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Rebalancing Amyloid in ATTR-CM: Emerging Therapeutic Insights

Dr. Blevins:

Transthyretin amyloid cardiomyopathy, or ATTR-CM, has primarily been thought of as a problem of protein misfolding. Transthyretin—a transport protein made largely in the liver—destabilizes, dissociates into monomers, misfolds, and aggregates into amyloid fibrils that deposit in the myocardium. The result is progressive stiffening, impaired filling, and ultimately heart failure.

But a new review in the *European Heart Journal* encourages us to see something more dynamic.

This is *AudioAbstracts* on ReachMD. I'm Dr. Hallie Blevins, and today, I'll be talking about how ATTR-CM may be driven by the imbalance between amyloid production and clearance.

Imaging modalities like serum amyloid P scintigraphy and cardiac magnetic resonance extracellular volume mapping show that amyloid burden isn't static. It's not just accumulating passively; it reflects a continuous tug-of-war between ongoing amyloid production and the body's attempt to clear it. But clearance of amyloid is very slow, and the speed at which amyloid is cleared varies per person and depending on the organ. The heart, unfortunately, appears to be particularly inefficient at clearing amyloid.

So, how are we intervening?

First, we can stabilize the protein. Tafamidis is the first disease-modifying example of this. In the phase three ATTR-ACT trial, tafamidis reduced all-cause mortality and cardiovascular hospitalizations by roughly 30 percent compared with placebo. However, survival curves didn't meaningfully diverge until about 18 months—and that's an important reminder that these therapies require time. We also saw a slower decline in functional capacity and quality of life, and long-term extension data suggested a 36 percent lower mortality in patients with New York Heart Association class three symptoms who remained on continuous therapy.

Acoramidis is another TTR stabilizer that takes stabilization further, achieving near-complete tetramer stabilization. In the phase three ATTRibute-CM trial, it significantly improved a hierarchical composite endpoint including mortality, cardiovascular hospitalizations, change from baseline in NT-proBNP, and a change in baseline in six-minute walk distance.

Interestingly, circulating TTR levels increased compared to patients receiving placebo and tafamadis, which raises the question of whether TTR concentration could serve as a biomarker of therapeutic effect for TTR stabilization. That's a fascinating possibility, but we don't yet know how well it correlates with clinical outcomes. However, the authors draw parallels with AL and AA amyloidosis, where suppression of serum TTR correlates with improved survival.

And that hypothesis seems intuitive: the lower the circulating TTR, the better the outcome. But in ATTR-CM, that direct association hasn't yet been demonstrated.

Another approach is to reduce production at the source. If stabilizers prevent dissociation, gene silencers reduce the total substrate. Patisiran is a small interfering RNA that blocks the synthesis of TTR at the mRNA level. In APOLLO-B, patisiran significantly slow decline in six-minute walk distance and KCCQ overall summary score over 12 months.

Vutrisiran is mechanistically similar to patisiran, but it's delivered stronger signals. In the phase three HELIOS-B trial involving 655 patients, vutrisiran significantly reduced the risk of all-cause mortality and recurrent cardiovascular events over 36 months and preserved functional capacity and quality of life.

And then there's inhibiting TTR synthesis using gene editing. Nexiguran ziclumeran—using CRISPR–Cas9 technology—was evaluated in a phase one open-label study of 36 patients. A single infusion achieved an 89 percent mean reduction in serum TTR at 28 days, and

that reduction was sustained at 90 percent at 12 months. Biomarkers like NT-proBNP and troponin T remained stable, as did NYHA class and CMR measures—that's notable when you consider the expected natural decline in untreated ATTR-CM patients. It's early data, but it raises a compelling possibility that a one-time intervention could alter disease trajectory.

Other genetic therapeutic approaches include small interfering RNA and antisense oligonucleotides, which promote degradation of mRNA prior to TTR protein synthesis.

Enhancing the clearance of amyloid is another target. Monoclonal antibodies like ALXN2220 target misfolded TTR within deposits and signals ATTR aggregates for removal via phagocytosis. In a first-in-human, randomized, double-blind, placebo-controlled phase one trial of 40 patients, higher doses were associated with reductions in cardiac extracellular volume, suggesting actual amyloid removal. Biomarkers trended favorably, and safety was acceptable. And ALXN2220 is currently being investigated in a phase three trial.

So we now have stabilizers, silencers, gene editors, and emerging antibody therapies. As the therapeutic landscape continues to expand, the take-home message here is that ATTR-CM may not simply be a disorder of production—it may be a problem of balance. And if we can tip that balance decisively toward clearance, we may change the trajectory of this disease.

This has been an *AudioAbstract*, and I'm Dr. Hallie Blevins. To access this and other episodes in our series, visit ReachMD dot com, where you can Be Part of the Knowledge. Thanks for listening!

References

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