that goes into more detail about the mechanism of action of C5a receptor antagonists in AAV. Let's take a look.

Announcer:
Antineutrophil cytoplasmic antibody, or ANCA-associated vasculitis, known as AAV, is an autoimmune disease characterized by inflammation of the walls of small blood vessels that can result in organ damage, including kidney failure. Alternative complement pathway is key in the pathogenesis of AAV through neutrophil activation by the C5a peptide. C5a mediates pro-inflammatory processes as a potent chemoattractant that draws immune cells, particularly neutrophils, to the site of injury. C5a binds to C5a receptors, or C5aR, on neutrophils; this primes the neutrophils for activation by ANCA. ANCA activates neutrophils by binding to surface-expressed neutrophil target antigens, resulting in an explosion-like neutrophil death that releases toxic mediators. This reaction amplifies the inflammation and damages both blood vessels and the organs they supply. Additionally, the activated neutrophils produce neutrophil extracellular traps, or NETs, which induce further C5a production. Avacopan, an oral C5a receptor antagonist, inhibits the interaction between the C5a and the C5a receptor, preventing C5a-mediated neutrophil activation and migration, which are the crucial steps in vascular endothelium destruction. In this way, avacopan works to reduce inflammation and damage to small blood vessels in patients with AAV.

Dr. Jayne:
It has clearly demonstrated that C5a inhibition is directly relevant to the pathogenesis of ANCA-associated vasculitis and the positive feedback loop whereby C5a activates neutrophils, the neutrophil activation releases neutrophil NETs and microparticles, as well as many other substances that contribute to vasculitis occurring on the endothelial surface. But of particular importance, the neutrophil NETs and microparticles themselves contain complement convertase capable of splitting C5 and indeed C3 into further complement

fragments, further C5a, thus driving more neutrophil attraction and more neutrophil activation. And so the inflammatory response is maintained.

Bernhard, can you tell us more about how induction and maintenance therapies that we commonly use to manage ANCA-associated vasculitis compare in terms of safety and efficacy?

Dr. Hellmich:
Yeah. The recent guidelines from the ACR [American College of Rheumatology] and EULAR [European League Against Rheumatism] tell us that rituximab in combination with high-dose glucocorticoids are the cornerstone for induction treatment of ANCA-associated vasculitis. In patients with new onset disease and organ- or life-threatening manifestations, you may consider cyclophosphamide as an alternative to rituximab, while in patients without organ- or life-threatening disease, you may consider methotrexate as an agent of second choice. Usually, glucocorticoids are given at high doses of 50 to 75 mg per day starting dose, sometimes even higher doses. And then, subsequently, the glucocorticoids are tapered, and we have learned from the past that glucocorticoids are the main driver of infections in patients with active AAV, and infections are the main cause of mortality within the first year of treatment. So attempts have been made to reduce glucocorticoid exposure in these patients, and current recommendations tell us to taper glucocorticoids to a target dose of 5 mg after 4 to 5 months of treatment, and studies have shown that this is working as well as a slower taper and reduces the risk of infections. As an alternative to high-dose glucocorticoids, the new EULAR recommendations recommend the use of avacopan instead of glucocorticoids for induction of remission.

Once the patient gets into remission, we usually continue rituximab for a period of 24 to 48 months, then at a lower dose of 500 mg every 6 months. And after this time period, the patient is evaluated for risk factors for further relapses, and then it's important for shared decision-making to discuss with the patient if the treatment is continued beyond this 48 months based on these risk factors. If the patient is relapsing, he gets another course of induction treatment.

David, based on these recent clinical trials we have seen, what opportunities do we have to optimize treatment for our patients to achieve better outcomes?

Dr. Jayne:
The ADVOCATE trial demonstrated that when avacopan was compared to a steroid or prednisolone tapering regimen, there was equal efficacy at 6 months, in fact, superior efficacy at 12 months, but there was much reduced steroid use. And the benefit to patients was demonstrated in terms of the reduction of steroid-associated adverse events as assessed by a standardized tool called the Glucocorticoid Toxicity Index. So we do now have an alternative therapy to glucocorticoids, and this is going to free many patients from the burden of glucocorticoid toxicity that they've achieved.

Another learning from clinical trials is that the rates of sustained remission are still not very high. They're of the order of 60% to 70%, and there is the opportunity, with better agents, to try to improve complete remission rates. And by complete remission, I mean that a patient has no features of vasculitic activity, and we're able to withdraw glucocorticoids.

Now the ADVOCATE trial demonstrated an improvement in sustained remission rates by about 12% when compared to the prednisone taper group assessed at 12 months. So this is a useful improvement in complete response rates. A surprising result from the ADVOCATE trial was a more rapid recovery and a higher recovery of quality of life in the patients who received avacopan as compared to those who received the prednisolone taper. A further result of note from the ADVOCATE trial was the effect on the kidney, where approximately 80% of the patients being recruited had evidence of kidney disease, as is typical in an AAV population, and those patients who received avacopan showed more rapid falls in proteinuria and a greater increase or recovery in kidney function as measured by glomerular filtration rate than the control group given the prednisolone taper.

So when comparing C5a receptor inhibitors, such as avacopan, to prednisone, we have a number of factors to consider; that is, the increased efficacy in terms of sustained remission, the reduction of requirement for steroids, so an improved safety benefit, the kidney improvement, and the improvement in quality of life.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. David Jayne, and here with me today is Dr. Bernhard Hellmich. We're discussing how to incorporate novel targeted therapies when managing patients with ANCA-associated vasculitis to ultimately improve the lives of our patients.

Bernhard, how do you make sure that you are selecting the right therapy for the right patient?

Dr. Hellmich:
Yeah, David, it's very important to assess your patient, not only for disease activity and damage caused by the disease or its treatment, but also for comorbidities. Long-term complications of glucocorticoids include osteoporosis, skin abnormalities, fractures resulting from

osteoporosis, hormone problems, and of course, infections. And there are also acute complications which cause problems in the early phase of treatment with glucocorticoids. These include deterioration of an existing diabetes and, of course, infections. So it really depends on how to select the ideal candidate for glucocorticoids therapy or the alternative, which is avacopan.

So for treatment with avacopan, patients who already have glucocorticoid-related toxicity or who are at risk to develop these complications, they are the ideal candidates for a first-line treatment with avacopan, of course, always in combination with another agent like rituximab. Finally, patients may also be candidates for avacopan therapy who have not adequately responded to a standard of care treatment.

Dr. Jayne:
I think that's a great summary highlighting those patients who are particularly likely to benefit from a C5a receptor inhibitor such as avacopan, namely those at high risk of steroid toxicity, those with low GFR, and those with refractory disease, and I think avacopan can be considered, as you say, for all patients as a component of induction therapy. And the patient voice is important in the eventual decision as to which treatment they should receive.

Well, this has been a fantastic conversation, but before we wrap up, Bernhard, can you share your one take-home message with our audience?

Dr. Hellmich:
We have new opportunities to spare glucocorticoids, which may help the patient to improve his quality of life and to reduce glucocorticoid-associated side effects and improve organ function like kidney function.

Dr. Jayne:
Thank you. I think my take-home message is we have a new treatment for ANCA vasculitis, and we're really quite restricted in the number of drugs that we have available to treat patients, and a new treatment provides options, and that will improve the quality of care that patients receive.

That's all the time we have today, so I want to thank our audience for listening in, and I would like to thank you, Dr. Bernhard Hellmich, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Hellmich:
Thank you, David, and goodbye.

Announcer:
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