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Tracking Disease Progression in ATTR-CM

Announcer:
This is *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'm joined by Dr. Joban Vaishnav, Assistant Professor of Medicine and Director of the Comprehensive Amyloidosis Center at Johns Hopkins Medicine in Baltimore. We'll be exploring disease progression in transthyretin amyloid cardiomyopathy, or ATTR-CM.

Dr. Vaishnav, thank you so much for being here today. Really appreciate you taking the time out to join us.

Dr. Vaishnav:
Thank you, Ryan, to ReachMD, for having me. I'm really excited to be here.

Ryan Quigley:
Absolutely, likewise. So, Dr. Vaishnav, to start us off, how would you define disease progression in the context of ATTR-CM?

Dr. Vaishnav:
I think that's a great question to get us started off, and an important one. Disease progression used to be inevitable before treatment, but now it's less inevitable, and we're slowing disease progression quite a bit.

I think a universal definition for disease progression doesn't exist. Basically, what we're trying to capture is a worsening of the disease. And I think, given that ATTR-CM is quite heterogeneous, this can span many different domains. And so I think that a take home is that defining disease progression should, in fact, be multimodal, and capture the whole spectrum.

And so, broadly speaking, I think certainly, if someone's experiencing worsening symptoms—worsening heart failure symptoms, worsening cardiac symptoms— that to me signifies disease progression, as well as worsening of their labs like cardiac biomarkers. One that has been studied and shown to predict subsequent mortality is NT-proBNP as well as worsening renal function.

And then we also know that worsening of functional status and quality of life is important. And so I think a worsening in any one of these domains, and certainly a worsening in more than one domain, is consistent with disease progression from a cardiomyopathy perspective.

Ryan Quigley:
And now, what are some of the biggest challenges that clinicians face when it comes to identifying early or subtle signs of progression in these patients?

Dr. Vaishnav:
Thankfully now in large cohorts, multicenter cohorts, we are starting to investigate disease progression. I think there certainly needs to be more validated markers studied in patients on treatment. A lot of the data we have right now were identified in cohorts of patients who were treatment naive, and that's not fully reflective or representative of the vast majority of patients now who are thankfully able to get on disease-modifying treatment. I think the key is, in your question, how do we identify disease progression early?

No longer should we be waiting for heart failure hospitalizations, which we know are a really significant event in a patient with amyloidosis in terms of their disease course. And I think probably a big challenge is that the disease is quite heterogeneous. I think symptoms can overlap with other comorbidities.

I also think that there has been a lot of emphasis on objective imaging and biomarker criteria, which are important and easily replicated in different patient populations. But I do think if we only focus on these markers, we'll miss some of the nuance, in quality of life and functional status.

And so I think if you ask our patients what matters to them, it's probably gonna be more so quality-of-life measures and functional status as opposed to, for example, a proBNP or a kidney function measure. So I think more work ought to be done on capturing these quality-of-life measures with our patients, and actually dialoguing with our patients on what matters to them when it comes to disease progression and balancing all of the different criteria.

And so I think these are some of the challenges. I also think we as a community need to come together and pool our data so that we have larger patient populations and more heterogeneous patient populations being studied when it comes to disease progression, and perhaps that would be a way to identify novel markers.

Ryan Quigley:
And something else that I'm curious about is the different subtypes. So there's wild-type and hereditary. How does the pattern of progression differ between those subtypes?

Dr. Vaishnav:
I love that you're bringing this up because I actually don't think there has been as much dialogue about this and how different the diseases can be. So we know that wild-type ATTR-CM manifests differently, specifically in patients who are older compared to hereditary and with different organ involvement.

So hereditary patients may be far more likely to get neuropathic disease, they may be younger, they may have more mixed phenotype compared to wild-type patients. Yet we haven't really studied disease progression separately in these cohorts. And so I do think that there probably needs to be individualized investigation in wild-type and different genotypes.

So different genotypes will have different phenotypic presentations. And I certainly think that, subtype can impact what disease marker or disease progression marker may be more likely to manifest. There have been cardiac markers of disease progression identified, including—I mentioned some of them—proBNP and worsening renal function. We know that increased diuretic dosing, outpatient diuretic dosing, is a marker of progression and a marker of downstream poor outcomes. So I think we've identified some really important cardiac disease progression markers. I don't think that we've identified, or I'll say done as rigorous of an investigation for neuropathic disease markers. And I think this is a nice future area of investigation that would be important to our hereditary patients who would be more subject to neuropathic disease.

So I think it's important to recognize that wild-type and hereditary are related but somewhat different diseases, and hereditary patients may be more likely to have progression in not only cardiac but neuropathic domains. And then we, at the same time, need to identify what those neuropathic markers of disease progression are going forward.

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. Joban Vaishnav about disease progression in ATTR-CM and how it shapes long-term patient management.

So Dr. Vaishnav, I'd like to shift over now to treatment. How does identifying progression early influence your decision making around initiating or even adjusting therapy over time?

