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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

ATTRibute-CM Findings on Acoramidis and Cumulative CV Events

Announcer:
You're listening to *On the Frontlines of ATTR-CM* on ReachMD. And now, here's your host, Ryan Quigley.

Ryan Quigley:
This is *On the Frontlines of ATTR-CM* on ReachMD. I'm Ryan Quigley, and today I am joined by Dr. Ahmad Masri, an Associate Professor of Medicine in the Division of Cardiovascular Medicine at Oregon Health and Science University. We'll be diving into an exploratory analysis of ATTRibute-CM, which focused on the impact of acoramidis on cumulative cardiovascular outcomes.

Dr. Masri, thanks so much for being here today.

Dr. Masri:
Happy to be here, Ryan.

Ryan Quigley:
So, Dr. Masri, to start us off, what was the main clinical question you set out to answer with this exploratory analysis?

Dr. Masri:
The way to look at any clinical trial is that you can decide ahead of time whether you want to look at the first event that happens on a drug versus placebo. Do you want to look at multiple events? Do you want to look at a composite or singular outcome?

And in general, over time, our understanding of transthyretin cardiomyopathy has evolved to the point where we're now thinking that it's not just a singular outcome that matters. There are multiple of these outcomes, but also, more importantly, what are the cumulative events—the cardiovascular events—that we are able to reduce or prevent when you are treating someone with a transthyretin-targeted therapy as it compares to placebo or to another active therapy?

Ryan Quigley:
Now, as I understand it, in this study, you observed a separation in event curves as early as one month. How do you interpret that rapid onset of benefit?

Dr. Masri:
I think one of the things to keep in mind is that our priors tell us that if you are using transthyretin-targeted therapy that works through the TTR pathway, either by stabilizing it or silencing it, you shouldn't expect to see differences in the outcomes of these patients early on. So, that is essentially how this evolved, and this started by the ATTR-ACT trial, which led to the approval of tafamidis for this indication.

However, what was observed in this trial was that patients were having an observed effect of reduction in cardiovascular events—heart failure, hospitalizations, and urgent heart failure visits—earlier than usual, which means that earlier than that six to 12 months we usually used to think about. And so here, what we saw is that if you focus on cumulative events, you see that even though the drivers early on are a very small number of events, you start to see that trickling in and you can statistically model that as well.

But the more important piece is that if you focus on three months or six months, which, again, are periods of time that we usually did not really focus on before in the past, you'll see significant changes and reduction in the number of these events, and that essentially is summarized by the fact that we should be looking for diagnosing these patients quickly and instituting treatment quickly because it is not necessarily true that it'll take a long time to prevent such an event from happening.

Ryan Quigley:

Thank you for that. And one of the most striking findings was that 53 events were avoided per 100 patients over 30 months. Can you walk us through the clinical relevance of that number?

Dr. Masri:
So, I think this is the benefit of having targeted therapies for diseases as well as of the duration of follow-up as we know that these patients are being diagnosed slightly earlier. As such, the mortality rates are coming down—naturally speaking, not even just necessarily from the intervention. So, even if you look at the placebo mortality, it has come down, which usually means that you are able to observe more the reduction of these events that are non-fatal over the duration of the study.

Using this recurrent event analysis, you can essentially derive a rate of these events. And as you alluded to, these are not necessarily separate events in each singular patient. This is accounting for all the events that accrued throughout the study, and when you compare the placebo group versus the treatment group, you can comfortably see that over that duration of treatment, you can prevent that significant number with essentially a number needed to treat of almost two to prevent one patient from suffering either a heart failure event, urgent visit, hospitalization, or mortality, which tend to be on the smaller scale over that period of time.

So, that's the power of combination of few things. One is you're looking at the totality of the evidence and all the recurrent events that happen. And you have a targeted therapy that works in these patients on the pathway of disease that is leading to the problem at hand.

Ryan Quigley:
For those just joining us, this is *On the Frontlines of ATTR-CM* on ReachMD. I'm Ryan Quigley, and I'm speaking with Dr. Ahmad Masri about the impact of acoramidis on cumulative cardiovascular outcomes in the ATTRibute-CM trial.

So, Dr. Masri, if we continue to look at your findings here, nearly a quarter of all cardiovascular events occurred within the first six months. What does that suggest about timing in clinical care?

Dr. Masri:
I think this highlights a few things within that concept. One is that time-sensitive nature of such a diagnosis. I don't think it's at a level where we say it's an emergency to get this essentially figured out. There are some other kinds of amyloidosis similar to that, like light chain amyloidosis, where you really have to quickly figure things out.

But this is clearly showing that if a quarter of your events that accrue throughout a rigorous clinical trial that is being conducted are happening in the first six months, then that means you really have to try and shrink that time you take from the initial suspicion to the multiple levels of workup that you conduct to the final diagnosis and the start of the treatment.

So, historically, this takes months and months of work to do, and lately, because of this data and some of our other conviction in terms of earlier treatment, we've actually worked very hard to shrink that duration more and more if possible. So, that is one of the major highlights.

The second highlight is that you really are not taking a year to derive benefit from this. So, if that's the case, then you really should focus on earlier diagnosis, early initiation of treatment, and understanding that this idea that, “Oh, it's a chronic disease, let it take years for this to happen.” It's not necessarily true.

Ryan Quigley:
Now, Dr. Masri, before we wrap up our discussion, what key takeaways would you like to share with clinicians caring for patients with suspected or confirmed ATTR-CM?

Dr. Masri:
Time is of the essence. Try to find these patients, diagnose them early, and initiate treatment early. It's important, and preventing a hospitalization or cardiovascular event is not a minor thing to achieve. It's an important thing to achieve.

And stabilizing patients and not having them progress with their disease is another important goal of the treatment. A lot of these patients have events when they're diagnosed, and so initiation of treatment in this trial example led to reduction of these events early on, even within the first few months of treatment. As such, we should be vigilant about diagnosing these patients early and instituting the treatment as well early.

Ryan Quigley:
And with those key takeaways in mind, I want to thank my guest, Dr. Ahmad Masri, for joining me to discuss his findings on acoramidis and cumulative cardiovascular outcomes among patients with ATTR-CM.

Dr. Masri, thank you so much for doing this. It was great having you on the program.

Dr. Masri:
Thank you, Ryan. My pleasure.

Announcer:
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