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Bridging the Gap to Care: What You Need to Know About ATTR-CM Amyloidosis

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Dr. Hanna:
Although previously thought to be a rare condition, amyloid transthyretin amyloidosis with cardiomyopathy, or ATTR-CM, is increasing in incidence. This is due in part to heightened awareness among clinicians and the availability of diagnostic imaging. So what strategies do we use to diagnose ATTR-CM, and what are the latest treatment options available?

This is CME on ReachMD, and I’m Dr. Mazen Hanna.

Dr. Fontana:
I am Dr. Marianna Fontana.

Dr. Hanna:
So, Marianna, let’s take a look at the epidemiology of this disease. What do we need to know about the prevalence of ATTR-CM and its impact on our patient?

Dr. Fontana:
Thank you very much, Mazen, for your question. So ATTR amyloidosis is emerging as an underdiagnosed and under recognized cause of heart failure. So in ATTR cardiomyopathy, what happens is that there is a protein called transthyretin which is normally produced by the liver, but in various conditions it misfolds and then it deposits this amyloid into the different organ and tissues. And at the cardiac level, it deposits at the level of extracellular space and it causes heart thickening with systolic and diastolic failure and increase in LV [left ventricular] mass, leading to a typical restrictive cardiomyopathy. And these are associated with significant reduction in the overall survival of patients affected by this condition and also significant reduction in the quality of life and functional capacity.

There are 2 main types of ATTR cardiomyopathy, wild-type ATTR cardiomyopathy where the TTR gene is in its wild-type form, and hereditary ATTR cardiomyopathy where the TTR gene presents a variant. The most common variant in hereditary ATTR cardiomyopathy is the V122I which is present in up to 4% of patients of Afro-Caribbean origin. So it’s extremely important to be aware of the disease, especially in specific ethnicities.

ATTR cardiomyopathy remains a significantly under recognized and untreated cause of heart failure, and so what happens is that, unfortunately, we still keep diagnosing patients fairly late, when there is little that can be done to actually improve the prognosis. So it is absolutely of paramount importance to raise the awareness of this condition, because this is nowadays a treatable condition where there are various treatment options that we can provide to the patients, and these treatment options can improve the prognosis, but also the quality of life and functional capacity of our patients.

Dr. Hanna:

Thanks, Marianna. I would agree this remains an underdiagnosed condition, and as our population ages, there will be more patients presenting with wild-type ATTR cardiomyopathy as the prevalence of this disease increases with age. And furthermore, as far as the hereditary ATTR-CM, here in the United States the most common variant we see is the Val122Ile variant, now named Val142Ile, and this is found in 3.5% of African Americans who are heterozygote carriers, putting them at risk for late-onset cardiac amyloidosis. So indeed, I think our antennas have to be up. Suspicion has to be increased to ultimately make this diagnosis.

Dr. Fontana:
Mazen, you mentioned diagnostic imaging in your introduction. Can you tell us a little bit more about some of the strategies that are currently used to diagnose patients with ATTR cardiomyopathy and on the impact that noninvasive diagnostic pathway had on our patient population?

Dr. Hanna:
Thanks, Marianna. Process of diagnosing ATTR cardiomyopathy first starts with clinical suspicion that is generated from the clinical history and 2 basic cardiac tests that we're all familiar with, the echocardiogram and the electrocardiogram [EKG]. On clinical history, clues or, quote, red flags include a history of bilateral carpal tunnel syndrome, spinal stenosis, biceps tendon rupture, or rotator cuff tear, as the incidence of these orthopedic manifestations of systemic ATTR amyloidosis often precede symptoms of cardiomyopathy. The echocardiogram, which is the main imaging test to lead one down the path of diagnosis, shows increased septal and posterior LV wall thickness; typically a nondilated left ventricle with normal or mid-range ejection fraction but can be reduced; typically dilated atria and abnormal diastolic function; and when available, longitudinal strain imaging may show what's called an apical-sparing pattern.

