Novel Agents Targeting the Source of HCM Disease

CMEO Podcast Transcript

Martin S. Maron, MD:

Hello, I'm Dr. Martin Maron. On behalf of CME Outfitters thank you for joining us for another episode of the CMEO Snack series, titled, *A Global Response to Hypertrophic Cardiomyopathy: Sharing Experience, Sharing Resources*. This activity is supported by an educational grant from Bristol Myers Squibb. This is the third of three CMEO Snacks, and we will today explore novel agents targeting the source of HCM disease. Again, I'm Martin Maron, I'm the director for the Hypertrophic Cardiomyopathy Center at Tufts Medical Center in Boston, Massachusetts, and I'm really thrilled to be joined today by a world expert and friend Dr. Harry Rakowski, who has led for many, many years, the world renowned HCM Center and Referral Clinic in Toronto with Toronto General Hospital. I'm going to let Harry also introduce himself, but he's going to provide an incredible perspective today on this topic. Harry, you want to just say a few words of introduction as well.

Harry Rakowski, MD:

Martin, thanks very much for having me participate in this. So, as you mentioned, I run the Hypertrophic Cardiomyopathy Center at the University Health North Work in Toronto. This is a center that Doug Wigle, one of the giants of this condition, founded. So, I was pleased to be his successor and to hold a chair in his name. You and I have been involved in HCM research for decades, and this very interesting and challenging condition remains an enigma in many ways with lots of opportunities to improve how we deal with our patients.

Martin Maron:

Sure. I think we're going to be talking about another one of those potential options today, before we get to that, though, here's a learning objective for today's activity. After participating in this activity, learners should be better able to assess study results of emerging HCM disease-specific treatments targeting cardiac myosin. Okay. So, with that said, let's get into it a little bit. We're charged today, Harry, with discussing a hot topic, which is the emergence of new therapy for hypertrophic cardiomyopathy. For those that haven't been following this as closely as you or I have, maybe we could start first with defining what we're talking about. That's the emergence of a novel drug class called myosin inhibitors and the first generation of those that's been under investigation now for several years and that may, in fact, reach regulatory approval soon, although isn't yet, is called mavacamten. The second-generation myosin inhibitor, which is not quite as far along in development is called aficamten. Why don't we start with getting your... For the audience going to be taking them through a little bit about, what is this drug? What does it do? And what is it really being advanced for in HCM?

Harry Rakowski:

So, Martin, I think that's very important. We have a condition where up to two thirds of patients have a dynamic outflow tract obstruction, and our belief is that this is due to rapid ejection, with overactive myocardium ejecting blood through a narrowed outflow tract drawing the mitral valve up and obstructing left ventricular tract. This causes gradients, and in most patients, symptoms. The conventional therapy that we have has been negative on atropic agents, such as beta blockers, which never really were tested, but we know in clinical practice are somewhat effective and then disopyramide, an off-label anti-rhythmic drug that's used for risk negative inotropic properties, and then some calcium channel blockers, such as verapamil. We typically use these drugs in patients who have dynamic outflow tract obstruction, but many patients don't respond adequately to treatment, still have class three symptoms, and need Septal Reduction strategies such as myectomy or alcohol ablation. So, the hope is that there might be a medical therapy that might prevent you from having to have a surgical myectomy or even an alcohol ablation that has some risk, some need for hospitalization. So, I think this is where the excitement is, that if we believe there's an overactive heart muscle and we use negative Inotropic drugs, is there something that is more targeted to the actual heart muscle proteins and working at that molecular level to decrease their contractility and thus reduce outflow tract obstruction without the need for surgical or interventional approaches?

Martin Maron:

Okay, good. So, the myosin inhibitors really are being advanced, at least initially, as an additional medical therapy option sounds like for symptomatic obstructive HCM by leveraging their unique mechanism of action at decreasing the number of myosin interactions at the sarcomere level, at the tissue level, which results in, I think, a decrease in the force of contractility, as you were saying. So, they decrease myocardial contractility, is that correct?

Harry Rakowski:

That's my understanding of it.

Martin Maron:

Yeah.

