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Redefining oHCM Care: Efficacy and Safety of Myosin Inhibitors

Announcer:
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Dr. Owens:
This is CE on ReachMD. I'm Dr. Anjali Owens, and here with me today is Dr. Michael Nassif.

Michael, our question for today is really to discuss the clinical trial evidence behind the efficacy and safety of cardiac myosin inhibitors for patients with obstructive HCM. I wonder if you can walk us through that clinical trial data with a specific emphasis on the pivotal phase 3 SEQUOIA-HCM trial, which, as you know, looked at aficamten versus placebo for patients with symptomatic, obstructive HCM.

Dr. Nassif:
Thank you so much, Dr. Owens. And yes, as you elaborated, SEQUOIA was very common among patients with significant LVOT obstructions and obstructive hypertrophic cardiomyopathy. Patients in the trial had resting obstructions near 60 mm Hg and provocable obstructions of 80 mm Hg and did have symptoms.

And when we see HCM patients in clinic, we kind of think of 3 key things and those kind of mirrored the endpoints. And so 1 is functional status. We think of this as a limiting disease, and the primary endpoint of SEQUOIA was functional status measured by VO_2 max. And for those less familiar with VO_2 max, this is a treadmill or bicycle test, and we generally consider a 1 mL/kg/min difference in VO_2 max to be clinically significant in cross-sectional studies, that's what correlates with mortality and morbidity. And in SEQUOIA, the aficamten arm as compared with placebo had a 1.7 mL/kg /min improvement, so highly clinically relevant and very highly clinically significant.

And then, likewise, we also think of echocardiogram as kind of the hallmark of especially obstructive hypertrophic cardiomyopathy. In the aficamten arm had nearly a 50 mm Hg reduction in the LVOT gradients, whereas the placebo group actually had a minor increase in LVOT gradients.

And lastly and probably most importantly, as this is a very burdensome disease, the aficamten arm, nearly 60% of the patients had at least 1 class improvement in their NYHA class and probably a little bit more precise and detailed, the Kansas City Cardiomyopathy Questionnaire is 23 questions about signs and symptoms of heart failures. And the aficamten arm had nearly a 13-point improvement in KCCQ versus the placebo. And so highly clinically meaningful and again highly clinically significant.

So we generally think of the myosin inhibitors as having the triple effect, improving the functional status of patients, improving their echo

hemodynamics and likewise their biomarkers of stress on the heart and then probably, arguably most importantly in my mind, is improving the patient's symptoms and quality of life.

Dr. Owens:
Fantastic results. What can you tell us about the safety of this class of medications, the cardiac myosin inhibitors, which, as you know, have a novel mechanism of action? How does that translate into safety in our patients?

Dr. Nassif:
Yeah, that's a great question. And so in the SEQUOIA trial in particular, the total adverse events were matched very well between the aficamten and the placebo group. The only adverse event that occurred slightly more often with aficamten was hypertension, but we actually think that's predominantly due to its mechanism of action as we're improving cardiac output and we're reducing gradients. And so we see the same thing when we fix aortic stenosis. When we do myectomies, patients, at least transiently, have increased blood pressure, which I tell my patients is a feature not a bug.

But otherwise, the concern everyone had, or I think the most highly monitored, is decrease in ejection fraction or causing symptomatic heart failure due to low ejection fraction. I think the single most important safety endpoint for SEQUOIA-HCM is no patient had to permanently discontinue drug due to an ejection fraction less than 40%.

Dr. Owens:
Wonderful. So we have a drug that is highly efficacious and really targets the things that we want to see for our patients who have LVOT obstruction. And finally, the medication was safe, so really a win all around.

As you know, data from the pivotal phase 3 EXPLORER-HCM trial looked at mavacamten versus placebo in patients who have symptomatic, obstructive HCM and were already on standard of care therapy with either a beta blocker or a calcium channel blocker. And in that study, we saw improvements in LVOT obstruction, improvement in functional status by peak VO_2, improvement in NYHA functional class, and in quality of life as measured by KCCQ. The medication was well tolerated with only temporary discontinuation for an ejection fraction less than 50% occurring in a small number of individuals. We know that this can be expected by mechanism of action.

Thank you for joining us. This is all the time we have for today and we hope to see you during our next episode. Thanks, Dr. Nassif.

Dr. Nassif:
Thank you.

Announcer:
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