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Improving quality of life in patients with HCM

Hello, I'm Carolyn Ho. I'm the Medical Director of the Cardiovascular Genetic Center at Brigham and Women's Hospital, and I'll be speaking on improving quality of life in hypertrophic cardiomyopathy. Here are my disclosures.

With normal cardiac relaxation and contraction, there's a very highly orchestrated and coordinated interaction between the myosin head and the actin thin filament which results in normal contractility and effective relaxation. In relaxation, there's an optimal balance between a more energy-expending disordered relaxation state where one head of myosin can still engage with the actin thin filament and a super relaxed state in which both myosin heads are fully relaxed and cannot engage. When leading model of HCM pathophysiology is at the sarcomere variant result in a shift of the DRX and SRX ratio with a preponderance of myosin heads in the disordered relaxed state, this leads to a substantially higher consumption of ATP, hypercontractility, and impaired cellular relaxation. More myosin heads engaged with actin thin filament causing these issues. At the organ level, HCM pathophysiology is dominated by hypercontractile left ventricular systolic function, impaired relaxation, diastolic dysfunction, impaired myocardial energetics, and also myocardial fibrosis.

Our traditional therapies are aimed at reducing left ventricular tract outflow obstruction and improving symptoms that are referable to the obstruction. This is accomplished medically by giving beta blockers calcium channel blockers and Disopyramide to try to slow down the heart rate to allow for more diastolic filling and also to slightly decrease the contractility of the heart to try to attenuate obstructive physiology. If medical therapy is not adequate and symptoms persist, invasive septal reduction therapy can be considered or pursued, and this involves either alcohol septal ablation, or surgical septal myectomy, which serves to physically remove or reduce the thickness of the left ventricular septum and thereby physically improve outflow tract obstruction. These traditional therapies treat symptoms but do not target the underlying disease biology.

There have been small trials who look more carefully at our traditional therapies which are largely based on anecdotal treatment and not rigorously assessed. In this trial, looking at Metoprolol versus placebo in 29 individuals, there was a signal that Metoprolol might be able to improve New York Heart Association functional class, as well as Angina and the Kansas cardiomyopathy questionnaire score, but Metoprolol was not able to improve exercise capacity, pVO2 or NT-proBNP. More recently, there's been a lot of excitement with hypertrophic cardiomyopathy because, for the first time in the history of managing this disease, we have more disease-specific and mechanistically targeted agents. These are cardiac myosin inhibitors and they target the core of HCM pathophysiology. The first agent to market is Mavacamten, which is an Allosteric inhibitor of myosin ATPase. It is thought to improve the balance of myosins and the SRX to DRX confirmations, and therefore reduce the number of myosin actin cross bridges that are engaged, decreasing contractility and also potentially improving left ventricular diastolic function, relaxation, and energetics.

This slide shows the chemical structure of Mavacamten, which is the first myosin inhibitor through FDA approval in the United States, and then the current myosin inhibitor that's being tested for use is Aficamten. It's undergoing phase 3 clinical trials for symptomatic obstructive hypertrophic cardiomyopathy, and some notable differences include a slightly shorter half-life and no significant interaction with the cytochrome P450 isoenzyme system. This may allow for more facile dose titration and also ease of dosing because of lack of drug-drug interactions.

In the clinical trials, looking at the use of cardiac myosin inhibitors for symptomatic obstructive hypertrophic cardiomyopathy, the outcomes have really focused on feel and function. Luckily for patients with hypertrophic cardiomyopathy, hard clinical outcomes such

all-cause mortality, heart failure, hospitalizations, and the like, are relatively infrequent, and therefore rather than powering the trials who will get those outcomes that we were really focusing on helping patients feel better and have better functional capacity.

In EXPLORER trial with Mavacamten, the primary end-point was to look for either a 1.5 milliliter per kilogram per minute increase in peak VO2 and at least, a one-class improvement in NYHA functional class, or a more robust increase in peak VO2 of 3 milliliters per kilogram per minute, and no worsening of NYHA class. You can see that Mavacamten met its primary endpoint with a significant improvement and improving these metrics compared to placebo. Also, a significant benefit in a more aggressive endpoint of both a 3 milliliter per kilogram per minute increase in peak VO2 and a one class improvement in NYHA class.

We can focus again on how patients feel in improving their quality of life. You can see that Mavacamten was associated with a significant improvement in NYHA functional class. Also, in the phase 2 REDWOOD-HCM trial, looking at Aficamten in roughly 41 patients with symptomatic non-obstructive HCM, you can also see that there's a signal towards improved NYHA functional class during the 10 week treatment period, which then regresses as treatment is washed out at week 12.