Harry Rakowski:

This is a class of drugs that has a lot of opportunity. We just have to figure out exactly where its place is in what we can offer patients with HCM and its cost effectiveness.

Martin Maron:

Mm-hmm. So, the initial benefit we're going to talk about in a minute in terms of the clinical trial that work has been done, is based on the fact that the drug, the myosin inhibitor drugs can lower the outflow tract gradient by decreasing the force of contractility and anything, as you were just pointing out, anything that lowers gradient will make patients feel better in this condition. Just to be clear for the audience, are there other potential mechanisms of action of the drug that are being either proposed or looked at that may also be potentially advantageous here? Or is it directly a hemodynamic negative inotropic effect?

Harry Rakowski:

You know, Martin, there are other possible effects where there's the potential to reduce the amount of hypertrophy. Those studies are not nearly as well advanced, the studies that have primarily been done have been safety studies and efficacy studies to look at reducing dynamic outflow tract gradients, and that's how the drug would initially be marketed. I think there's a lot more work that has to go on to see if it truly can modify disease progression. If you treat somebody early in their disease, say when you identify they have a genetic abnormality, but before they fully express the hypertrophy and scarring, can it modify that? There are some potential mechanisms, but I don't think they're very far along.

Martin Maron:

Right. Okay. So, you would say that at this point in time, which is still pretty early in terms of the overall initiative and experience, that this term disease modifying drug is probably... We're not really yet ready to... we don't have the data or evidence to really support that. Is that true?

Harry Rakowski:

Yeah, that would be my understanding. I think it's exciting. Anything that can modify disease is useful, but we also know there have been probably 10 other drugs that have been looked at, that had the potential to modify disease based on renin-angiotensin system, based on angiotensin-converting-enzyme (ACE) inhibition, ARM inhibition, that didn't work. So, we have to go from concept to proof. We don't have the proof.

Martin Maron:

Right. Think it'll probably take a while for us to really try to answer that question for sure. So then coming back to what we have learned, in a way, from the experience so far with mavacamten, is that most of that's coming out of phase two and phase three clinical trials. The phase three trial that was published about a year and a half ago or so was called Explorer HCM and I believe that drug mavacamten was looked at in a randomized way in symptomatic obstructive HCM patients. Most of the patients enrolled in that study almost all were on traditional background therapy of beta blocker and calcium channel blocker, not norpace. That study did not have patients on norpace.

Harry Rakowski:

Right.

Martin Maron:

They were randomized to mavacamten at different dosing and placebo over several weeks at least, 30 weeks I believe, of treatment and then had a clinical endpoint in terms of determining efficacy of a combination of subjective improvement by New York Heart Association (NYHA) or objective improvement in functional capacity by measuring it by peak VO2 by cardiopulmonary exercise testing. Tell us a little bit about your high-level thoughts about that trial, the results, how you would describe those results and what they mean to us today in terms of what we can expect potentially out of this drug, if it is in fact approved from the regulatory standpoint sometime soon.

Harry Rakowski:

Sure. So, I think the results were exciting. Any new drug that can be used to modify gradients through a novel mechanism is going to be very important, and there are lots of patients who are either unsuitable for surgery or unsuitable for other septal reduction strategies, or who may prefer not to have them where they would be very excited to have this opportunity. In that study they randomized roughly 130 people to each treatment arm. The benefit was there, the safety was generally there, there were a number of patients who had a significant deterioration in heart muscle function and ballooning of the apex. We have to make sure that in any drug that reduces heart muscle function, that it doesn't have some Idiosyncratic effect on heart muscle function, or that in people who have lots of scar and have the potential to have that heart muscle function get worse quickly, that it's not going to have that negative effect.

So, if we can sort out who is at risk of reduction in heart muscle function, that is going to be symptomatic and problematic, that if we can look at people who are going to benefit from that, and we haven't fully defined that, but there will be a sizable population for whom this drug could be beneficial. So again, you have to look at what the alternatives are and what the cost effectiveness is before this goes from a niche drug for a small number of people to a more widespread applicability to our outflow tract obstructive patients.

Martin Maron:

So, did everybody get better?

Harry Rakowski:

No.

Martin Maron:

Okay.

