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ATTR-CM Management: Pearls From Recent Clinical Trials and Tailoring Therapy

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Dr. Fontana:
The treatment landscape of amyloid transthyretin cardiomyopathy, or ATTR-CM, is rapidly evolving. Recent clinical trials have unveiled promising new options, offering hope of improved patient outcomes. Today, we will explore the design of recent trials, examine the role of outpatient diuretics used in ATTR-CM management, and unpack what clinically meaningful benefit means in this context.

This is CME on ReachMD, and I am Dr. Marianna Fontana.

Dr. Witteles:
I'm Dr. Ron Witteles.

Dr. Fontana:
So, Ron, let's begin with the clinical trials in ATTR cardiomyopathy. So what are the main considerations driving the design of current trials? And how might these advances in trial design impact our future approach to managing patients with ATTR cardiomyopathy?

Dr. Witteles:
Well, thanks. That's a really great question, and it's an evolving one. And so as you know, well, when the trials first began in this field, A, there were no treatment options available, and B, it was a disease that tended to have a pretty predictably bad, often devastating, outcome for a couple of reasons. One was that there were no therapies, and two was that patients tended to be diagnosed quite late in the course of the disease. And so for clinical trials, there were lots of events that one could count on happening, including mortality and cardiovascular hospitalizations.

And so when you look at the first major cardiomyopathy trial in this space, it was the ATTR-ACT trial of tafamidis versus placebo. And it was designed looking at very hard endpoints, at tiered endpoints, looking at mortality and cardiovascular hospitalizations. And because of the high rates of events in the disease and the effectiveness of the agent that was tested, tafamidis, there was a very positive result.

Now the disease then changed over the subsequent years for, really, 3 reasons. One, there was now an approved treatment, tafamidis; two, there was much more awareness of the disease because of, well, things like this, educational efforts like this, but also all that goes on at meetings and in the scientific literature, and even direct-to-consumer advertising, a lot more awareness; and finally, the ease of making the diagnosis really changed, because it went from an era when, to make the diagnosis, everybody had to have a biopsy, typically a cardiac biopsy, so where the vast majority of patients are, of course, now diagnosed noninvasively, using bone scintigraphy and laboratory testing. And so you get to the point that patients are being diagnosed much earlier in the disease, and we have successful interventions, at least one with tafamidis.

And so when it comes to designing clinical trials, it's important to take that into context of recognizing event rates are going to be lower and how can we rationally define trials to be able to detect real benefits where they're there, but with practical trial designs.

Dr. Fontana:
Ron, I couldn't agree more. And it's interesting how, as clinicians and academics, we always want to try to make comparison and take trial A and compare with trial B and compare to trial C. But when we look at actually the main trial that we've seen the results for, for example, the ATTR-ACT trial, the ATTRibute-CM trial, and the APOLLO-B trial, we really need to think about putting this trial into the context of when the trial was done. So in a way, the size of the treatment effect cannot really be compared across trials because the patients' phenotype have been so dramatically evolving that we need really to take the results into the context of the patients that actually were recruited. And also, the time at which the patients were recruited, because also, we learned a lot on how to manage these patients. If, I think, 15 years ago we didn't really know anything about how to manage heart failure in these patients, and now we are understanding about MRAs [mineralocorticoid receptor antagonist] treatment or eplerenone, spironolactone, or even SGLT2 [Sodium-glucose cotransporter 2], we are treating our patients better even from a heart failure point of view.

Dr. Witteles:
I was just going to say that all one needs to do is look at what happens in the placebo arm in each of the trials. And you can look at something like 6-minute walk distance and look at what happened over the first 12 months in ATTR-ACT versus APOLLO-B versus ATTRibute-CM. And you're talking about, you know, in ATTR-ACT, the average person on placebo, this has taken treatment effect out of it, dropping by close to 60 m in the first year, versus about 20 m in APOLLO-B and versus fewer than 10 m in ATTRibute-CM, and realize we're just looking at different patient populations.

Dr. Fontana:
Let's take a closer look at diuretics, which are the mainstay of heart failure management. So their use in ATTR-CM can be nuanced. So what can you tell us about outpatient diuretic intensifications, or ODI, as an endpoint? What have we learned from recent clinical trials?

Dr. Witteles:
Yeah, thank you. It's a great question. I think that it is an important marker to look at. So I'll say first off that in the field of ATTR cardiomyopathy, there are multiple staging systems for the disease. The most common, of course, was developed in the UK and using a combination of cardiac biomarkers and kidney function. There's another one out of Mayo Clinic that looked purely at cardiac biomarkers. And then there's an interesting one that was developed by a couple centers here in the United States that was simply looking at diuretic doses at the time of diagnosis as staging. And it performed actually, really, in many ways, just as well as the other two. What that gets at, of course, is that, as you were just highlighting, the need for diuretics in the disease is actually pretty reflective of how advanced the disease is; it's not a perfect correlation, but it does track pretty well.

Now, if you look at other contemporary clinical trials, there has been good data in the HFpEF [heart failure with preserved ejection fraction] population, looking at trials like DELIVER and TOPCAT. That outpatient diuretic intensification has tracked really quite well with some of the harder endpoints in those trials.

