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Treating ATTR-CM With a Novel Therapeutic Approach: Understanding the ATTRibutes to Success

Announcer:
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Dr. Grogan:
Once considered a rare condition, there have been some dramatic changes in transthyretin cardiac amyloidosis in the overall landscape, both from diagnosis to treatment. So we're seeing increased incidence, in part due to heightened awareness, and then noninvasive techniques to recognize the disease earlier, along with some new data being released from clinical trials. So what are some of the updates in this area, and what are the treatment options available?

This is CME on ReachMD, and I'm Dr. Martha Grogan.

Dr. Fontana:
And I'm Dr. Marianna Fontana.

Dr. Sarswat:
I'm Dr. Nitasha Sarswat.

Dr. Grogan:
So, Marianna, I'd like to hear your thoughts on this. What have been some of the updates in the ATTR [amyloid transthyretin] disease state in the past decade that you can share with us?

Dr. Fontana:
Well, thank you so much, Martha, for the question. In the last 20 years, we've seen a complete transformation within the field of ATTR cardiomyopathy. When we looked at what happened in the UK over the last 20 years, we've seen an exponential increase of the cases referred to the centers. Not only the cases where the diagnosis was confirmed, but also the cases where the diagnosis was finally excluded, highlighting that there's a lower threshold for physicians to refer patients for further investigations. And it is probably due to increased awareness of the condition, but also the perception that ATTR amyloidosis is a treatable condition of heart failure. And finally, for the use of advanced imaging modality, ie, cardiac MR and bone scintigraphy. With cardiac MR, we can have a deep phenotyping on the patients with a hypertrophic phenotype. So we can identify if it's cardiac amyloid or if it's one of the differentials that do exist in the hypertrophic phenotype. And with bone scintigraphy, what we can do, once we've raised the suspicion with other ECHO, CMR, or just clinical findings, we can confirm the diagnosis of cardiac ATTR amyloidosis without a need of biopsy in 70% of our patients. But to do that, we need to do a bone scintigraphy coupled with blood and urine tests.

So ATTR amyloidosis is a typical form of cardiomyopathy where the pathobiology is really well known. So in ATTR amyloidosis, what happens is that a protein, the transthyretin, which is normally produced by the liver, for various reasons it misfolds and deposits as amyloid into different organ and tissues. And it's the amyloid deposition that destructs the tissue structure and also lead to organ dysfunction. There are 2 main types of amyloidosis. Wild-type TTR [transthyretin] amyloidosis and hereditary TTR amyloidosis. In wild-type of TTR amyloidosis, patients present with a predominant cardiomyopathy. In hereditary TTR amyloidosis, there is a variant which is present in the TTR gene. And patients can present with a predominant polyneuropathic phenotype, a predominant cardiomyopathic

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phenotype very similar to wild-type, but now we know that actually the mixed phenotype where both coexist at the same time is the most common phenotype.

There are now more than 130 mutations that have been associated with hereditary TTR amyloidosis. However, the way we need to look at the disease is like a single disease with a continuum that goes from predominant polyneuropathic phenotype to predominant cardiomyopathic phenotype, acknowledging that the mix is the far more common one. And a beautiful example was V122I was considered a cardiomyopathic phenotype, and now we know that in 50% of the patients, polyneuropathy is also present.

Dr. Sarswat:
What's really interesting is that we know of these deleterious mutations and that the different mutations cause that protein tetramer to be more or less unstable and that certain mutations portend more instability of the protein and, therefore, more severity of disease. We also know of stabilizing mutations, or variants in the DNA that have actually done the opposite. For instance, the T119M variant actually stabilizes that tetramer more than the average population, and those patients actually live longer and have improved cardiovascular health in nature. And what we have gleaned from that is to take that stabilizing mutation and take the benefit of that stabilizing mutation to create a potential therapy that is aimed at stabilizing the protein in patients with hereditary or wild-type cardiomyopathy.

Dr. Grogan:
So, Nitasha, tell us a little bit about the actual mechanism of action of some of the therapies for TTR amyloidosis and some of the statistical analyses that – it might be a little bit hard for a clinician when they start reading papers about win ratio, and how do they evaluate the results of these recent clinical trials?

Dr. Sarswat:
Yeah, I think it's really interesting to understand that a lot of the new treatments that we have, that are up and coming, are really based on the underlying molecular abnormalities that we see in TTR. And I always tell patients the TTR protein is like a four-leaf clover. It's a tetramer that becomes unstable, and when that's unstable it falls apart into one-leaf clovers that then bunch together and can deposit in a lot of places. And a lot of our treatments are really aimed at stabilizing that four-leaf clover, and there are some aimed at preventing the four-leaf clover from creation in the first place.

Really interesting mechanism and I remember the first time I heard about the mechanism of acoramidis, using a variant that changes the DNA and makes that protein less stable, that causes disease-producing mechanisms. And then a variant that actually makes this protein, or the four-leaf clover, more stable, and that has been targeted, actually, as a mechanism for a drug improvement, and that's acoramidis. And the T119M mutation – that's actually a favorable mutation, a stabilizing mutation – has been the target for this treatment and has stabilized that tetramer in a very interesting way.

So we really saw this and how this played out in the recent ATTRibute cardiomyopathy trial, and that was looking at, placebo versus acoramidis, and what we saw was what you're alluding to in the statistical analysis, was this win ratio, really in favor of drug over placebo. Win ratio, I like to think of as a way of understanding a hierarchical method for endpoints, for classifying which type of endpoint in a clinical trial is more important than another. So to say that death is a more important endpoint than hospitalization. And so that's exactly what they did in this trial. I think it's important for us as clinicians to also realize that things like the win ratio are not only used in this trial but in a lot of up-and-coming trials with similarities in ATTR-ACT; that was the study for tafamidis, which is also a stabilizer. And what we see is when we make a hierarchical comparison of death being the most important is that there was a favorable endpoint in both death and heart failure hospitalizations.