Harry Rakowski:

I think, if I remember the data correctly, there were about a third of people who didn't get significantly better, and again, it depends on how you define it. There's exercise time, there's objective symptoms, there is comparison to the placebo group, but generally the drug was reasonably effective. The challenge I have and, you may or may not want to discuss it now, is the cost of a new drug that is an orphan drug and whether that is going to limit its applicability.

Martin Maron:

Sure. No cost is huge here. I definitely want to get to that in a minute, but before we get there, I think it's important for everybody to realize that in the construct of the phase three study that we've been talking about, mavacamten was compared to placebo, and so it wasn't compared to other current therapies that we know improved symptoms as well, medical or invasive, like norpace or surgery or alcohol ablation. So, there was no comparison to those treatments.

Harry Rakowski:

There wasn't. If you were on a beta blocker, for example, and they thought that you were going to have a stable dose during the trial, they allowed you to stay on beta blockers but not on norpace. The rationale there was that norpace is a stronger negative Inotropic drug and they didn't want to have heart failure outcomes because of the combination of the two not knowing whether it was mavacamten, or whether it was norpace related.

Martin Maron:

Okay. So, you don't really... Obviously it's to no one's fault, of course, there's the design of the trial. We weren't able to really take away from that. Any clear sense of how the efficacy of the new drug class compares to, for example, the gold standard myectomy for symptomatic obstructive HCM or the alternative alcohol ablation at this point.

Harry Rakowski:

Yeah. Correct. I think if you look at the data and if you compare it to what the myectomy results are in centers of excellence, I think it's very unlikely that this drug is going to work as well as myectomy does. When you do a myectomy, you have a near immediate resolution of the gradient. There are a lot of people even still traumatized by having open heart surgery who, when they leave hospital, feel better than they did before surgery. So, the bar to get to that degree of clinical symptomatic improvement in gradient reduction, is going to be very hard for a drug. In the study so far, as good as they are, they don't appear to be as good as myectomy. Now, obviously that comparator trial with randomization to medical therapy and surgical therapy hasn't been done and may be done, but I don't think it's going to be as good as surgery.

Martin Maron:

Okay, good. Those are important insights to give everybody. Then maybe we could just talk a second about the other thing you had mentioned, this is a negative Inotrope obviously, so it can decrease systolic function. That's how it works to lower gradient. You were mentioning that it was generally well tolerated and reasonably safe in the phase three study, but there were some patients on mavacamten that experienced an overshoot or excessive decrease in systolic function, including, I think you mentioned some that may have had a Takotsubo like event on mavacamten.

Harry Rakowski:

Correct.

Martin Maron:

Hard to know, obviously since the numbers are small, of course, or anything, but overall, the issue of systolic dysfunction, why is that important here?

Harry Rakowski:

Well, it's important because you want to make people better, but the risk is overshooting the mark. So, you have to titrate how much systolic reduction and function you're going to create, that's enough to get rid of the gradient, but not so much the overshoot. You cause either diffuse dysfunction or whether this Takotsubo, a stress cardiomyopathy like pattern, was just a bad accident, it's too bad that it happened but it wasn't due to the drug, or it might truly be a drug effect that you'll only know when you study the drug in many hundreds of patients.

Martin Maron:

Right. Yeah. I think that's right. You're thinking about it like a see-saw. You want to try to lower the systolic function enough to get the gradient mitigated so patients feel better, but not overshoot of course, because overshooting may have other potential implications acutely. If you drop the ejection fraction, obviously too much in a patient, we all have concern about that. In that sense then, do you have any understanding or thoughts on how you think that this will be handled in terms of, if it is approved from a regulatory standpoint, how we're going to have to monitor this issue in patients?

Harry Rakowski:

Well, Martin, I think all drugs have to go through post-marketing surveillance and there has to be a reporting structure where adverse events are recorded and reported. So, this is going to be important in the follow-up studies once the drug is hopefully approved and people are on it, it'll have to be that reporting to see what that concern is. Now, when I see a patient who has dynamic outflow tract obstruction, and it goes away on its own, I don't cheer and say, "Wow, this patient got better." It's the opposite. You worry that the patient is starting to develop systolic dysfunction often because of progressive scar burden and their gradient went away because their heart muscle got weaker. This group of patients wasn't studied with based on MRIs to look how much scar burden there was.

