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Modern Obstructive HCM Care: From Unmet Needs to Individualized Myosin Inhibitor Therapy

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. Here with me today is a colleague and friend, Dr. Ahmad Masri.

We're going to talk about how clinicians should approach management in patients with newly diagnosed and also established obstructive HCM. What are the clinical hemodynamic and patient reported factors that are the most relevant?

And we'll start by examining these questions through a real-world patient case. Ahmed, I understand you have a case to share with us today.

Dr. Masri:
It's really a typical scenario. A patient of mine, which is, again, a very typical scenario of someone who's coming in with obstructive hypertrophic cardiomyopathy. They have a gradient above 50 mmHg at peak with Valsalva, they have symptoms, and they're asking what to do beyond the beta-blocker they're on. They were started on metoprolol previously; it didn't help them with symptoms. They continue to have symptoms, and they're asking what the options are.

So as usual, we go through the options of which medications can be used next or if there's an intervention that is warranted, such as surgery or catheter ablation. And in this scenario, what we ended up talking about is the class or the family of cardiac myosin inhibitors that can be added on top of whatever standard of care they're on. So this patient was on metoprolol, and we discussed that we'd like to minimize the metoprolol dose, but then we can move to mavacamten or aficamten as a cardiac myosin inhibitor.

And our strategy had been to discuss with patients what are the individual differences between the 2 medications and what are the implications of these monitoring programs that they have to be enrolled in.

When we look at safety in clinical trials, it's meant to be really not that high of a number where the patients end up having an adverse event. And so that ended up translating into what the FDA recommended for their risk mitigation program, or what we call REMS.

And so far we spoke about mavacamten, how the patient would have to be started on 5 mg, and then they would go from the day 1 to week 4 to week 8 to week 12, so 3 months where they can only be on 5 mg or lower, 2.5 mg, and if they hit certain criteria, they actually have to temporarily pause the medication.

And then the patient asked me actually, “What will happen if I need more of the drug?” So we then spoke about the cycles of 12 weeks, where at 12 weeks you would go from 5 to 10 mg if necessary and it's safe to do so, but then you have to wait to week 24 to see if by then 10 mg are sufficient or if the patient will require 15 mg, which then will result in an additional 12 weeks of monitoring the patient on that dose.

Also I was asked what happens if the body doesn't like the drug and there is reduction in systolic function. And we went through the process of what happens with the REMS program, that if your ejection fraction goes below 50, then you will have to temporarily hold and stop mavacamten, and then you will have to repeat an echo 4 to 6 weeks. Usually, even the guidance says 4 weeks. We like 6 weeks typically to give more time for the EF to return to normal and then will reinitiate at the lower dose.

And so then the conversation went in the direction of aficamten, which is how does the REMS program for aficamten look like. We really followed the same blueprint where we spoke about the fact that there is a lot more flexibility driven by the design of these trials, the performance of the drugs, and its pharmacokinetics, where you can go on the 5 mg lowest dose for 2 weeks, and then you have a choice anywhere between 2 and 8 weeks to get another echo. In this particular scenario, the patient was very interested in having her symptoms get under control quickly.

So we spoke about that when we initiate on the 5 mg, we can really, in 2 weeks, reassess, if need be, go to 10, and then in 2 more weeks go to 15, and 2 more weeks go to 20. So the idea is that one can maximize the dose required within 1 to 2 months. However, some patients might not want to do that. Some patients might want to slow and take things slowly, and that's also allowable.

And then we talked about the same thing regarding maintenance, which would require 2 echoes a year, and there is much less problems in relationship to drug-drug interactions.

And then finally, we spoke about the temporary discontinuation versus down-titration. With mavacamten, you have no room for down-titration for an ejection fraction less than 50%, while with aficamten, it is allowable for EFs in the 40s, which is the majority of the patients, that you can down-titrate without going through cycles of stop and start.

Dr. Owens:
And you really need time, I would say, with our patients to discuss what the options are. And as you said, we individualize to the patient in front of us and what their goals are, what their timelines look like, what they prefer, and it's great to have flexibility.

And I think that translates not just for the patient side of it but also for the clinicians and the healthcare system. Right? We know that these drugs are followed by serial echocardiograms for safety, both of them. And so depending on how your echo lab is set up, what sort of collaborative associations you have with your local partners and their imaging programs, that it's good to be able to have options, whether you want to come back in 2 weeks or 8 weeks, whether you want to be on a more fixed schedule. All of those things are important to have in terms of options for our patients, and I think it's reflected nicely in the 2 programs.

And a summary statement of sort of what you told us about the 2 drugs is, yes, they're in the same class, but they're not the same drug, right? They're in the same class of medications, meaning that overall mechanism of action. And as you said, our goal is to bring down the gradient, to resolve that LVOT obstruction, and that the mechanism of action for both of the drugs has that as an aim, but they're not the same medication. And so the pharmacology of the 2 medications is worth noting, and it's worth learning about the 2 as 2 separate medicines, as we do with other drugs that are in the same class but of course don't have the same pharmacology.

I do want to dig a little bit more into that temporary discontinuation versus down-titration piece, because that is a part that we've noticed that patients, mostly when they come in, as you highlighted, if they have a transient excursion to below 50%, it tends to be just under 50%, right, in that kind of 45% to 49% range. And many times, your patient is feeling quite well, asymptomatic, no obstruction left, and they're feeling great. And so when you're talking to them about potentially stopping a medication when they're feeling very well, it can be a little bit disconcerting or confusing to them. And so to be able to say you've got a little too much of the drug, we either need to stop it or, now with aficamten, in that situation, you can say we're just going to come down on the dose. And the reason for that, of course, is that the half-life is shorter, and so you're able to metabolize it, get it out of the system a little more quickly, and just down-titrating can take care of that. You come back in a few weeks, and as short as 1 week, and your ejection fraction may already be back above 50%. And I think that's worth highlighting for the clinicians who are treating these patients in the real world.

Well, we have about a minute left. Are there any tips or tricks that you would give to our practicing clinicians? Maybe those that aren't caring for very many patients with HCM but they're just starting to get started and think about maybe they'll put their first couple of patients on a CMI

Dr. Masri:
Yeah, great question. I think the principles are make sure that you're very clear of the diagnosis. Obstructive HCM means that you have a gradient in the left ventricular outflow tract. It doesn't extend to all other forms of HCM. So just be mindful that you have the right diagnosis at hand and you've uncovered the obstruction or proved that it exists or not. Some patients, you might not see it on the resting echo, so you might need to end up having provoked echo or even sometimes exercise them in order to see their hemodynamics.

The second piece of it is that you really have to become familiar. Even if you have 5 to 10 patients, I think you really have to become familiar with the 2 medications that are available to us, mavacamten and aficamten. And if you want to really serve your patients well and have a well-informed discussion, I think you should do that, and you should dive deep into the characteristics of each. You should familiarize yourself with the REMS program so that you can have that productive discussion with the patients.

Dr. Owens:
Fantastic advice, as always. Thanks again for joining us today, everyone. This is all the time we have left, and we hope to see you on another episode.

Announcer:
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