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Transforming amyloidosis care: a new era of targeted therapies

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Take Home Messages

- Cardiac amyloidosis is underdiagnosed and can lead to debilitating heart failure and poor survival.
- Vutrisiran, a gene silencing treatment, was shown in the HELIOS-B trial to significantly reduce the risk of death and recurrent cardiovascular events in patients with transthyretin cardiac amyloidosis.
- Gene editing holds promise as a treatment option for cardiac amyloidosis.
- Future therapy may combine gene silencers with amyloid-fibril clearing agents such as monoclonal antibodies.

Background

Transthyretin (ATTR) amyloidosis is a systemic disorder particularly affecting the heart and nerves resulting from the misfolding and aggregation of transthyretin (TTR) protein into amyloid fibrils. Cardiac amyloidosis can lead to debilitating heart failure, arrhythmias, and poor survival, with a median life expectancy of 2–6 years following diagnosis (1). Although TTR stabilisers like tafamidis have been demonstrated to slow disease progression, emerging gene-silencing therapies are revolutionising the treatment landscape (2,3) . These therapies target TTR protein production at the genetic level, providing more potent disease modification. The recently completed HELIOS-B trial highlights the efficacy of a gene silencer, vutrisiran, in ATTR amyloidosis and cardiomyopathy, advancing hopes for improved outcomes in this challenging condition (4).

ATTR amyloidosis and vutrisiran

ATTR amyloidosis manifests in two forms: hereditary (hATTR), caused by mutations in the *TTR* gene, and wild-type (wtATTR), which is of unclear aetiology but may relate to the normal aging process.

Vutrisiran employs RNA interference (RNAi) targeting wild-type and mutant *TTR* mRNA to

reduce TTR protein production in hepatocytes. Its chemical structure allows for quarterly subcutaneous dosing, simplifying treatment compared to earlier RNAi therapies like patisiran which is administered intravenously once every three weeks(5).

HELIOS-B trial results

The HELIOS-B trial is a groundbreaking Phase 3 study evaluating vutrisiran's efficacy in patients with ATTR cardiomyopathy (ATTR-CM), including both hereditary and wild-type forms. This double-blind, placebo-controlled trial enrolled 655 patients randomised to receive vutrisiran (25 mg) or placebo every 12 weeks for up to 36 months (4). Mean age was 76 years with 7% female, and 40% taking tafamidis at baseline.

- Primary Endpoint: Vutrisiran led to a 28% relative risk reduction in the composite endpoint of all-cause mortality and cardiovascular events (HR: 0.72; 95% CI: 0.56–0.93; $P = 0.01$).
- Mortality Benefit: All-cause mortality was reduced by 35% at 42 months (HR: 0.65; 95% CI: 0.46–0.90; $P = 0.01$).
- Functional Capacity: Baseline mean 6MWT on vutrisiran was 372m and 377m in the placebo arm. Vutrisiran slowed the decline in 6-minute walk test (6MWT) performance compared to placebo, with a significant mean difference of 26.5 metres (95% CI: 13.4–39.6; $P < 0.001$).
- Quality of Life: Vutrisiran significantly mitigated the deterioration in Kansas City Cardiomyopathy Questionnaire (KCCQ-OS) scores, with a mean difference of 5.8 points (95% CI: 2.4–9.2; $P < 0.001$).

Subgroup analyses showed consistent benefits across age, baseline disease severity, and ATTR type (wild type vs. hereditary). Importantly, vutrisiran preserved quality of life and reduced cardiovascular hospitalisations even in patients receiving background tafamidis therapy. The HELIOS-B results mark a significant milestone for RNAi therapies in ATTR-CM, confirming that vutrisiran slows disease progression, and improves clinical outcomes in ATTR-CM (4). However, vutrisiran is not yet licensed for ATTR-CM in the UK, Europe or the USA.

Future therapeutic directions

ATTR-CM therapies may include monoclonal antibodies, gene editing and gene silencers (Figure 1). Combining gene-silencers with TTR stabilisers or amyloid fibril-clearing agents may offer synergistic benefits. Integrating vutrisiran with tafamidis or monoclonal antibodies could address both TTR production and fibril accumulation.

Gene silencers – what's next in ATTR-CM?