It may be that if somebody already has a moderate or 10% or greater amount of scar burden in their myocardium, that they may not be the right patients to get this. So, I think that in some of the subsequent studies, it would be useful to have had a baseline MRI to see what the scar burden is so if complications or systolic dysfunction or heart failure even occur, that you know whether it occurred in that group of patients who already have significant scar burden and perhaps those patients shouldn't be treated with this drug.

Martin Maron:

Right. Do you think also, that because of this issue that we saw from the Explorer trial, where there were some patients that had an over exaggeration of systolic dysfunction in terms of ejection fractions (EFs) going low that, and I think that was within the confines of serial echoes and I think even blood work to monitor that. Will this require, in other words, I'm asking whether this drug will ultimately require, initially at least, surveillance to ensure that patients don't have a significant decrease in EF by having patients come back over a certain period of time for serial or longitudinal echocardiographic studies, it's not going to be, just give the patient the drug and see you in six months kind of thing.

Harry Rakowski:

So, Martin, I think that's a very important point. Not only should they have echo studies looking at left ventricular ejection fraction, which still is a somewhat crude and not early marker dysfunction, but just like in oncology therapy where we follow those patients with strain, and changes in strain pre-date changes in ejection fractions. So, I think when they're followed, they're going to need to have a regular serial strategy for whether it's three in six months and 12 months, probably three, six, and 12 months, to make sure, A, their ejection fraction didn't drop too much, also to see what happened to their strain. You would think that the reduction in strain, it's going to happen within the first three months, if that were to continue, then again, you're going to be concerned that these are the patients who might develop a complication, and hopefully it's only going to be a very small number and the drug will still be safe and effective, but you may have to parse who is at risk of this complication by that pre-treatment MRI and by very careful clinical and Echocardiographic following.

Martin Maron:

Right. It's interesting. 'Cause you know, I was just thinking, I don't think we have... it's an interesting time in a lot of ways, as we're talking about it with these new drugs for HCM, but this particular issue that we're talking about for mavacamten, obviously we don't know, for example, what the regulatory agents are going to require in terms of monitoring, but we have a suspicion or good idea based on the design of the Explorer trial and what you've just said, that it will require echocardiographic studies done longitudinally to make sure that patients don't have low EFs, but also to adjust dose in that sense too. That would really represent, as far as I know, the first cardiovascular drug that I'm aware of in which drug dosing over time is dictated in a way by the results of a cardiac imaging test, an echocardiogram. I don't think I know of another example really, in cardiovascular therapeutics where we have to do that. It's interesting. You agree?

Harry Rakowski:

I totally agree.

Martin Maron:

Yeah. It's interesting. So, we'll see. It's going to be an interesting in that sense. Let's talk a second about, shifting for a minute, in terms of your view and there's probably nobody in the whole world that has the perspective that you have in terms of trying to look into the future a little bit, before we get the cost, obviously that's a big issue, I want to hear your thoughts on that in a minute, but in terms of what we know about mavacamten right now, and your large, enormous experience over many decades in managing patients with HCM at a major referral center for the disease, that's included the ability to do both alcohol ablation and surgery at the highest of levels and excellent, incredible outcomes. How do you see, for you and more globally, where this drug will fit into the treatment algorithm? How do you see that going?

Harry Rakowski:

Martin, that's an important issue. I think the low hanging fruit initially are patients who are either too high risk for surgery or who really don't want to have surgery and where affordability isn't an issue. We also know that for alcohol ablation, there's probably 10% of patients who don't have a suitable septal perforator, another 10% when it comes time to try and do the procedure the contrast study shows that the profusion bed is in the wrong place. You're either going to do too much or too little. So, there are a pool of patients already who, if they progress to class three symptoms of full medical therapy and aren't suitable for the usual septal reduction strategies.

I think that's the group that you can initially focus on and, to a larger extent, justify the high cost of this drug. Once you get into, people who are low risk, who can have surgical myectomy, at well below a 1% mortality and an extremely high likelihood of an excellent result, that's where that competition of, is a drug for the rest of your life in a 40 year old, at an expensive annual cost, worth it, comparing to, do the surgery once, get it over with and highly likely get better for the rest of your life? So, I think that's where the tension is going to be in figuring out where the proper positioning of this drug's going to be.

