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Heart Transplant in ATTR-CM: A New Look at Referral and Candidacy

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

Dr. Jackson:
Welcome to *On the Frontlines of ATTR-CM* on ReachMD. I'm Dr. Steve Jackson, and joining me to share his perspective on heart transplantation for patients with transthyretin cardiac amyloidosis, or ATTR-CM, is Dr. Alex Reyentovich. In addition to being a Professor in the Department of Medicine at NYU Grossman School of Medicine, he's also the Co-Director of the Amyloidosis Program at the Perlmutter Cancer Center at NYU Langone Health.

Dr. Reyentovich, thanks for being here today.

Dr. Reyentovich:
Thank you for the invitation.

Dr. Jackson:
Let's start with context. Patients with ATTR-CM were once generally considered poor candidates for heart transplantation; what's changed in recent years?

Dr. Reyentovich:
I think there's much greater awareness of disease progression, and we're identifying patients earlier in the disease. So, for example, ten years ago, we really had no therapies that prolonged survival of the disease. So by the time patients got to us, they were really pretty sick, and we weren't really sure what was going to happen after you transplanted them, or whether any of those things were going to get better. And often, if you tried, they didn't.

So the big thing that's changed is with our new therapies and our new imaging modalities, we're diagnosing patients much earlier. They ease into their advanced disease. They do it in front of our eyes, and we can get them plugged in a little bit earlier, not when they're bed-bound and cachexic. So I think we're selecting a different group of patients for transplantation with transthyretin amyloid than we would have a decade ago. I'd say the disease hasn't changed; it's our understanding of it, the time of diagnosis, and which patients are best suited for heart transplant.

Dr. Jackson:
Sure, and I think those advances also prompted some updated allocation policies for stable patients with ATTR-CM. So with more opportunities available now, what factors should prompt clinicians to refer these patients to an advanced heart failure or transplant center?

Dr. Reyentovich:
Yeah, that's really a great question. The therapies that we have—and there are three approved therapies by the FDA to treat transthyretin cardiac amyloid—are really efficacious at treating patients at the early stages of disease, with functional class one, two, or let's say the low end of class three heart failure. And in those patients, the drugs do a good job slowing down the progression of disease, so you stay at an early stage. But by the time you have advanced symptoms, if you start those therapies when you have class three or four symptoms, the momentum is there. It's like rolling a rock down the hill. It's easy to stop at the top, but once you have momentum and speed, it's hard. So it's very similar. It's almost like diagnosing someone with stage four cancer. So when you're at the advanced stages, there's not a lot of drugs that can pull you back, at least not yet.

So the patients who should be considered for transplantation are very similar to the ones that you would consider for transplantation with other forms of heart failure. So the type of patient who keeps on getting admitted for heart failure or has trouble doing their activities of daily living, like having trouble going up one flight of stairs or walking to the store. Patients who really have life-limiting symptoms related to heart failure with transthyretin amyloid are the ones who you should really consider getting to a center that has expertise in both treating amyloid and heart transplantation.

Dr. Jackson:
And once a patient is referred for transplant, what does the evaluation actually look like, and why is it particularly important to understand the burden of extra cardiac disease?

Dr. Reyentovich:
We're focusing on transthyretin amyloid, and I will just briefly say something about AL amyloid in that context. So if somebody comes to us with amyloid, the only part that you're going to change is their heart. Within that context, patients come to us, and I would say about half the patients are referred as an inpatient, so they're hospital-to-hospital transfer. Half the patients are referred as outpatients. And when they come into the program, one of the big things is to make sure that the patient's capable of taking care of their heart, they have a support system, and they don't have any other sort of terrible comorbidities that would limit their life expectancy or the ability to take care of a heart.

So make sure they don't have cancer or major hematologic abnormalities or lung disease or liver disease that we haven't diagnosed. And once we've gotten through all that part, we have to make a good assessment of what other organs are involved. And really, AL amyloid is a more complicated type of amyloid. It affects almost every organ system. And you're much more likely to have extracardiac manifestation, whether that's kidney involvement, neurologic involvement, or pleural-based involvement. So there's a little bit different complexity to that.