Looking more carefully at the Kansas City Cardiomyopathy Questionnaire overall symptom scale, you can see that with EXPLORER-HCM, there was also a significant improvement in KCCQ's score. You can see here, this slide puts into context how Mavacamten compares to other medication trials in heart failure versus the procedural trials where we would expect a more robust improvement in quality of life. Mavacamten has a much more substantial improvement in quality of life than we typically see with medications and almost approaches that, which we can see in procedural trials such as with transcatheter aortic valve replacement or mitral valve intervention. Similarly, the Kansas City Cardiomyopathy Questionnaire was assessed in the phase two REDWOOD-HCM trial, and you can see that there was also a good signal towards improvement in this metric with a mean improvement of 10.6 points, and the majority of patients, 58% showing some clinical improvement.

Most recently, the Valor HCM trial with Mavacamten was completed. This was taking patients who were eligible for septal reduction therapy, so they were more symptomatic. They were considering invasive septal reduction therapy, either alcohol septal ablation or myectomy, and then randomized to receive either Mavacamten or placebo. At the end of the day, Mavacamten provided adequate clinical improvement for the majority of patients to choose to defer invasive septal reduction therapy. Because these medications are cardiac myosin inhibitors, they will reduce contractility, and so ejection fraction has been closely watched in the trials to confirm and assess safety.

With these, with the myosin inhibitors, we typically see a relatively modest change in left ventricular ejection fraction, so about four to five-point reduction. If you start off with ejection fraction of 74% it goes to 70% with active therapy. With that relatively modest change in the LVEF, we can see a large decrease in left ventricular outflow tract gradient with gradients following almost 40 millimeters of mercury. This is far more robust than we typically see with standard medical therapy and almost approaching what we can expect from invasive septal reduction therapy. Some patients across the board for both myosin inhibitors, between 5% and 10% had a more dramatic but reversible decrease in left ventricular ejection fraction where it fell below the protocol's defined set point of less than 50%. Because of this, when Mavacamten was approved by the Food and Drug Administration in the United States, a REMS, or a risk evaluation mitigation strategy program was required to closely monitor left ventricular ejection fraction as we are getting more experience in the clinical compressial realm with these agents. Patients are required to have echocardiographic monitoring, initiation of therapy at 4 weeks, 8 weeks, and 12 weeks after therapy is started, and then every 12 weeks thereafter.

Where do myosin inhibitors currently fit into clinical practice? Well, I think that their main role is in looking at symptomatic obstructive HCM and offering a really powerful option for effective medical therapy for our patients. We can think about using it in three different ways, as an exploratory metric to test the impact of improving obstruction. This might be very helpful in our patient that has multiple comorbidities, be it deconditioning, obesity, intrinsic lung disease, as well as outflow tract obstruction thus gradient reduction help to improve symptom burden in our patients. If we can take outflow tract obstruction out of the picture, how much better can patients feel? We can think about it as destination-type therapy where it would be long-term therapy with medications to address symptomatic obstructive HCM and then it could also potentially be used as a bridge for decision in the patients who are seeking symptomatic improvement and not sure if they're ready for an invasive procedure, so they can see how much better they feel with effective outflow tract reduction. Some may choose to have more definitive therapy with invasive septal reduction therapy to potentially reduce the number of medications that they need to take, and some patients may opt to continue on long-term medical therapy.

In the future, we want to be confident about the long-term safety and efficacy of these agents and long-term extension trials are in place both from Mavacamten and Aficamten. Hopefully, we will get enough data to support use as first-line therapy. There's great interest in using it in a non-obstructive HCM and also pediatric HCM user trial, so thus far have been conducted only in adults. Also, there's great excitement in the potential for using these medications for disease modification starting earlier in the subclinical early stages of disease to see a phenotypic progression can be attenuated. Then thinking about diastolic abnormalities in use in symptomatic non-obstructive

HCM, this is a key area because we currently have no effective therapies for treating our symptoms with symptoms related to non-obstructive HCM. Presumably, the symptoms are related to impaired relaxation, ultra myocardial energetics, but there are no effective medical or procedural options.

Cardiac myosin inhibitors are being tested in phase 3 clinical trials. The ODYSSEY trial using Mavacamten is ongoing, and the ACACIA trial, which we'll use Aficamten will be starting in 2024. This is just an overview of the Aficamten clinical trial program, ACACIA to be added. The other interesting trial along this spectrum is the MAPLE-HCM trial, which is a head-to-head comparison of Aficamten versus Metoprolol currently and rolling and that will potentially give us evidence to support the use of first-line clinical therapy with cardiac myosin inhibitors. Thank you very much for your attention.