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Safety in oHCM Therapy: How and When to Transition Treatment?

Announcer:
Welcome to CE on ReachMD. This activity is provided by Medtelligence and is part of our MinuteCE curriculum.

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Dr. Owens:
This is CE on ReachMD, and I'm Dr. Anjali Owens.

In patients with recently diagnosed obstructive HCM, which clinical, hemodynamic, and patient-reported factors guide our management? We'll examine these considerations through a real-world patient case.

Here's a patient I saw recently in clinic, a 63-year-old male with obstructive HCM. He had NYHA class II symptoms with occasional presyncope that occurred with heavy exertion. A resting LVOT gradient was 75 mmHg. With Valsalva, that gradient went up to over 100 mmHg, and he was taking verapamil extended release 360 mg daily. This is a patient in our current guideline framework who would be a candidate to start a new class of medication called a cardiac myosin inhibitor, which is the first targeted treatment for obstructive HCM with symptoms.

It's important to always get a baseline echo before starting a cardiac myosin inhibitor, which is what we did for this patient. You have to make sure that the ejection fraction is above 55%, which is important before starting myosin inhibition, which can reduce contractility on average by 3% or 4%. This patient's pre-starting echo showed an ejection fraction that was in the normal range.

When starting a cardiac myosin inhibitor, we do periodic follow-up echocardiograms at rest and with Valsalva, and that's to measure 2 things. One, the ejection fraction, to ensure that systolic function remains normal, and our goal is to keep the ejection fraction above 50%. The second reason is to measure the LVOT gradient. As we start these agents, we expect that gradient to come down, and our ideal target is to reach a gradient of less than 30 mmHg, which is our definition for obstruction. This is guidance that's followed through the REMS program for cardiac myosin inhibitors, and that's what we did for this patient.

You can see on the images that the gradient goes down and the ejection fraction remains in the normal range. We titrate the dose of cardiac myosin inhibitors based on the gradient and the ejection fraction. Once a patient reaches a stable state, we space out the echoes, ideally to every 6 months.

In this patient, as the gradient resolved, we were able to reduce his background therapy, which was verapamil in this case, and over time we did see that he developed a higher blood pressure. Hypertension can manifest as a result physiologically of resolving LVOT obstruction. And when that occurs, fortunately, now that there's no longer the physiology of outflow tract obstruction, you can use other

agents that you would be hesitant to use in a patient who's still obstructed, namely vasodilators and even low-dose diuretics. In his case, we started an angiotensin receptor blocker. This patient did very well with that treatment and was able to come off of verapamil entirely.

The latest data from the long-term extension FOREST-HCM trial shows that extended treatment, and in this study that was recently published out to 168 weeks of treatment with aficamten in patients with symptomatic obstructive HCM, yielded early and sustained hemodynamic and clinical responses, importantly with an excellent safety profile.

There were very low incidences of new-onset atrial fibrillation on the order of about 2% and very low incidence of LVEF less than 50%, on the order of 3% of patients. Importantly, there were no patients with heart failure that was attributed to aficamten, and no one had to stop therapy due to an LVEF less than 40%.

The other important finding from FOREST-HCM with regard to efficacy is that after the 168 weeks of treatment, over 90% of patients improved their NYHA functional class by at least one. And as a reminder, everyone who came into the study was NYHA class II or III at baseline.

A marker that we frequently check in clinical trials, but not as much in the real world, is a marker of a patient-reported outcome. In this case, the FOREST-HCM study looked at the KCCQ score. Just as a reminder, a minimally important difference in KCCQ is about 5 points, and in the FOREST-HCM study we saw an average of 15 points increase in KCCQ, which is a pretty dramatic improvement in health status, quality of life, which of course is 1 of our 2 important goals in patients with obstructive HCM, how they feel and how they function.

In summary, this provides evidence that there is a durable response to aficamten in patients with obstructive HCM for both efficacy and safety.

Additional data came out of ACC conference on patients with obstructive HCM. In the first abstract, a subset of the MAPLE-HCM study, hypertension was examined. In the main trial, we did see a change in systolic blood pressure of about 3 to 4 mmHg in the aficamten group. Importantly, many of these patients, about 50%, had a history of hypertension at baseline. Many of them were treated with a beta-blocker or a calcium channel blocker. And although blood pressure increased a small amount with aficamten, the overall control of hypertension was similar in patients with obstructive HCM treated with aficamten versus metoprolol, whereas measures of efficacy were not affected by the hypertension status and uniformly favored aficamten.

In a smaller real-world study looking at hypertension in a cohort of patients treated with cardiac myosin inhibition, we saw that LVOT gradients improved significantly over a 3-month period regardless of whether the patient had hypertension or not. And importantly, in the group of patients with hypertension, the use of vasodilators concomitant with the use of myosin inhibition was safe and effective. This supports the need for further investigation and a larger study, but we know that at least for now we can treat hypertension with various agents, including vasodilators, once their obstruction is resolved, with the use of a cardiac myosin inhibitor.

In another interesting secondary analysis, this time coming from the pivotal phase 3 SEQUOIA trial that looked at aficamten versus placebo in patients with symptomatic obstructive HCM, this study looked at a qualitative EKG analysis, particularly focusing on the assessment of ST changes and the presence of left ventricular hypertrophy strain pattern. What they found was aficamten significantly reduced the LVH strain pattern and the ST changes. The benefits of aficamten on cardiac structure and function that we've seen by echo appear to also be consistent and remarkable with regard to the EKG.

In this final abstract, also presented at ACC, a question that we frequently face in the real world was answered, and that's whether or not it's safe to stop a cardiac myosin inhibitor, such as aficamten, if a patient needs to discontinue temporarily for a noncardiac reason. And this study looked at the SEQUOIA-HCM patients from the pivotal trial who stopped treatment at the end of the study and then reinitiated treatment as part of the long-term open-label extension study, FOREST-HCM.

And in this analysis, the LVOT gradient returned to baseline, as we would expect after stopping aficamten, but rebound criteria were only met in 1 aficamten patient, manifesting as a mild worsening of heart failure. That patient also had an acute drop in hemoglobin, which may have accounted for part of the symptomatology.

Reinitiation of aficamten in the FOREST cohort for 24 weeks resulted in similar clinical improvements to what we saw in SEQUOIA-

HCM, including gradients, NT-proBNP, and markers of patient-reported outcomes.

So in conclusion, this abstract found that cessation of aficamten, if needed for a noncardiac reason as a brief interruption, can be done so safely without the increased risk of rebound.

Thank you to all of our listeners. That's all the time we have for today, but we hope you'll join us next time.

Announcer:
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