Dr. Fontana:
For those just tuning in, you're listening to CME on ReachMD. I am Dr. Marianna Fontana, and here with me is Dr. Ronald Witteles. We are discussing recent approaches to clinical trial design and how to define clinically meaningful benefit in ATTR cardiomyopathy trials.

Dr. Witteles:
I don't think we're at an era where a drug is going to get approved for an indication solely on the basis of outpatient diuretic intensification. But you can say with pretty good confidence that these will track quite well with harder endpoints that we think of as the typical main endpoints in clinical trials, obviously survival, cardiovascular hospitalizations, et cetera.

Dr. Fontana:
Yes, I completely agree, but especially because I called it outpatient diuretic intensification even on my question, but actually, in many ways, what we are referring to is heart failure worsening in the outpatient settings. Because an outpatient diuretic intensification is something that happens because a physician has assessed the patients and, based on the sign and the symptoms, thought that there was a worsening of the heart failure and so the diuretic dose was increased.

So we are very familiar with considering hospitalization and death as hard endpoints, but what happens in the outpatient settings is also important. And almost the outpatient diuretic intensification just represents the kind of what happens just one stage before the hospitalization. So more and more, we are really interested in looking into these endpoints across all the different clinical trials.

And so, Ron, now that we have explored the new approaches to clinical trials, how do we look beyond just numbers and define what a

clinically meaningful benefit is? I know this is a very challenging question, but I would be grateful if you could say what you think about this clinically meaningful concept of for our patients?

Dr. Witteles:
Yeah, absolutely. Thanks for that, because I think this is, though a challenging question, it's such an important one overall, in the clinical trial landscape and definitely for heart failure patients, and in particular ATTR cardiomyopathy patients. Because yes, survival matters, of course, and yes, hospitalizations matter. But as you know well, when you talk to patients with this disease, they're going to point to things like their quality of life as they see it, what we'll often think of now as patient-reported outcomes. They will think about, you know, am I able to walk down to my mailbox and back, and so on and so forth. What is the threshold is this big question of when do we consider something a clinically meaningful benefit?

What I would say on that is that in this disease, in my opinion, what we've seen from really every clinical trial to date is that, thankfully, all of these markers track with one another. And I might use it as an analogy. Something that's quite different would be the treatment of a patient with cancer, where often you might be trading off should we give this therapy, which is going to be toxic, that a patient won't tolerate well but it'll make them live longer, and, well, how much longer to have them live between how much toxicity? Fortunately, we don't have that in this disease, that in every trial, the same interventions that help with survival, help with hospitalizations, help with quality of life as measured by something like the KCCQ [Kansas City Cardiomyopathy Questionnaire] metric, help with 6-minute walk distance, help with biomarkers, help with imaging parameters. They all line up, because the benefits that you're getting on quality of life all happen because you are meaningfully changing the course of their heart failure.

So from my standpoint, utilizing all of these different aspects, very much including a patient's own reported symptoms, their take on how is this affecting my quality of life, is key. And we've seen now, and the APOLLO-B data showed this, I would say, quite clearly, where there was somewhat of a deeper dive into how well these things correlated with, let's say, KCCQ score and harder endpoints. And they clearly do correlate well. So I think these are exceedingly valid endpoints to look at, and it's frankly what matters to patients.

Dr. Fontana:
Absolutely. So instead of just picking up one parameter and assessing and deciding a cutoff and saying, oh, if you don't reach this cutoff, then actually the drug is not useful, it's really about taking a look at the overall results of the trial and seeing this consistency, which you described beautifully, about everything has to go in the right direction. So it's not just the blood biomarkers, but it's the functional capacity and, most importantly really, the patient-reported outcomes. In a sense, everything has to be consistent, consistently going in the right direction. And this is, for us, it's what really proves that the drug is really beneficial in the patient population more than just picking up one of these single parameters and trying to stick to a cutoff, which often is not even very easy to define.

Dr. Witteles:
If you look at something like KCCQ – take APOLLO-B. So where the group who was on the active treatment, patisiran, had a complete flat result in their KCCQ, meaning that their quality of life, on average, did not change at all over the 12 months. That is not what we expect to see with the natural history of this disease.

Now, then if you look at the placebo arm, they dropped by, on average, about 4 points on the scale. Now, one could argue, well, gee, how big is that 4-point difference? Remember, of course, that that's an average. And you can then break down the data with whatever threshold you want to choose for that change in KCCQ. And when you do that with the APOLLO-B data, and I think you'll probably find that in every amyloid study, every positive amyloid study that is, you're going to find that whatever threshold you choose, that that active treatment arm looks considerably better than the placebo arm.

Dr. Fontana:
Ron, I've really enjoyed our conversation today. But before wrapping up, do you have one key take-home message for our audience?

Dr. Witteles:
Yes, I think this is such an exciting time in the treatment options for this disease. In the United States, we currently have one approved treatment option, but I think many more that are likely on the way. And from when we consider a disease that was thought to be this rare, niche disease that there was nothing we can do just a few short years ago, to where I think we're coming in the next few years, which is a, dare I say, almost common disease, at least in older populations, with many different effective treatment options, it's extraordinarily exciting.

Dr. Fontana:
And that's all the time we have. So I want to thank our audience for listening in. And thank you, Ron, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Witteles:
Thank you.

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