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The Role of TTR Stabilization in ATTR-CM Treatment

Announcer:
Welcome to *On the Frontlines of ATTR-CM* on ReachMD. Here's your host, Dr. Steve Jackson.

Dr. Jackson:
This is *On the Frontlines of ATTR-CM* on ReachMD. I'm Dr. Steve Jackson, and today I'm joined by Dr. Sumeet Mitter, Director of the Infiltrative and Restrictive Cardiomyopathy Center at Inova Schar Heart and Vascular in Virginia, and Co-Director of Site-Based Research. We'll be exploring how transthyretin stabilization can play a role in managing transthyretin amyloid cardiomyopathy or ATTR-CM.

Dr. Mitter, thanks for being here.

Dr. Mitter:
Thank you for having me.

Dr. Jackson:
To set the stage for our conversation, Dr. Mitter, what happens to the transthyretin protein in ATTR-CM, and why is protein stability such an important part of the disease process?

Dr. Mitter:
So transthyretin is a protein that everyone makes. It is primarily synthesized in the liver. It's also made within the eye, in the retinal pigment epithelium, and also in the choroid plexus of the brain.

But in terms of the hepatic version of transthyretin, it is a four-unit tetramer protein whose primary function is actually in the name of itself, transthyretin. It transports thyroxine and retinol-binding protein, so T4 or vitamin A complex, and it is a four-unit structure. All of us make it. In terms of how much it contributes to carrying thyroid hormone, that's probably a minority of the amount of thyroid hormone that's actually carried within the body. It's about five percent, but it is the primary carrier of vitamin A within the body. So it has a biologic function for all of us.

And in terms of hepatic production, sometimes with age, this transthyretin protein, also known as prealbumin, for those of us who often look at nutrition, is a nutritional marker. With age, we notice that this level can go down. And statistically, individuals who have lower levels of transthyretin over their lifespan have vascular complications, cardiovascular problems, or dementia. In the pathogenic state of transthyretin systemic amyloidosis, in terms of the heart, with normal aging—and we're talking about individuals who are above the age of 70, 75—this four-unit protein can break apart into two-unit structures and then one-unit structures called monomers. And then these monomers misfold and coagulate into these waxy clumps called amyloid. And then these amyloid proteins then deposit throughout the body.

And often, in the lead-up to transthyretin amyloid cardiomyopathy in an individual without a genetic variant, this can lead to a milieu of problems in terms of bilateral carpal tunnel syndrome. Individuals often will have a history of orthopedic complaints, knee replacements, rotator cuff injuries, bicep tendon rupture. And in terms of the heart, as these waxy amyloid proteins deposit between the heart cells, it starts making the heart look thicker. So the cells aren't necessarily getting thicker, but it's depositing between the cells, and that makes the overall myocardium or wall thickness of the heart increase, and the heart looks very thickened. As that happens, the heart stiffens.

I like to use an analogy in explaining this to patients that, imagine you're trying to blow air into a balloon that can't expand. So when the heart is thickened and very rigid and filled with blood, pressure increases, much like a balloon would have high pressure if it can't

expand. And so individuals often feel that transmitted elevation of pressures in their lungs because it has to back up somewhere. It goes from the left ventricle back up to the left atrium into the lungs, and patients feel it. And what that manifests is shortness of breath while walking around, trouble breathing when laying down, or seeing fluid or edema in their legs, and they'll feel it in their abdomen. They'll bloat. And that is the syndrome of transthyretin cardiomyopathy and associated initially heart failure with preserved ejection fraction that many patients who are older are afflicted with when they have the wild-type version of this disease.

The other side of it is that in this transthyretin protein, there's over 130 known genetic variants in different groups around the world that lead to an earlier destabilization or breaking apart of this tetramer four unit of protein into the dimers and the monomers that then misfold. In the variant case, there is also deposition within our nervous system, and we probably underappreciate it in individuals without a genetic variant. But at least in the patients with a genetic variant, we actually start seeing a combination depending on the genetic variant of both neuropathy and cardiomyopathy.

And so one of the more common genetic variants with neuropathy is called V30M. We'll find these in individuals in Portugal and Brazil, and they'll often have an early neuropathy and then later on a cardiomyopathy as they age based on the predication of where the amyloid deposits are. Similarly, there's Irish American variants—T60A, depending on the nomenclature we use for the variant—which traces lineage back to Donegal, Ireland. And those individuals will often present in their 40s or 50s with a mixed phenotype at that time of both neuropathy and cardiomyopathy.

But in terms of the United States, the most common variant is called V122I or V142I, and that's prevalent in three to four percent of our Black American population as well as our Afro-Caribbean and Afro-Hispanic population. And in this case, it's more the individuals have primarily cardiomyopathy, rarely neuropathy, and individuals often present with disease in their 60s as opposed to their 70s or 80s. And when they present earlier in life, we also know through natural history studies that these individuals will also have worse clinical outcomes in terms of hospitalization, longevity, and complications of the disease state.

