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Molecular Precision: How Myosin Inhibitors Redefine Control

Announcer:

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Dr. Owens:

This is CE on ReachMD. I'm Dr. Anjali Owens, and here with me today is Dr. Ahmad Masri. We're going to take a deep dive into treatment of obstructive hypertrophic cardiomyopathy with cardiac myosin inhibitors.

Ahmad, thank you for joining. And can you start by telling us some of the similarities and differences between the 2 available cardiac myosin inhibitors, aficamten and mavacamten?

Dr. Masri:

Thank you, Dr. Owens, it's a pleasure being here with you today.

So as many of our listeners are aware, we have 2 cardiac myosin inhibitors, mavacamten and aficamten. And while they are lumped in the same class, they actually are somewhat distinct in terms of their binding sites, energy metabolism, downstream action, and how they were tested and investigated in clinical trials, as well as really distinct pharmacology.

So diving a little bit into this, both of these medications, the goal is to reduce the excessive hypercontractility through inhibition of myosin ATPase so that you have less myosin interacting with actin. But there are individual differences there. One of them is that it has to do with the half-life. For example, aficamten has a much shorter half-life, typically quoted as about 3.4 days or 80 hours or so, while mavacamten has a much longer half-life; it can be 9 days plus based on the metabolism status. It has a quick off action, kind of an approach for aficamten, where you have the terminal half-life is actually over 1 to 2 days. It's out of the system in terms of the steady state, slowly getting out, while with the mavacamten can be much more prolonged.

In terms of the peak-to-trough variability, that's something that may be a new concept to some of you, but when you're dosing someone with a drug that is affecting their hemodynamics, you want it to be soft and smooth over time, not having a lot of fluctuation. And aficamten, as it happens to be based on recent publication from the SEQUOIA-HCM trial, shows you that the peak to trough variability is pretty minimal, and that is very advantageous usually.

In addition, this relationship between the dose of the drug, its level in the body, as well as its effect on ejection fraction, it's a lot smoother and linear with aficamten as compared with mavacamten, and that translated to a lower number of cases of reduction in ejection fraction enabled the program through which you can down-titrate aficamten without having to stop it for small excursions of

LVEF <50% and also resulted in typically very uncommon scenarios related to heart failure.

And then finally, drug–drug interactions. I think this is a big one for many of us who take care of these patients, is that, as it happens to be, aficamten has much less drug–drug interactions. It is metabolized through a different CYP2C9 pathway, compared with mavacamten.

And so there are much less things to consider when it comes to using this drug, which makes me actually want to ask you, Dr. Owens, is with all of these properties, how has this translated back into the FDA’s opinion, onto the regulator’s opinion with the REMS program, and its real-world use of these drugs?

Dr. Owens:

Yeah, it’s a great question.

We follow these patients serially by echocardiogram, and that’s true for both of the cardiac myosin inhibitors. But in the case of aficamten, the FDA approved the drug with a 2- to 8-week window for when you need to bring the patient back to do that safety echo. And so you can titrate more quickly every 2 weeks, if you wish, for patients who are initiating aficamten and wish to come in at that increased cadence, to go up on their dose. But you also have the flexibility to start a patient and not bring them back in 2 weeks. You can bring them back in 8 weeks, so 2 months later for their next echo and titration.

And I think that built-in flexibility allows us to individualize therapy and care, which is ultimately, in the real world, something that is important.

The other major point is that we don’t have mandated medication drug–drug interaction checks to be done by a specialty pharmacy. This is now back in the clinician’s realm, and when you do your usual office visit, you run through the meds, you look for drug–drug interactions. That is the guidance given by the FDA for aficamten, as opposed to what we have from mavacamten, which a specialty pharmacy needs to do medication checks at each dispense.

So with that, hopefully we’ve given you some food for thought in terms of translating clinical trial results into real-world care, and we hope you’ll join us for the next episode.

Announcer:

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