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From Beta-Blockers to Myosin Inhibitors: Initial Decision-Making in Obstructive HCM

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Dr. Owens:

This is CE on ReachMD, and I'm Dr. Anjali Owens. Here with me today is Dr. Ahmad Masri.

Ahmad, when you evaluate a patient with obstructive HCM who remains symptomatic despite first-line guideline-directed therapy, what are the key clinical hemodynamic and patient-reported factors that guide your next management decision? And how do these considerations shape treatment selection in the real world? We're going to explore these issues today by looking at a patient case.

But first, let's hear from an actual patient with symptomatic obstructive HCM. Ahmad, is this patient consistent with what you see in clinical practice?

Dr. Masri:
Thank you, Anjali, for the question. I mean, this is very, very common. I mean, if you're running an HCM-focused practice, a lot of the patients come with symptoms, they've already been considered and/or usually started on a beta-blocker. Depending on where you live, usually, at least in the United States, metoprolol is a very commonly used beta-blocker for this scenario.

In our practice, we try to teach people that you don't actually have to go to the maximum dose if you're not seeing relief or benefit from lower doses, because that's where you start to get more side effects, usually from these medications.

Usually patients remain on a maintenance dose for quite some time, and physicians typically give it actually a lot of time to try this out before making a decision on change, or different approach. So by the time a patient like that comes and sees us, we do few things and think through a few things. One is, we investigate if they felt any better on the beta-blockers, if they have any side effects from the beta-blockers, which is actually pretty common, from fatigue to depression to weight gain, to erectile dysfunction in men, through some other issues that could happen. So that's one.

The second thing is, we evaluate the dose. Do we need to keep it, lower it, or do we even need to get rid of it? If it's inducing symptomatic bradycardia, for example, which also sometimes happens, and the patients will not volunteer it until you dig into it.

And then finally, we speak about, okay, what are the next steps? Our goal in hypertrophic cardiomyopathy is to treat symptoms and

have that essentially lead to improvement in quality of life. And in conjunction with, in my opinion, that we should see improved hemodynamics in obstructive HCM. That's where cardiac myosin inhibitors come into play. That's where the MAPLE-HCM trial also comes into play, where we have our second-line therapy, a cardiac myosin inhibitor like aficamten or mavacamten, and you have the option of proceeding to potentially septal reduction therapy like myectomy or alcohol septal ablation. Most of the patients would like to try medications and see how things go first with that, unless there's a very strong rationale or indication to go in different direction.

And as such, I would use the MAPLE-HCM trial in this scenario and apply it to the patient. If the patient is having an adverse reaction to metoprolol, or if they don't feel well on it, or if they didn't gain sufficient improvement from it, then it could be a choice, really, after a detailed discussion, is that we can add on a cardiac myosin inhibitor like aficamten or mavacamten, depending on the scenario and the discussion and how it goes. Or you could potentially consider applying the phase 3 MAPLE-HCM trial, which tested aficamten as a frontline monotherapy against beta-blockers, showing that it is more effective in relieving LVOT gradient, it is more effective in improving symptoms and quality of life, and it improves biomarkers and measures of stress and wall stress in the heart, while metoprolol did not do any of that and worsened exercise capacity, worsened measures of stress and biomarkers.

So there's really a very strong rationale to approaching it that way. However, in your local area, if you are not allowed still to do that, you could always layer it on top of a lower-dose beta-blocker.

Obviously, once you do that, there are some practical limitations that you have to talk to your patients about. Beta-blockers, you can just prescribe it. They can pick it up from their pharmacy. A myosin inhibitor like aficamten requires a specialty pharmacy intervention.

And this translated into our ability to use aficamten as part of its REMS program. Initiation at 5 mg. There is a lot of flexibility built into this risk mitigation program. The dose range is 5 mg to 20 mg. You can go by increments of 5, so from 5 to 10 to 15 to 20, if you need that, to target lower LVOT gradients to become nonobstructive, as well as improving symptoms for these patients.

You have anywhere between 2 and 8 weeks to do that. Meaning, if someone comes to you, they're highly symptomatic, you can do these dose increments every 2 weeks, if you'd like, so that by really 6 to 8 weeks, you're already maximized on the dose, and they have the maximum relief needed, which these are real-world scenarios that we dealt with. Some patients really need quick relief, and they can't wait for many months to get to that point.

On the other hand, there are patients with mild to moderate symptoms who it's more important for them to actually not do follow-up echocardiograms over a short period of time. And in that scenario, for every dose escalation, you have up to 2 months, up to 8 weeks, to do that. And so that also provides an important flexibility, and logical approach to how we would titrate these medications and how we would help patients with.

Finally, once they are on the optimized dose, they actually just need 2 echoes a year after that. And so these echoes can also just be confirmation of EF, that it's stable.

We also educate the patients that you could have lower ejection fraction when you are on a drug like aficamten; however, consistent with its pharmacokinetics and pharmacology, the FDA also allows us now to just down-titrate the medication for an EF between 40% and 50% which is the most common scenario, instead of having to stop and go through a cycle of start and re-evaluate.

So I think all of these are advantages for our patients, and I think this would be exactly my approach in this scenario.

Dr. Owens:
Great. Thank you for walking us through that in detail. I think I totally agree with you. When you see a patient in clinic who remains symptomatic, it's just no longer enough to just let them go on. And we see so much of that clinical inertia, where patients come in just saying "I feel fine," but by objective testing, by echo hemodynamics, they're still obstructed and they're still limited functionally, and that you don't have to let your patients go on like that anymore, because we have better therapies and, exactly your point, where you don't have to up-titrate beta-blockers anymore to 200 mg a day and sort of blunt their adrenergic response and their heart rate response.

And that it's easy to start and to follow once you get accustomed to the REMS program. And so in the beginning, it may seem a bit daunting, but really what you want to do is have a structure, have help in your clinic with physician assistants, nurse practitioners, nurses.

One additional feature of the aficamten REMS is that you no longer need to do a monthly drug–drug interaction checklist by the specialty pharmacy, which is a requirement for the mavacamten REMS. So there's a difference there, because there are fewer drug–drug interactions with aficamten and other medications. The only absolute contraindication is concomitant use with rifampin, which, fortunately in our cardiac population, is relatively rarely used. There are other medications that may require dose adjustment, and so it is important to do that medication check, but it's done in the context of a regular office visit, much the same as other medications that are used and not solely the requirement of the specialty pharmacy.

Communication with your patients is always key, and for them to let you know how they're feeling. And I would say, an approach that we've had for a long time, since the approval of the first cardiac myosin inhibitor, would be to leave the patient on standard of care therapy, start the myosin inhibitor, and then come back on discontinue the background standard of care.

And you have published on this from trial data as well, Ahmad, that is also a very effective approach.

So now with MAPLE, we have a new option, which is to say, do we even start a beta-blocker? Do we go first-line to aficamten? And I think we'll see how that plays out in the real world. Some insurance companies, and as you said, other constraints do require a trial of AV nodal blockers, which is reasonable, but by no means do you have to up-titrate to 200 mg of metoprolol in this day and age, I would argue.

Dr. Masri:
Agree.

Dr. Owens:
So I think that's all the time that we have left today. Thank you so much, and hopefully our audience now has additional data when they see that next patient in the clinic with HCM.

Announcer:
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