

Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:

<https://reachmd.com/programs/cme/myosin-inhibitors-recent-clinical-data-and-applications-in-hcm-and-hf/26492/>

Released: 07/18/2024

Valid until: 07/18/2025

Time needed to complete: 49m

ReachMD

www.reachmd.com

info@reachmd.com

(866) 423-7849

Myosin inhibitors: recent clinical data and applications in HCM and HF

Dr. Coats:

I'm going to take you through the myosin inhibitor class, talk about the recent clinical data and applications in hypertrophic cardiomyopathy and heart failure. These are my disclosures.

So since we learned of the first gene responsible for hypertrophic cardiomyopathy in the 1990s, HCM has been considered a disease of the sarcomere. By combining our insights from genetics as well as structural analysis of myosin, we start to understand that it's the number of myosin molecules available for interaction with actin that is a primary driver of this disease.

We sought to learn that hypertrophic cardiomyopathy at sarcomere level, is a disease of hypercontractility, and based on this hypothesis, a small molecule to inhibit myosin activity was developed as a proof of principle to treat hypertrophic cardiomyopathy. Less than a decade later, that molecule appears in clinical practice guidelines.

So let's look at some of the evidence behind this recommendation. The pivotal Phase 3 study was EXPLORER-HCM. Not only was it the largest randomized controlled trial in hypertrophic cardiomyopathy, enrolling 251 patients across 13 countries, but it also met its primary endpoint. This was a combination of improvement in peak oxygen consumption and New York Heart Association class. Over a 30-week treatment period, you can see that mavacamten lowered left ventricular outflow tract gradients both at rest and Valsalva, with a small decline in left ventricular ejection fraction. The population in this study, 40% of people had hypertension, 75% were on a beta-blocker, and combination treatment with disopyramide was not allowed.

VALOR-HCM followed. The question here was could mavacamten reduce the need for septal reduction treatments, myectomy, or alcohol ablation? This was a highly selective group. The follow-up was much shorter with 16 weeks of treatment. Over 100 patients were enrolled, having been listed or considered for septal reduction treatments. They were randomized 1:1 to placebo and standard of care. 46% were on a beta-blocker, 15% on a calcium channel blocker, 32% on combination treatment, and here, 20% were on disopyramide. The primary endpoint was the decision to proceed with surgical intervention, and that endpoint was reached by 18% in the mavacamten group, compared with 77% in the placebo group.

So this led to both regulatory approval and inclusion in both the European and recent American hypertrophic cardiomyopathy guidelines. However, these trials also showed that exposure to cardiac myosin inhibitors gave a potential for excessive reduction of ejection fraction and symptomatic heart failure. So there was still a question and challenge about implementing them in practice.

This led to development of the next-in-class molecule, aficamten, which was specifically engineered with pharmacological properties to allow for flexible dosing and increased safety. You can see the phase 2 and phase 3 studies listed at the bottom of the slide.

SEQUOIA-HCM is the phase 3 trial looking at aficamten versus placebo in a similar population to EXPLORER-HCM. The study was designed to have a representative and balanced population. It therefore capped enrollment of patient-specific characteristics. It capped beta-blocker enrollment at 70%, disopyramide at 10%, background atrial fibrillation at 15%, and it required a balanced use of both exercise and treadmill exercise testing. It was different in that it had a sole primary endpoint of peak oxygen consumption. SEQUOIA-HCM met its primary endpoint with a significant improvement in peak oxygen consumption of 1.74 mL/kg/min.

So myosin inhibitors will be the first class of medication that we are using to treat hypertrophic cardiomyopathy that has both robust clinical trial evidence, but also targets the fundamental mechanism of hypertrophic cardiomyopathy pathogenesis. In the last 12 months, we've seen a lot of long-term data, both on safety and efficacy, from both mavacamten and aficamten, and there's more to come later this year. The gradient reduction is sustained, the ejection fraction fall is reduced, and symptom improvement persists.

An important observation and exploratory endpoint from these studies is that reductions in outflow tract gradients and improvement in exercise capacity occur concurrently with reductions in levels of plasma biomarkers, both natriuretic peptides, the marker of myocardial stress, and troponin, a marker of myocardial injury. Both important prognostic markers in this disease. The baseline biomarker levels in both aficamten and mavacamten studies are largely similar.

Another important observation is remodeling. Since no medical therapy has been shown to impact remodeling in obstructive hypertrophic cardiomyopathy, this is an important milestone. There was a CMR sub-study in EXPLORER-HCM enrolling 35 patients. In that, it showed a favorable impact both on left ventricular mass, a reduction in left atrial volume, and changes in wall thickness. To date, there's been no improvement in late gadolinium enhancement, the marker of fibrosis. The aficamten data comes from 16 patients participating in the open-label FOREST-HCM study. A similar remodeling appearance was observed.

You'll know that beta-blockers have been considered a first-line treatment in obstructive hypertrophic cardiomyopathy for decades despite a lack of clinical trial evidence. So alongside these cardiac myosin inhibitor studies, an important contribution to the literature has been this study, a small randomized trial in 29 patients, showing that beta-blockers lowered outflow tract gradients, although did not improve exercise capacity, albeit over 14 days of treatment.

This led to the hypothesis and design of MAPLE-HCM, which is a head-to-head comparison of aficamten and metoprolol. This will tell us whether myosin inhibitors may be first-line treatment in obstructive HCM. The trial is currently enrolling, and we expect to read out early 2025.

So where are we now? We have a good amount of evidence, but there are still areas of unmet need. I've spoken about comparison with beta-blockers. We are yet to have phase 3 readouts from nonobstructive hypertrophic cardiomyopathy, a subset of this disease, which really has very limited treatments for improving symptoms. ODYSSEY-HCM is the first study that has now completed enrollment, and ACACIA-HCM is a similar study with aficamten. We've also heard recently about the announcement of trials specifically addressing mavacamten and aficamten in children and young people.

We are starting to see that large registries addressing some of the real-world implications of implementing these medicines and some studies looking specifically at remodeling. The first study in a subset of HFpEF patients is also due to start enrolling. ODYSSEY-HCM will be the first large randomized controlled trial in nonobstructive hypertrophic cardiomyopathy. From the MAVERICK study, we saw an improvement in symptoms and biomarkers with treatment. This trial has completed enrollment, and we expect topline results in the next 12 months.

So we're really now in an era of clinical trials in hypertrophic cardiomyopathy. Alongside some of the key milestones in this disease, we've really seen a rapid rise in the number of trials to provide an evidence base for treating our patients.

So what about implementation? Mavacamten is approved. It requires echocardiography for dose titration. So in the US, a REMS scheme is in place, whilst in Europe, genotyping is required to identify slow metabolizers that need a lower dose. Poor metabolizers of mavacamten can have a threefold exposure and risk of systolic dysfunction. A new drug application for aficamten is planned for autumn this year.

In the last 12 months, we're now gathering real-world experience of using mavacamten and we hope that this will grow not just from specialist centers, but from many district hospitals, and a much broader population of patients receiving these medicines.

So my take-home messages for you: Cardiac myosin inhibitors are a new drug class for obstructive hypertrophic cardiomyopathy with positive phase 3 trials now in mavacamten and aficamten. There are large phase 3 trials of both drugs in nonobstructive hypertrophic cardiomyopathy. You will expect to hear more data on both long-term efficacy, safety, and remodeling in both of these drugs.

There is an unmet need not only to treat young people, but also in people with early disease, perhaps without symptoms, that allowed them to be included in these studies. And finally, randomized controlled evidence is an essential part of research to progress the field of hypertrophic cardiomyopathy.