The electrocardiogram can show low voltage, or relative low voltage, and not uncommonly, conduction abnormalities. However, only 30% of patients with ATTR cardiomyopathy have a low voltage on EKG, and 10% of biopsy-proven ATTR-CM can meet LVH [left ventricular hypertrophy] criteria by EKG.

Once the foundation of suspicion is established, there are various imaging modalities that help us to arrive at the diagnosis. Cardiac MRI [magnetic resonance imaging] is an excellent imaging modality that gives tissue characterization using gadolinium enhancement patterns, T1 mapping values, and characterization of extracellular volume fraction. And while the findings on cardiac MRI do not make the final diagnosis of ATTR-CM, it can direct the work-up of undifferentiated LV thickening and has excellent prognostic utility.

Now up until a decade ago, we had to confirm the diagnosis with an endomyocardial biopsy. What has revolutionized our ability to make the noninvasive diagnosis of ATTR-CM without an endomyocardial biopsy is an imaging modality called bone scintigraphy. When positive, in conjunction with ruling out AL [amyloid light chain] amyloidosis with the appropriate lab testing, this has a very good sensitivity and specificity for the diagnosis of ATTR-CM. It is important to note that anytime there is conflicting information, an endomyocardial biopsy is still necessary.

And note, a fat pad biopsy to diagnose ATTR-CM is typically of low yield, in particular with wild-type ATTR-CM. Biomarkers such as NT-proBNP will commonly be elevated. In particular, you may see a low-level chronic troponin elevation, which can be a clinical clue. And one final point is that it is not uncommon that hypertension or aortic stenosis can coexist with ATTR cardiomyopathy. As such, the presence of one or both conditions should not dissuade one from pursuing the diagnosis of ATTR-CM should there be factors that raise suspicion, such as in the history, the electrocardiogram, and the echocardiogram and/or cardiac MRI find.

Dr. Fontana:
Thank you very much, Mazen, for the very detailed description of all the available noninvasive techniques that we use in our daily practice to make a diagnosis of ATTR cardiomyopathy. And looking back at the last 20 years, it's extremely interesting to observe how the introduction of noninvasive diagnostic pathways, so without the use of any biopsy, into the clinical practice has been associated with significant increase in the diagnosis of patients with ATTR cardiomyopathy and has also transformed the clinical phenotype of the patients that we see nowadays in clinic.

Dr. Hanna:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Mazen Hanna, and here with me today is Dr. Marianna Fontana. We're discussing what you need to know about amyloid transthyretin amyloidosis with cardiomyopathy, or ATTR-CM.

Now that we've discussed the burden of ATTR cardiomyopathy and strategies to diagnose, Marianna, what can you tell us about possible treatments?

Dr. Fontana:
Thank you very much, Mazen, for the question. So the treatment landscape in the last 10 years has completely changed. Ten years ago when I was seeing the patients with ATTR cardiomyopathy in clinic, I was able to confirm a diagnosis using invasive approaches, but then I was not able to offer absolutely any disease-specific treatment because there was not any treatment available. But now the

landscape is dramatically changing. So the first significant change was the publication of the ATTR-ACT trial, so a trial testing tafamidis in a large population of patients with ATTR cardiomyopathy. The publications of the ATTR-ACT trial was a major breakthrough for all clinicians and academics working in the field because it was the first drug that had been proven to be associated with better outcome for our patients. Indeed, in this trial in patients with transthyretin amyloid cardiomyopathy, tafamidis was associated with reduction in all-cause mortality and cardiovascular-related hospitalization and reduced the decline in functional capacity and quality of life as compared to placebo. So tafamidis is TTR stabilizer, so what it does, it stabilizes the protein and inhibits the misfolding and so inhibits the new production of amyloid.