But if you're going into transthyretin amyloid, then you have two major categories. You have the wild type, and you have patients with mutations. Patients who have wild-type amyloid and are referred for transplant primarily have cardiac involvement. That is a disease where the vast majority of the symptoms relate to cardiac involvement and ligamentous involvement—spinal stenosis, carpal tunnel, other joint involvement, and really not a significant neurologic component. So what you're mostly dealing with in patients who have wild-type amyloid is making sure that they aren't debilitated from their ligamentous involvement and they don't have terrible spinal stenosis that they can't ambulate and recover. That's the main thing.

For patients who have the variant type, what you're really worried about is neurologic involvement. So patients can get neuropathy that limits their ability to walk and rehab. They can get terrible dysautonomia, which can lead to both constipation and diarrhea and can lead to some malnutrition. So you have to make sure that you know what you're getting into and that they don't have life-limiting symptoms related to the extracardiac manifestations.

And then the other reason we really need to know what they have outside of their heart is making a case for continuing treatment with some of those other agents that I mentioned after the fact because even though you've replaced the heart, the other things continue to progress—the neuropathy and the ligamentous involvement. So we do our best after transplantation to make sure patients stay on some kind of treatment. So it's good to understand where they are at the time of referral to understand what you need to continue to treat after the transplant.

Dr. Jackson:
For those just joining us, this is *On the Frontlines of ATTR-CM* on ReachMD. I'm Dr. Steve Jackson, and I'm speaking with Dr. Alex Reyentovich about when to consider heart transplantation in patients with ATTR-CM.

Can you explain how a patient's ATTR subtype influences transplant decision-making?

Dr. Reyentovich:
There are about 60 to 70 different identified mutations in the transthyretin protein that lead to pathology, and most of those mutations have some balance of cardiac and neurologic involvement. Really, those are the two primary areas where in transthyretin amyloid, the variant type is involved. And the neurologic manifestations can be quite variable, from having some peripheral neuropathy and tingling to having neuropathy where you could barely walk, or having dysautonomia where patients faint and have a lot of bowel dysfunction as well.

So depending on the mutation is the likelihood of developing the neurologic manifestations and what the relative burden is of cardiac versus neurologic manifestation. So for example, I'm in New York, and by far, the most common variant that we see is V122Y mutation. That mutation is present in three percent of individuals who have Western African ancestry. So in the African American population in

New York, about three percent carry that mutation. And that is a mutation that predominantly affects the heart and has minimal neurologic manifestations. So it behaves very much like a wild-type amyloid.

And in those individuals, if you fix the heart, those patients are pretty well off. In other parts of the country, or other parts of the world, for example, an ala 60 mutation will have significant neurologic involvement. And if all you do is replace their heart, you want to make sure that one, they're able to rehab from their heart, and two, they're not on a path to get neurologic manifestations.

It's a little bit different now because we have such good therapies. But you definitely have to do your due diligence and parse out what neurologic involvement they have before you steer them towards transplant. And again, that is based on understanding how these different mutations behave.

Dr. Jackson:
And finally, Dr. Reyentovich, if a patient does undergo a successful heart transplant, what should clinicians and patients understand about what transplantation does and doesn't change about the underlying pathology in ATTR disease?

Dr. Reyentovich:
We haven't seen recurrence in the heart, not in any meaningful, significant way. So if you've transplanted their heart, that part is good. The heart part is okay, but the rest of it will continue to progress. You definitely have to stay tied to providers who are facile and knowledgeable about amyloid. And for the vast majority of patients you will still require disease-modifying treatments and close monitoring to make sure the other organ systems or other symptoms don't progress while your heart has been treated.

Dr. Jackson:
And with those insights in mind, I want to thank my guest, Dr. Alex Reyentovich, for joining me to discuss heart transplantation in patients with ATTR-CM.

Dr. Reyentovich, it was great having you on the program.

Dr. Reyentovich:
Thank you for having me.

Announcer:
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