Martin Maron:

Yep. We're going to see probably soon. Well, we're getting toward the end here of our time. Maybe we'll conclude with the question that gets asked a lot in this conversation, we've been talking about these drugs for the treatment of symptomatic obstructive HCM. Are they also going to be drugs or what do we know about their efficacy in the one third of HCM patients that have non-obstructive disease? What do we know? Do you think that's going to be something that's going to be fruitful therapy in those patients for the future here with these drugs or not?

Harry Rakowski:

I think that it needs to be studied very carefully. I think it's going to be harder to prove. I think you're going to have, to have studies with serial MRI studies to show either there's reduction in left ventrical (LV) mass, a reduction in scar burden. We know scar burden progresses, but it progresses relatively slowly.

Martin Maron:

Right.

Harry Rakowski:

And so does LV mass, right? There are groups of patients where they do progress, others that stay stable. So, I don't think it's going to be that easy to prove and certainly to prove that it's worth, a 50 or $75,000 a year cost, for that benefit. We know lots of other drug trials to reduce scar burden and hypertrophy that worked in mice because they're a relatively solitary population of inbred mice, genetically the same, humans aren't like that. So, I have to say, I would be hopeful, but I'm not optimistic that this drug is going to show that benefit.

Martin Maron:

Yeah. It's a much more challenging group. You're right. I mean, if you look at the phase two study that was done in the non-obstructive patients, I think it was for mavacamten, it was a phase two, small numbers of patients but profound impact on biomarkers, improving other surrogate points like tissue doppler on echo, but the clinical endpoints of symptomatic improvement and functional capacity were neutral, like they have been in other therapies that have been applied to other forms of heart failure with preserved. Yeah. So, it'll be interesting to see, I think, but you're right. It's a very challenging group. So, we just don't know the answer yet, essentially.

Harry Rakowski:

Correct.

Martin Maron:

Great. Well, I think we're up against our end of our time here, really it was an honor and pleasure Harry, to get your thoughts on the emergence of new therapy for hypertrophic cardiomyopathy. I have no doubt that the

audience learned a tremendous amount from your wisdom and insights and I want to just thank you very much for your time. Appreciate it.

Harry Rakowski:

Martin, always a pleasure to interact with you. Thanks again for having me on the program.

Martin Maron:

Now, by way of summer, I'd like to offer a few what we call SMART Goals for our audience and I think I'll summarize that by saying, it's an exciting time for hypertrophic cardiomyopathy. There's no doubt. I think one of the major messages that you've heard over the last 25, 30 minutes talking with Dr. Rakowski is that, the first time that we've ever had new therapy directed specifically for hypertrophic cardiomyopathy, obviously the myosin inhibitor drugs that we've been talking about, mavacamten and aficamten are not yet regulatory approved, but we hope that, we were on the lookout to see that will happen. If it does, it'll be an exciting time. They're being investigated, as you heard, as another additional drug option for symptomatic obstructive HCM and we still have a lot to learn as well as you heard.

I think we have to better understand who the right patients are for the drug in terms of efficacy. We also need to better understand what efficacy looks like, not just short, but also long term, given the young age that these patients will be receiving the drug potentially, and also of course, shorter and longer term issues related to safety. As you heard, systolic Dysfunction, and how best to handle that in terms of drug dosing and Longitudinal follow-up in patients that may be candidates for the drug if it becomes available. So, lot to learn, super exciting time for HCM and I think all of us are going to be on the lookout for more information to help answer these questions and better treat our patients in the future with established therapies, which have done incredible job at both improving how patients feel as well as improving longevity and, of course, the ability of newer drugs potentially to aid there as well. Thank you very much. Appreciate your attention. As I mentioned, this is the third of three new CMEO Snacks on HCM. Please visit the Cardiology Education Hub @CMEOutfitters.com to participate in part one and two and don't forget to complete the evaluation to claim credit for today's activity. Thank you again for your attention and we hope you will find the information useful in caring for your HCM patients. Thank you again.

