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Exploring Deeper Silencing in Transthyretin Amyloidosis

Ryan Quigley:

For clinicians following the rapidly evolving landscape of transthyretin amyloidosis, also known as ATTR, one key question has persisted in the background of small interfering RNA therapy development: does deeper transthyretin suppression actually matter, and are all silencers equally effective at achieving it?

You're listening to *AudioAbstracts* on ReachMD. I'm Ryan Quigley, and today, we're taking a closer look at a new observational crossover study published in *Circulation,* which compared sequential treatment with patisiran and vutrisiran in patients with variant ATTR amyloidosis.

The study focused on serum transthyretin, or sTTR—the circulating precursor protein that drives amyloid deposition in ATTR. Both patisiran and vutrisiran are small interfering RNA therapies designed to silence hepatic TTR messenger RNA, thereby lowering production of transthyretin protein. Vutrisiran differs mechanistically through N-acetylgalactosamine conjugation, which enhances targeted delivery to hepatocytes and allows for quarterly subcutaneous dosing.

Rather than asking whether these agents work—a question already addressed in phase three trials—the investigators explored whether switching patients from patisiran to vutrisiran leads to even greater suppression of circulating TTR.

The analysis drew from TRANSCEND, a long-term observational study conducted at the United Kingdom National Amyloidosis Centre. Investigators evaluated 112 patients with variant ATTR polyneuropathy who had received both therapies sequentially: patisiran between 2016 and 2023, followed by vutrisiran once it became available in the UK.

Most patients also had cardiac involvement, with 85 percent carrying concomitant ATTR cardiomyopathy. Disease severity ranged across polyneuropathy disability stages, creating a clinically heterogeneous cohort reflective of real-world practice.

Importantly, this was not a randomized trial. Patients effectively served as their own crossover controls. Investigators compared serum TTR levels before treatment, after patisiran, and again after transition to vutrisiran. Those receiving TTR stabilizers or other gene silencers were excluded.

The laboratory endpoint itself is worth emphasizing. Serum TTR concentration functions as a pharmacodynamic marker of gene silencing activity. In amyloidosis, the logic is straightforward: less circulating precursor protein may translate into less amyloid formation over time. That paradigm has been established in AL and AA amyloidosis, though its precise clinical implications in ATTR remain under active investigation.

But the findings were remarkably consistent. Baseline mean serum TTR concentration was 210 milligrams per liter. Following patisiran therapy, mean post-treatment levels fell to 38 milligrams per liter, representing an 80 percent reduction from baseline. After switching to vutrisiran, mean levels declined further to 13 milligrams per liter—a 93 percent reduction. Both absolute and percentage reductions significantly favored vutrisiran.

One of the most striking observations involved near-complete suppression. Serum TTR levels below the assay detection threshold occurred in just 13.1 percent of post-patisiran samples, compared with 58.8 percent of post-vutrisiran samples. Overall, 90 percent of patients achieved lower TTR concentrations after transitioning to vutrisiran.

The investigators also attempted to address an important potential confounder: declining nutritional status, which can independently lower transthyretin levels. By comparing the final post-patisiran measurement with the first post-vutrisiran sample, they still observed an

additional 33 percent reduction associated with vutrisiran, supporting a genuine drug-related effect.

A linear mixed-effects model adjusting for time since dosing further reinforced the signal, showing significantly lower mean sTTR concentrations with vutrisiran versus patisiran, with an average difference of minus 27 milligrams per liter.

So, what do these results mean clinically? It's not clear quite yet; the study stops short of proving superior clinical outcomes with deeper TTR suppression, and the authors are appropriately cautious about that distinction. This was a retrospective, single-center observational analysis without randomization, and patients were not allowed to return to baseline TTR levels before switching therapies.

Still, the data raise an increasingly relevant therapeutic question: if profound TTR suppression is biologically desirable, should clinicians begin thinking beyond "effective" suppression and towards "maximal" suppression?

For clinicians involved in systemic amyloidosis care, the broader takeaway may be less about one drug outperforming another and more about the emerging importance of precision pharmacodynamics in ATTR management, like N-acetylgalactosamine conjugation in vutrisiran.

Prospective studies linking suppression depth with neurologic and cardiovascular outcomes will ultimately determine how much these laboratory differences matter in practice. But for now, this crossover analysis offers one of the clearest real-world signals that not all TTR silencing may be equivalent.

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

Reference:

Razvi Y, Rauf MU, Porcari A, et al. Efficacy of Suppression of Serum Transthyretin With Patisiran and Vutrisiran in Variant ATTR Amyloidosis: An Observational Crossover Study. *Circulation*. 2026;153(5):364-366. doi:10.1161/CIRCULATIONAHA.125.076330