Transcript Details

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Treating ATTR-CM: Current Strategies and Emerging Options

Announcer:
You're listening to *Heart Matters* on ReachMD. On this episode, we'll hear from Dr. Frederick Ruberg, who's the Thomas J. Ryan Professor of Cardiovascular Medicine and a Professor of Radiology at Boston University Chobanian and Avedisian School of Medicine as well as the Chief of Cardiovascular Medicine at Boston Medical Center. He'll be discussing current and emerging treatment strategies for transthyretin amyloid cardiomyopathy, or ATTR-CM. Let's hear from Dr. Ruberg now.

Dr. Ruberg:
Treatment for ATTR cardiac amyloidosis involves two principal strategies in 2025. One involves agents that stabilize the TTR tetramer and keep it from breaking apart, misfolding, and causing amyloid. And the other strategy is to silence or turn off TTR production. Tafamidis is a TTR tetramer stabilizer that was approved in 2019 for cardiac amyloidosis. It was approved on the strength of the ATTR-ACT trial that was published in *The New England Journal of Medicine*. Tafamidis, when administered to individuals with cardiac amyloidosis, resulted in a significant mortality reduction from about 43 percent to about 29 percent. The drug was highly effective and very safe. In fact, it has a very favorable safety profile, and so on the strength of that, it was approved and had been, until 2024, the only approved therapy for cardiac amyloidosis.

In late 2024, another TTR stabilizer, acoramidis, was approved for cardiac amyloidosis. Acoramidis efficacy was demonstrated in the ATTRibute-CM clinical trial that was published in 2023 in *The New England Journal of Medicine*. And looking at something called a win ratio analysis, acoramidis resulted in improved survival, hospitalization, and burden of disease as measured by proBNP worsening and six-minute walk distance decrement. So on the strength of the ATTRibute-CM trial, acoramidis was approved.

Both of these agents are most effective if administered early on the course of therapy. Patients who have less significant cardiac amyloidosis, as determined by cardiac biomarkers, biomarker staging, or other measurements, such as extracellular volume by cardiac MRI or global longitudinal strain by echo—patients with more favorable values respond better to these agents. So there's a strong push to identify people early in the course of disease where we know these agents are more likely to be effective.

We expect the approval of one of the TTR-silencing strategies, vutrisiran, sometime in 2025 based on the strength of a clinical trial called HELIOS-B that was published in *The New England Journal of Medicine* in 2024. The drug vutrisiran improved survival and hospitalization for patients with cardiac amyloidosis compared to placebo. On the strength of the HELIOS-B trial, we expect that vutrisiran will likely also be approved.

In addition, in clinical trial now, there is a strategy using a CRISPR-Cas9 approach that will permanently silence TTR production. This agent is called nex-z, and the clinical trial is called MAGNITUDE. It's presently enrolling. The promise of nex-z is it's a single administration that permanently silences TTR, which then would not require recurrent administration of either an oral therapeutic like tafamidis or acoramidis or a silencer like vutrisiran.

One other point from the therapeutic standpoint is there's a lot of excitement around antibodies that bind to TTR and facilitate reabsorption. There are two antibodies—one in clinical trial and one soon to be in clinical trial. ALXN2220 is in the trial called DepleTTR-CM, and another agent called coramitug is also approaching clinical trial. These agents work by facilitating the reabsorption of deposited amyloid so that if a patient already has cardiac amyloidosis, the approach can be to remove the deposited amyloid and, we hope, improve the phenotype.

Announcer:
That was Dr. Frederick Ruberg discussing the treatment of transthyretin amyloid cardiomyopathy. To access this and other episodes in

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