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Evidence-based novel therapies in HCM

Dr. Michels:

The topic of my talk today is evidence-based novel therapies in hypertrophic cardiomyopathy. These are my disclosures.

If we're talking about novel therapies in hypertrophic cardiomyopathy, we're actually talking about novel therapies in hypertrophic cardiomyopathy with obstruction. This is a flowchart as presented in the 2023 ESC guidelines for the management of cardiomyopathies. This slide tells you how to manage a patient with hypertrophic obstructive cardiomyopathy, which is defined by a resting or provokable left ventricular outflow tract obstruction equal or exceeding 50 mmHg.

If a patient is symptomatic, the first line of treatment is beta blockade. If a patient is intolerant or there's a contraindication for beta blockade, you can also use calcium channel blockers. If a patient remains symptomatic on monotherapy, you cannot add another drug, so combine beta blockades and calcium channel blockers, but if a patient still remains symptomatic, you have the choice between or a new drug, which is called mavacamten and will be the main topic of my talk today. If a patient remains symptomatic despite all medical therapy, then there's still an indication for septal reduction therapy.

So mavacamten is a myosin inhibitor, that has been developed based on the fact that we know that in hypertrophied hearts, there are is an exceeding number of between actin and myosin, which can be adjusted and controlled by mavacamten.

So if you know patients with hypertrophic cardiomyopathy in your practice, you know they often present with hypercontractile left ventricular output tract obstruction, leading to symptoms. From basic science, especially based in patients with myosin heavy chain mutations, we know there's a gain of function and that more myosin. And this has been the basis to develop a targeted molecular approach to treat hypertrophic cardiomyopathy, and myosin inhibitors have been developed.

Preclinical data shows that this myosin inhibitor, mavacamten, reduced contractility, increased compliance, increased energetics, and decreased left ventricular outflow tract gradient, and also fibrosis. This preclinical data led to the development of phase 3 clinical trials called the EXPLORER and VALOR-HCM trials in hypertrophic obstructive cardiomyopathy, and the ODYSSEY hypertrophic cardiomyopathy trial, which is still ongoing, and that is based on patients with nonobstructive hypertrophic cardiomyopathy.

So in this slide, you see an overview of the conducted clinical studies done with mavacamten in hypertrophic cardiomyopathy with obstruction. The first trial performed in the U.S. was the PIONEER- HCM study. This was a phase 2 open-label, non-randomized trial in 21 patients, NYHA class II. And the primary endpoint was a reduction of left ventricular output tract gradient. This trial was positive, and there there were also no safety issues.

And this, therefore, the EXPLORER-HCM trial was developed, a phase 3 double-blind, randomized trial, including 251 patients, both in Europe and in the U.S., patients NYHA class II or III, hypertrophic obstructive cardiomyopathy. And there was an exercise capacity, symptom burden as primary endpoints. This trial was really positive, both on left ventricular output tract gradient, exercise capacity, reduction of NYHA class, reductions of biomarkers.

In the U.S., the VALOR-HCM trial was performed. This was also a double-blinded, randomized trial, including 112 patients. These patients were more symptomatic because they had to be eligible for septal reduction therapy. So NYHA class III patients, and a primary endpoint was eligibility for septal reduction therapy. And mavacamten again showed a very positive response. So less patients eligible for septal reduction therapy, and again, reduction in left ventricular outflow tract gradient and NYHA class and biomarkers.

So these trials were really positive. Was it too good to be true? Were there any safety issues? I think we were all a little bit worried about

the effect on ejection fraction, because we know that the ejection fraction reduces with the introduction of mavacamten and myosin inhibitors. But in the EXPLORER trial, there was actually no difference between serious adverse events in the mavacamten group or in the placebo group. And more important, there was no severe heart failure.

There are, however, points of attention. So, mavacamten is metabolized through the, cytochrome P450. And in Europe, you have to genotype your CYP2C19. And this is because there can be drug-drug interactions, especially with CYP2C19 and CYP3A4 inhibitors. The drug is contraindicated in pregnancy, and there's close echocardiographic monitoring needed. There's a relatively long half-life, especially important metabolizers, which you have to take into account.

Last summer, the summary of product characteristics has been published and what you can see here is that the scheme to start mavacamten is quite complex. So you can start mavacamten in a patient with hypertrophic obstructive cardiomyopathy with a left ventricular outflow tract gradient exceeding 50 mmHg and a left ventricular ejection fraction exceeding 55%. In poor metabolizers, you have to start with 2.5 mg. In normal or fast metabolizers, you start with 5 mg. And then you see your patient back at 4 weeks and 8 weeks. At both time points, you again perform an echo, check left ventricular ejection fraction, left ventricular outflow tract gradient, and you can either reduce the dose or maintain on the same dose. At week 12, so again after 4 weeks, you see your patient back again, perform an echo. And at that time, you can also, if the patient is still with severe obstructive, you can also increase the dose, which is really what is really important, if that there is if there's a reduction of ejection fraction below 50%, you should immediately stop the drug and see your patient back in 4 weeks. And also, every time you do an increase in dose, you have to see your patient back in 4 weeks, including echo.

Mavacamten is available in the U.S. for quite some time now. I saw the real – the first real-world data have been presented. This is a slide showing the data for Milind Desai in his first 150 patients treated with mavacamten. And what he did see is that there was actually the same results as we saw in the EXPLORER trials. So a nice reduction in left ventricular outflow tract gradient, both in rest and with exercise, increase or decrease in NYHA class. and he had to adjust the treatment for drug-drug interactions in 60% of his patients. And these are cases where you, for example, switch from a proton pump inhibitor that is metabolized through cytochrome P450 to a proton pump inhibitor that isn't. He temporarily had to interrupt mava due to an ejection fraction below 50% in three patients.

These are data from Philadelphia presented on the ACC and quite recently, published, also showing the first real-world data with the same patient profile and a good efficacy and safety also in this HCM center of expertise.

So this is an example of one of our own patients that we put on mavacamten recently. So this is a female patient, 68-year-old. You can see in the upper panel the apical three-chamber view with hypertrophic obstructive cardiomyopathy. You can see the systolic anterior motion. And in the panel below, you can see the peak for gradient, which is far exceeding 50 mmHg. We introduced mavacamten 5 mg. She was a normal metabolizer, and this is her echo after 4 weeks, in which you can see that there is no systolic anterior motion anymore, and the left ventricular outflow tract gradient is gone. And this patient actually improved from NYHA class II to NYHA class I in just 4 weeks.

Is mavacamten the only new kid on the block? No. Actually, during this meeting, the results of the SEQUOIA-HCM study will be presented, and this is a second-in-class myosin inhibitor also in hypertrophic obstructive cardiomyopathy patients. We do know from a press release is that the study is positive.

And with that, I'd like to conclude my talk. I think the future looks bright for patients with hypertrophic cardiomyopathy with now novel treatments entering our clinical area. Thank you very much for your attention.