Dr. Grogan:
And I think one of the things about the win ratio – it's something new. It was first really used – most cardiologists became familiar with it with the ATTR-ACT study. One advantage is in relatively rare diseases, being able to do a study with lesser number of patients, so that's some of the reasons. As Marianna said, we are diagnosing patients earlier, so between the ATTR-ACT study and the ATTRibute study, significant differences, with earlier-stage patients in the acoramidis study. So it's not intended that we compare these head-to-head. That's really not something that we can do. But the trend is so exciting because they're basically both showing us the same thing – very favorable.

Marianna, anything to add to that discussion?

Dr. Fontana:
I mean, I guess that, going back to the win ratio, the very simple way as a clinician to approach the win ratio is that, yes, they met the primary endpoint. And what I find interesting about the win ratio is that it weighs different things in different ways. So death is more important than hospitalization, and so giving a different weight to events that clearly have a different impact on the life of the patient is quite an interesting approach.

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Dr. Grogan:
For those of you just tuning in, you're listening to CME on ReachMD. I'm Dr. Martha Grogan, and here with me today are Dr. Marianna Fontana and Dr. Nitasha Sarswat, we're discussing how to best diagnose and treat patients with transthyretin cardiac amyloidosis.

Very important. And so it's really been an exciting time, that we see these changes, new trials. One important thing that you highlighted as well is that at 12 months in the ATTRibute study, the placebo patients did extremely well on their 6-minute walk distance. So it shows us that we're in a new era of clinical trials. In ATTR-ACT, patients declined much more rapidly.

Dr. Sarswat:
I agree, and I think a lot of that is exactly what you said. We're just catching patients earlier, for those same reasons that Marianna highlighted at the beginning. It's a change in medical education, the way that residents and fellows today are thinking about the disease or having a higher index of suspicion. And we're picking up the disease earlier and earlier, and that's when we know that patients are most likely to benefit from treatment as well.

Dr. Grogan:
So we already talked about ATTRibute. So, you know, very strongly positive trial and supportive of the fact that ATTR-ACT was positive. So right now in the United States, we simply have tafamidis approved for TTR amyloid with cardiac involvement alone. Then other studies, APOLLO-B is a study of patisiran versus placebo in patients with TTR amyloidosis. As many of our audience probably know, patisiran is approved for patients with hereditary TTR with neuropathy. And some of those patients may have cardiac involvement, but they have to have neuropathy, and the previous studies were with neurologic endpoints. So this was the first silencer trial to report that had cardiac endpoints. And the trial actually did meet its primary endpoint; however, this is only 12 months. So the 6-minute walk distance, you know, was thought by the FDA questionable, whether it's really clinically significant, but we still see the same trend with this data from APOLLO-B.

So right now, patisiran is not yet approved for patients with purely cardiac phenotype. However, there are ongoing studies of silencers. So CARDIO-TTRansform, which is the largest ATTR-CM study ever done, is in progress, and also HELIOS-B. So we have more silencer trials coming. And then, shortly following after that, we are starting depleter trials, so agents that are designed to disrupt the amyloid fibrils and deplete amyloid. So we have a lot going on, including, then, CRISPR therapy. So CRISPR is gene editing, snipping out the DNA that leads to the production of the TTR, in theory, a permanent solution. So, so many things happening in the landscape with a lot to watch in the very short term and intermediate term. Lots of excitement in cardiac amyloidosis, TTR amyloid for sure.

Dr. Sarswat:
Really amazing to see how the field has exploded over the last 5 years and really changed in a very wonderful way for our patients that will potentially have a lot of good options for treatment and improvement in quality of life.

Dr. Grogan:
It's really, really very exciting.

So this has certainly been a really fascinating conversation, but before we wrap up, Marianna and Nitasha, do you have any take-home messages that you would like to share?

I'll start with Marianna, a take-home message for the audience.

Dr. Fontana:
I mean, for me, the take-home message is that, really, ATTR amyloidosis is a treatable form of heart failure. So recognizing the disease, reaching the appropriate diagnosis to start treatment as soon as possible, is really a huge responsibility that we have as clinicians towards patients.

Dr. Grogan:
Nitasha?

Dr. Sarswat:
I'll just add that, again, I think it's really important for all of us as clinicians to be aware of the signs and symptoms of the disease so that we can pick this up earlier.

We know that it's treatable, especially now in this era when we have so many options to improve patients' quality of life and time with their families, time, you know, well spent. And I think that's one important thing, and I think it's also important for all of us to realize that this is one disease. Whether we're talking about neuropathic endpoints or cardiac endpoints, this is one disease that affects multiple organs, and attacking that disease in as many ways as we can to improve patients' quality of life is really the goal.

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Dr. Grogan:
And I think I'd like to just make sure the audience recognizes that it's crucial to understand the diagnostic pathway, as Marianna showed us, to make sure you have the diagnosis correct. Very important, and then to recognize that the treatment options are expanding. So working together with experts within your community, local, regional, national, to find out if there's a clinical trial for your patients, what are going to be the optimal therapies for your patients? Because these are changing pretty rapidly.

So unfortunately, that's all the time we have today. And I want to thank our audience for listening and thank you, Dr. Marianna Fontana, Dr. Nitasha Sarswat, for joining me and for sharing your valuable insights and expertise. It was really great speaking with you today.

Dr. Fontana:
Thank you very much.

Dr. Sarswat:
Thank you.

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