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Call to Action: Utilizing Avacopan to Improve AAV Care

Announcer:
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Dr. McAdoo:
ANCA-associated vasculitis, or AAV, frequently damages the kidneys. This damage can rapidly progress to end-stage kidney failure within just 5 years, necessitating dialysis, and this is associated with high mortality rates. So how can we effectively manage AAV to prevent patients from needing dialysis?

This is ReachMD, and I'm Dr. Steve McAdoo.

Avacopan is a selective inhibitor of the C5a receptor, and over the past 20 years, we've come to learn that C5a plays an important role in the pathogenesis of ANCA-associated vasculitis through its effects on neutrophil priming and neutrophil recruitment.

The ADVOCATE study was a large global phase 3 randomized trial that recruited over 300 patients. And it compared treatment with avacopan for 1 year to a 6-month standard glucocorticoid taper or background therapy with either rituximab or cyclophosphamide, followed by azathioprine. The study had 2 co-primary endpoints. The first was attainment of remission at 26 weeks, and the second was sustained remission without additional glucocorticoid use at 52 weeks.

The study found that treatment with avacopan compared to a standard glucocorticoid taper was noninferior at 26 weeks and superior to steroids at 52 weeks.

There were a number of secondary endpoints that were examined in the trial, and these found that treatment with avacopan was associated with a lower risk of relapse, with greater improvements in GFR [glomerular filtration rate], with lower exposure to glucocorticoids, and with that, reduced glucocorticoid toxicity scores and improved quality of life. Overall, there were no safety signals identified in the trial.

So the ADVOCATE phase 3 study excluded patients with an eGFR [estimated GFR] less than 15 at enrollment. However, the post hoc analyses of the ADVOCATE study suggested that patients with lower GFR at entry actually had the greatest GFR recovery during follow-up, which raises the important question: Should avacopan be used in patients with an eGFR less than 15?

We now have some observational and retrospective data coming through from real-world practice that suggests that avacopan is safe and tolerated in patients with an eGFR less than 15 and, indeed, that it may be associated with better GFR recovery, including in patients on dialysis.

Since the publication of the initial ADVOCATE report, we've now had the post hoc analysis of patients treated specifically with rituximab and either the standard glucocorticoid taper or avacopan in that study. And this analysis really replicated the findings of the overall study, and that was that in patients treated with rituximab and avacopan, there were more rapid normalization of urinary findings and greater recovery in GFR during 12 months' follow-up.

The 2024 KDIGO guidelines recommend that in patients with severe organ involvement or with life-threatening disease, treatment should be with rituximab or cyclophosphamide alongside either a glucocorticoid taper or treatment with avacopan. In patients with severe nephritis, the combination of rituximab and cyclophosphamide or the addition of plasma exchange may be considered.

So I've been using avacopan first line as an alternative to glucocorticoids during remission induction. So starting avacopan 30 mg twice a day as early as possible in the treatment course and using that as a means to really rapidly reduce glucocorticoid exposure for aiming to taper steroids really within 1 to 2 weeks, provided that patients show signs of renal recovery and entering disease remission or improvement in symptoms.

So the ADVOCATE study followed patients up for 12 months, so we've got no safety or efficacy data beyond 12 months' treatment with avacopan. So it's hard to know at the moment how avacopan may fit in during the maintenance phase of treatment. And but certainly for patients who have been intolerant of other therapies, who have an allergy to rituximab, who are intolerant of other disease-modifying drugs, or have had a particularly beneficial response to avacopan, there may be a role for avacopan during longer-term treatment.

The patients that I've prioritized for avacopan treatment include those who have established or who are at high risk of glucocorticoid toxicity, those with particularly bad nephritis who may have better GFR recovery with avacopan, and those with relapsing or refractory disease or those who've been intolerant to other standard therapies, particularly because these patients are at the greatest risk of receiving repeated courses of glucocorticoids and being at risk of glucocorticoid toxicity.

The standard dose of avacopan is 30 mg twice daily, and after initiating therapy, I think it is important to monitor for laboratory abnormalities such as transaminitis, which had occurred at a frequency of around 5% in the clinical development program, and also for neutropenia.

Preventing relapses is important because relapses are unpleasant for our patients and associated with impaired quality of life, but they're also associated with the accrual of both disease- and treatment-related damage at each relapse. So in patients with kidney involvement, each relapse may be associated with further hits on their GFR and a greater risk of kidney failure long term. And each relapse may be associated with reinduction treatment and exposure again to high-dose glucocorticoid or cytotoxic therapy, which can put the patient at risk of additional treatment-related damage.

So, Avacopan may improve outcomes in relapsing patients, because in the ADVOCATE study, there was a lower rate of relapses in patients treated with avacopan. So over 12 months' follow-up, the relapse rate in patients treated with a standard regimen was 20%, but this was halved to about 10% in patients treated with avacopan. So avacopan may have a role in the maintenance of remission, and of course, in patients who relapse, treatment with avacopan may minimize their exposure to glucocorticoids at each relapse.

I think this is a really exciting development for patients with ANCA-associated vasculitis. It's the first new therapy we've had in over a decade, and it's a therapy that may allow us to avoid prescribing high-dose glucocorticoids and avoid all of that glucocorticoid toxicity that I think we can sometimes underestimate in our patients. I think steroids are associated with really impaired quality of life, with mood disorders, with sleep disturbance, with metabolic disorders in our patients, and I think we can sometimes really underestimate the impact of that glucocorticoid toxicity in our patient population. So this is an exciting time to have a new option to glucocorticoids for the treatment of vasculitis.

And that's all I have time for today. Thank you for listening.

Announcer:
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