Dr. Vaishnav:
Great question. I think it's also an area that we need more information on and we need more collaboration on. Recapping, we have three approved therapies in the US for ATTR-CM, and these therapies span two different mechanisms. We have stabilizers and gene silencers, with gene silencers right now probably having more robust data for neuropathy compared to a stabilizer. So three different treatments. As a field, I don't think we've identified that one treatment is superior compared to another. And there are certainly a lot of questions in the treatment realm. I think one major one is, are there patients that may benefit from combination mechanism therapy: a stabilizer and a silencer?

If so, which patients may benefit from that therapy upfront? You can imagine that, if a patient is already experiencing disease progression and is already experiencing worsening heart failure or subject to heart failure hospitalizations, knowing that these therapies work upstream in the amyloid cascade and don't actually, from a mechanistic standpoint, deplete the myocardium of amyloid deposition, that may be too late then to escalate therapy. And we've shown this in our cohort. It hasn't been shown in a big way, but I think probably it's intuitive that if you're escalating therapy when there's already been significant cardiac disease progression, that may be too late. And so I do think that, probably, what we need to look at are patients who either have really adverse prognostic markers at diagnosis and/or,

to your point, have early markers of disease progression within that six month to one year timeline of being on treatment.

Is there a benefit in those patients to combination mechanism therapy? And that I think also should involve more deep neurologic genotyping. And then I think, on the horizon, from a treatment or therapeutic perspective, our depleters or antifibril therapies, these are medications that are being studied that are aiming to remove amyloid fibrils from organs in which deposited cardiac deposition.

Where in the landscape are depleters gonna fit in? I would think right now, if there's a patient who's got very severe disease markers or early signs of disease progression, I would be more eager to reach to a therapy like this, that may mitigate some of that damage compared to a therapy that may work upstream.

So probably right now there are more questions than answers, but identifying disease progression early I do think will shape our approach to therapy. We just need to look at this further in a more rigorous way.

Ryan Quigley:
Now, what role does multidisciplinary care play in long-term management, especially as disease progression begins to impact systems beyond just the heart?

Dr. Vaishnav:
I think with the advent of disease modifying treatment, patients with ATTR-CM are living longer and, if caught early enough, they're living with better quality of life for most of that time.

And so my clinic conversations in a way have shifted away from, how long am I gonna live and is my mortality inevitable, to now, what is my quality of life looking like and is my treatment working? And I think these are really wonderful conversations to be having as compared to the contrary, the other conversations.

But I do think now that we've found effective cardiac treatments, not only the amyloid therapies, but also effective heart failure therapies, I do find that patients have a higher burden of symptoms related to their orthopedic manifestations of disease or neurologic manifestations of disease. Some things that are hard to capture, like fatigue and frailty, for example.

All of these heterogeneous manifestations are coming out as patients are living longer with more stable cardiac symptomology. And so that's where the role for multidisciplinary care comes in. You need, I would say, ideally, evaluation and interventions for these manifestations.

So I think phenotyping and ascertaining disease burden upfront, and then longitudinal follow up while on therapy across all the different systems that are impacted is important as we're navigating disease progression.

I also think that when a patient is experiencing disease progression, cardiac disease progression or otherwise, like some of the challenges we talked about, and one that I'll point out is there's not one defined pathway for management right now. We don't know if switching or escalating therapy will provide meaningful benefit.

And while it's important to recognize disease progression, it's kind of hard to know what the next step is gonna be. And I think counseling patients on that and being transparent about that's important.

And, probably, this speaks to a role for palliative care or a support system that can focus on living with a chronic medical condition for a longer period of time. And so having a care team that can provide back and forth about optimal symptom management—whether that's the cardiologist, whether that's the palliative care provider—I think this is where it's a shared decision making and shared care approach. But, certainly, I think, our current amyloid patient population benefits from this multidisciplinary collaboration.

Ryan Quigley:
And finally, Dr. Vaishnav, before we close here, what advice would you offer to clinicians who are looking to take more of a proactive approach to caring for patients with ATTR-CM?

Dr. Vaishnav:
I've actually heard different philosophies on investigating disease progression. One philosophy, and probably the philosophy I take, is, we should be looking for it. We should be collecting markers that may help identify it. And so that's one philosophy. And then there's another philosophy, which is don't collect data where you don't have an intervention. I think those are two schools of thoughts. But I really do think to be proactive and to refine our approach to evaluation of disease progression, we do have to see our patients often, dialogue with them, and understand what is actually limiting them in the era now of disease-modifying treatment and living longer.

Many markers have been identified. There's no weighted risk score. We don't know, per se, which marker may hold significance compared to another, short of, of course, hospitalization or mortality. These are very bad things. And so I do think that leveraging your

own personal clinic resources to collect the multimodal markers across labs, functional markers, quality-of-life measures, and then collaborating multicenter studies is what I would recommend in terms of being proactive.

Ryan Quigley:
With that in mind, I want to thank my guest, Dr. Joban Vaishnav, for joining me to discuss how we can better understand and manage disease progression in ATTR-CM. Dr. Vaishnav, thank you so much for doing this. This was a great conversation.

Dr. Vaishnav:
Thank you so much for having me.

Announcer:
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