Another drug, which is part of the same class of drug, is acoramidis. The results of the phase 3 trial have been recently published in a press release, and what the authors found is that in patients with ATTR cardiomyopathy, acoramidis treatment reduced overall mortality, cardiovascular-related hospitalization, reduced also the declining functional capacity and quality of life, and increased the circulating TTR levels as compared to placebo. And so this was a second drug, then, within the same class. This was stabilized, was able to improve the prognosis and quality of life for our patients with this condition.

When we think about the drugs that can reduce the amyloid production, there is another class of drug which acts through a different mechanism, which is by silencing the TTR gene. And so what it does, it reduces the production of transthyretin and therefore dramatically reduces the production of amyloid cells. One of the drugs which is within this class is patisiran. Patisiran is given by infusion every 3 weeks, and what it does by inhibiting the production of TTR, reduces significantly the production of amyloid. The trial met the primary endpoint of reduction in the decline in the functional capacity, as demonstrated by 6-minute walking test, and also reduction in the decline in the quality of life as compared to placebo. This was a trial and the endpoint after the double-blind phase was at 12 months. So it's extremely remarkable how early we could see changes in this population which was as early as 12 months after the initiation of treatment.

Within the same class of drugs, so drug that inhibit the production of TTR amyloid by reducing the production of the amyloid precursor protein, there are compounds that are at different stages of drug development. In phase 3, there are 2 main compounds. One is vutrisiran, which is the generation after the patisiran. It's a sub-cut injection, and the safety and efficacy currently being tested in the HELIOS-B trial, which is a large, double-blind, randomized, placebo-controlled trial which is currently ongoing.

Another compound that is within the same class is eplontersen, which is, again, a sub-cut injection and is currently being tested in a large, phase 3, double-blind, placebo-controlled trial, and the name of the trial is TTRansform.

Other class of drugs are currently being developed, but are in earlier stages of development, and these, what they do, they target the existing amyloid deposits. The results of the phase 1 trials have been recently published in *The New England Journal of Medicine*, and a phase 1, although in a small number of patients, gave very positive and promising results.

So although in earlier stages of drug development, these drugs are very promising because they act through a different mechanism which is targeting the deposits compared to lowering the production. And it's very likely that in the near future, like a fast-forward in 5 to 10 years, we will be able to actually use a combination of drugs where we have a host of all new drugs targeting different mechanisms in the pathophysiology of cardiac amyloidosis. So some drugs targeting the production, others targeting the stabilizations, and others targeting the existing deposits.

Dr. Hanna:
Thank you for summarizing the treatment landscape for us. And we have been using tafamidis in our patients for about the past 5 years, and we've seen many patients remain stable, although the concept of using tafamidis is to slow down progression. We certainly look forward to seeing if these gene-silencing agents will possibly lead to slow reversal of amyloid deposition over time, and we're hopeful that these future trials that you mentioned with monoclonal antibodies can possibly actively remove the TTR amyloid fibril.

Well, this has certainly been an excellent conversation, but before we wrap up, Marianna, what's your one take-home message for our audience?

Dr. Fontana:
For me, the most important take-home message is that ATTR cardiomyopathy is currently a treatable condition and is an underdiagnosed and under recognized cause of heart failure, so it is absolutely crucial to proceed with the right investigations if there is the suspicion of ATTR cardiomyopathy, because then if we confirm the disease, we can start the appropriate treatment strategy that will dramatically change our patient prognosis.

Dr. Hanna:
I would agree with you, and I think the challenge does remain in timely diagnosis and making sure that bone scintigraphy is done and interpreted accurately to avoid false diagnoses and that AL amyloidosis is appropriately ruled out to avoid missing the correct diagnosis.

I think with approved treatment and ongoing and upcoming clinical trials, the future outlook remains bright for ATTR cardiomyopathy, and thus raising awareness and making the correct and timely diagnosis has become paramount.

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

Dr. Fontana:
Thank you very much, Mazen, for the invitation to have this conversation about the unmet needs in ATTR cardiomyopathy and the future perspective. The future is bright and the field is dramatically changing, so it's really important to be aware as clinicians of the importance of making the right diagnosis to really change the patient outcome.

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