Future RNAi therapies may offer greater potency and convenience by improving delivery systems and providing a longer duration of action. Additionally, antisense oligonucleotides like eplontersen represent complementary approaches for silencing *TTR* mRNA (6). A phase 3 cardiovascular outcomes study of eplontersen compared with placebo in ATTR-CM has completed enrolment and permits concomitant treatment with tafamidis (7,8).

Monoclonal Antibodies

These agents target and clear existing amyloid fibrils, potentially reversing organ damage. NI301A is a human monoclonal antibody that binds to the linear epitope WEPFA, which is only accessible on misfolded ATTR deposit. This triggers phagocytosis of ATTR aggregates by macrophages and accelerates fibril removal. NI301A is currently undergoing a Phase I clinical trial in patients with ATTR-CM (9).

Gene Editing

Early studies in polyneuropathy suggest gene editing using CRISPR-Cas9 could permanently silence *TTR* expression reducing its production in the liver, offering a one-time curative treatment (10). In a phase 1 study involving patients with ATTR-CM, gene editing with a single

dose of nexiguran ziclumeran was associated with consistent and rapid reductions in serum TTR levels (11).

Conclusions

The HELIOS-B trial has demonstrated that vutrisiran is a highly effective therapy for ATTR-CM, with significant reductions in mortality, cardiovascular events, and improvements in functional outcome measures (4). By silencing TTR production, vutrisiran offers a disease-modifying treatment with long-term benefits for patients.

The future of ATTR amyloidosis therapy will likely build on this success through combination strategies, fibril-clearing agents, and gene-editing technologies, paving the way for improved survival and quality of life for patients globally.

Disclosures

None to report.

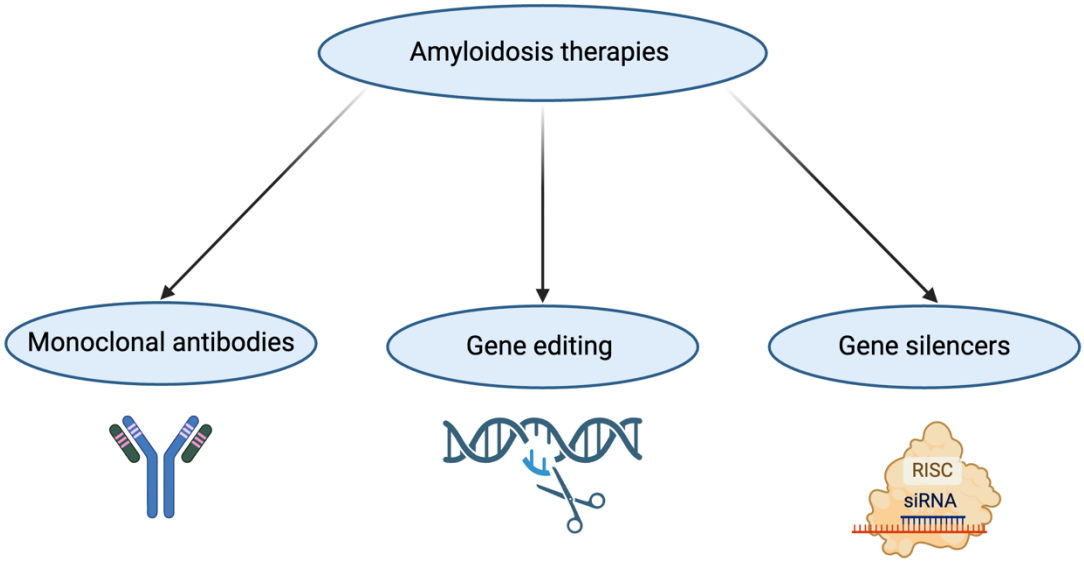

Figure 1 Emerging amyloidosis therapies for ATTR-CM. Monoclonal antibodies act by targeting and clearing amyloid fibrils. Gene editing using CRISPR-Cas9 works by cutting

DNA at a specific location preventing production of TTR. Vutrisiran, a gene silencing siRNA, causes degradation of *TTR* mRNA through RNA interference by binding and silencing mRNA. This is an original figure created with Biorender.com. *ATTR-CM, transthyretin amyloidosis cardiomyopathy; RISC, RNA-induced silencing complex; siRNA, small interfering RNA; TTR, transthyretin.*

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