So essentially, whether it's by normal aging or through genetic variance, this four-unit protein breaks apart, misfolds, turns into a waxy clump, and then deposits different organs. And depending on what the genetic makeup of one is, it can lead to similar but varying severities of this cardiomyopathy syndrome.

Dr. Jackson:
So about one in 200 people have a genetic mutation called T119M that leads to an interesting change to the normal TTR protein structure. Can you walk us through our current understanding of the T119 variant?

Dr. Mitter:
Yeah, that's actually really fascinating because up until now, we were talking about some of these destabilizing genetic variants that increase the risk of developing transthyretin cardiac amyloidosis in populations around the world. There are a few supra-stabilizing variants that lead to an increase in stability of the TTR tetramer, such that if someone has the T119 variant, and there's a couple others out there, but also a destabilizing variant, the molecule actually doesn't break apart as much. That four-unit tetramer protein doesn't break apart into the dimer two-unit protein or the monomer that's pathogenic and turns into amyloid clumps. So it almost creates extra stability in the TTR tetramer, so people can't really develop a pathogenic disease state. When individuals look at the crystal structure of this TTR tetramer, when this T119M variant is present, what they find is there's actually increased hydrogen bonds at the center of the molecule that maintain stability. The TTR tetramer can't break apart.

And aside from T119M, there's a couple other super stabilizing variants, but I think this T119M has the best properties we know of so far that can lead to an increase in stability of the protein.

Dr. Jackson:
And how has that understanding influenced the development of the transthyretin stabilizers for ATTR-CM?

Dr. Mitter:
Right now there are two commercially available stabilizers for transthyretin cardiomyopathy, the first of which is tafamidis, and that came to market in the US in around 2019. And then the other is acoramidis, which was approved by the FDA in late 2024.

The way tafamidis works as our first stabilizer is that it binds to that thyroxine binding site. We talked about the original function of a protein, and so it binds to the site where the thyroid hormone would be; the tetramer protein would carry, such that it reduces the ability of the TTR tetramer to dissociate into the dimers and monomers of the two-unit, one-unit subunits that then lead to the cascade of amyloidogenesis.

Acoramidis mimics the hydrogen bonding that's seen in the T119M variant to introduce those hydrogen bonds between the serine 117 residues and the opposite dimer in the tetramer compound, such that it can't really break apart. While it binds that T4 site, it also helps

create this hydrogen bonding formation between these serine 117 residues.

Both drugs work well in terms of stabilizing the overall tetramer so it doesn't dissociate. But that's the nuance of the difference between the stabilizers, and frankly, acoramidis is related to the supra-stabilizing ability of a genetic variant that was found to overall improve stability of the tetramer.

Dr. Jackson:
For those just tuning in, you're listening to *On the Frontlines of ATTR-CM* on ReachMD. I'm Dr. Steve Jackson, and I'm speaking with Dr. Sumeet Mitter about the biology behind transthyretin stabilization in ATTR-CM.

Dr. Mitter, where do the TTR stabilizers fit within the broader treatment landscape for ATTR-CM, and how do they differ mechanistically from other approaches?

Dr. Mitter:
So we are blessed at this point in 2026 to have a multitude of options for our patients afflicted with ATTR cardiomyopathy. As an anecdote, I remember being in medical school and reading about amyloidosis back in 2005 or 2006 and thinking, "I don't really need to know about this because there's no therapies out there, and I'm never going to treat this disease." And now, this is what I specialize in. And it's really fascinating because we've known about transthyretin cardiomyopathy for over a century, but we didn't have therapies. And now, there's at least two oral options to stabilize the TTR tetramer.

There's also a third agent that's commercially available called vutrisiran that acts as a silencer. Whereas tafamidis and acoramidis act to stop the formed tetramer from breaking down or slow down the dissociation of the TTR tetramer, the silencer class of medications—in this case, vutrisiran—acts before that within the liver. So it uses silencing RNA technology to shut off production of the TTR tetramer. So we're not editing DNA, but the translation of the protein through silencing RNA technology. Transcription is basically shut off, and so you can't have a formed protein. And this silences production when we look at data from the clinical trial by about 85 percent. So it works before you can even have a protein. But the nuance here is that if you actually turn off almost complete production of the protein, remember there's a natural function of this protein to carry also a vitamin A complex. It only carries a minority of thyroid hormone. And so patients have to supplement with vitamin A to avoid night blindness.

So in terms of the landscape, all three of these drugs—tafamidis, acoramidis, and vutrisiran—in their clinical trials, both from the primary datasets and then including some information for follow-up data, have shown an improvement in overall survival and hospitalizations. Within the clinical trials, there were different statistical methods used in components of the overall primary endpoint. But overall, they all show a treatment benefit, whether we're stabilizing the protein or silencing the protein.

Dr. Jackson:
And as those insights bring us to the end of our program, I want to thank my guest, Dr. Sumeet Mitter, for joining me to discuss how transthyretin stabilizers can play a role in ATTR-CM care.

Dr. Mitter, it was a pleasure having you on the program.

Dr. Mitter:
Thank you so much.

Announcer:
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