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Advances in ATTR-CM: Evolving Diagnostics and Therapeutics

Host:
This *Heart Matters* on ReachMD. On this episode, Dr. Kevin Alexander will discuss updates in the treatment of transthyretin amyloid cardiomyopathy, or ATTR-CM. He's an Assistant Professor of Cardiovascular Medicine at Stanford University School of Medicine, and he specializes in the management of advanced heart failure and transplant cases. Let's hear from him now.

Dr. Alexander:
A lot has happened in the last 10 years in terms of how we diagnose and manage ATTR-CM. The first thing I would say is that there's an increased awareness of the disease, and so there are more people looking for this than there were 10 years ago. That's led to an increase in the diagnosis rate.

But I think the thing that's really helped facilitate more diagnosis is that we have a non-invasive means to diagnose many of these patients. 10 years ago, many patients were still diagnosed with endomyocardial biopsy. That's how the majority of patients were diagnosed. But with the emergence of scintigraphy scans, patients, if they have a rule-out of monoclonal gammopathy, can be diagnosed with this non-invasive test rather than having to undergo a heart biopsy, which is an invasive procedure, and also a procedure that not every center has the capabilities to perform.

That increased awareness and access to a non-invasive means for diagnosis have really increased the diagnosis rates. I think if you couple that with the fact that we have therapies available that many groups are trying to use and automated screening protocols such as AI-assisted ECG and echocardiograms to identify patients with features that should warrant testing, those things have really helped to improve how we diagnose patients. And one thing that we see is that the trend is towards patients being diagnosed with earlier stages of disease. So, that's all been very encouraging, and hopefully that trend will continue.

That being said, we still do see many patients who present late and many patients who probably aren't diagnosed at all, so there's certainly a lot of work to do. I don't want to make it sound like we've solved the problem of how to diagnose this, but there's certainly been a lot of advances in the last 10 years.

From a treatment standpoint, we now have three FDA-approved drugs for ATTR cardiomyopathy and a number of trials for drugs in development. And so that's certainly modified this disease progression and led to improvement in outcomes. I think our understanding of the importance of non-ATTR disease modifying therapies has come to the forefront as well.

So we've gotten better at managing the heart failure associated with ATTR-CM, really optimizing diuretics, and then also appreciating the importance of rhythm control. And so many increasingly use atrial fibrillation ablations, for example, to manage atrial arrhythmias and a number of other things that have really helped us manage the heart failure arrhythmia burden of ATTR-CM. It's been complementary to the medical management that's emerged for the disease modifying therapies.

There's a number of therapies in drug development. There are some that are related to what we currently have. So when we look at therapies that decrease the production of transthyretin—silencers or knockdown agents—we have vutrisiran, which is currently FDA-approved. There's an antisense oligonucleotide, eplontersen, that's been in phase 3 clinical trials for a few years now, and we anticipate the results of that trial soon. There is a gene editing trial using CRISPR-Cas9 technology to decrease the production of transthyretin, which has been in clinical trials. So there's been advances in terms of lowering TTR to greater depth and with less frequent drug administration.

In addition to these therapies, there's been development of a number of monoclonal antibodies with the intent of removing amyloid from

heart tissue. These are what we call transthyretin depleters. They bind to different epitopes on the transthyretin fibril with the intention of clearing amyloid fibrils from the heart through macrophage mediated phagocytosis. So, there are a number of drugs being studied in various phase 2 and 3 clinical trials, and I think that that will be potentially a novel and third mechanism of action for how we approach this disease.

Host:
That was Dr. Kevin Alexander discussing updates in the treatment of ATTR-CM. To access this and other episodes in our series, visit *Heart Matters* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!