Transthyretin Amyloidosis: From Disease Mechanisms to Emerging Therapeutic Innovations

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Introduction

Transthyretin amyloidosis (ATTR) is a progressive and life-threatening disorder characterized by the misfolding of transthyretin (TTR) proteins into amyloid fibrils, leading to systemic deposition in various organs and tissues (Jain & Zahra, 2023). Over time, these deposits lead to organ dysfunction, with clinical manifestations including neuropathy, cardiomyopathy, and autonomic dysfunction, which significantly reduces patients' quality of life (Jain & Zahra, 2023). Patients with ATTR often experience symptoms such as progressive fatigue, shortness of breath, numbness or tingling in the extremities, and difficulty with mobility, which can significantly impact daily functioning and independence. Without timely diagnosis and treatment, ATTR is fatal, with life expectancy ranging between 3 to 15 years after initial symptom onset (Delgado et al., 2025). Despite recent therapeutic advancements, limitations in diagnosis, treatment efficacy, and accessibility continue to pose major challenges. This article will explore the pathophysiology, its clinical relevance, current treatment strategies, and emerging therapeutic approaches for ATTR.

What is ATTR & Pathogenesis?

Transthyretin (TTR) is a transport protein in the blood primarily synthesized in the liver (accounting for up to 95% of circulating TTR) with a smaller portion produced in the choroid plexus of the brain (Sanguinetti et al., 2022). Structurally, TTR exists as a homotetramer composed of four identical monomers, which provides stability and enables its function in transporting thyroxine (T4) and retinol indirectly through retinol-binding protein (Yee et al., 2019). In ATTR, this stability is compromised, leading to dissociation into monomers that misfold and aggregate into insoluble ?-sheet-rich amyloid fibrils (Yee et al., 2019). These fibrils deposit in tissues and lead to progressive organ dysfunction, most notably in the heart and peripheral nervous system, resulting in restrictive cardiomyopathy, arrhythmias, and neuropathy (Maurer et al., 2019).

ATTR exists in two main forms: hereditary ATTR (hATTR), caused by autosomal dominant mutations in the TTR gene, and wild-type ATTR (wtATTR), which occurs in the absence of mutations and is associated with age-related protein instability (Karam et al., 2024). In hereditary ATTR, over 130 mutations have been identified in various ethnic groups, each influencing disease onset and severity (Griffin et al., 2021). Common variants such as V30M are associated with early-onset neuropathy, while V122I is strongly linked to cardiac involvement (O'Dea, 2020; Connors et al., 2009). In contrast, wild-type ATTR occurs due to age-related destabilization of TTR and is frequently observed in individuals over 60 years old (Ruberg & Berk, 2012).

Prevalence & Clinical Relevance

ATTR manifests primarily as transthyretin amyloid cardiomyopathy (ATTR-CM) or transthyretin amyloid polyneuropathy (ATTR-PN) (Rintell et al., 2021). ATTR-CM is the more prevalent form and affects approximately 300,000-500,000 individuals globally, leading to restrictive cardiomyopathy and heart failure (Jain & Zahra, 2023; Alexion Pharmaceuticals, Inc., 2025). It occurs in both hereditary and wild-type forms, with wtATTR being more common in older males (Cleveland Clinic, 2026). ATTR-PN, although less prevalent, significantly impacts the peripheral and autonomic nervous systems, resulting in progressive sensory and motor impairment (Rintell et al., 2021).

Due to overlapping symptoms with more common conditions such as heart failure with preserved ejection fraction or peripheral neuropathy, ATTR is frequently misdiagnosed, contributing to delayed diagnosis and poorer clinical outcomes (Maurer et al., 2019). This pattern reflects a form of mismedicine, a concept developed by Dr. Pooya Beigi, which describes medical acts that result in harm, inefficiency, or failure to meet the standard of care across diagnostic, therapeutic, and systemic levels (Blissy, 2024).

Delayed or incorrect diagnosis allows continued amyloid deposition and disease progression, reducing the effectiveness of available therapies. In addition, disparities in treatment access represent another form of mismedicine, as high-cost therapies such as tafamidis and gene silencing agents can exceed hundreds of thousands of dollars annually, limiting availability and contributing to inequities in care (Kazi et al., 2020). Furthermore, current treatments primarily slow disease progression but do not remove existing amyloid deposits, meaning patients may continue to experience clinical decline despite therapy. These factors highlight systemic and therapeutic gaps that contribute to suboptimal outcomes in ATTR management.

Current Treatments

There is currently no cure for ATTR; existing treatment strategies aim to maintain TTR stability or reduce its production. The pharmacological approach includes TTR stabilizers such as tafamidis, which is an oral therapy for early-stage ATTR-CM and ATTR-PN by preventing tetramer dissociation, the rate-limiting step in amyloid fibril formation (Morfino et al., 2023). The ATTR-ACT Phase 3 trial conducted on 441 patients, demonstrated a 30% reduction in all-cause mortality and 32% reduction in cardiovascular-related hospitalizations over 30 months, along with improved exercise capacity and quality of life (Maurer et al., 2018; Griffin et al., 2021). However, these therapies do not remove pre-existing amyloid deposits and are associated with high costs, limiting accessibility (Kazi et al., 2020).

Gene silencing therapies, including RNA interference agents such as patisiran and vutrisiran (administered via intravenous infusion and subcutaneous injection, respectively), and antisense oligonucleotides such as inotersen (administered via subcutaneous injection), reduce hepatic TTR synthesis at the genetic level, thereby lowering the amount of circulating TTR available for amyloid fibril formation (Brannagan et al., 2022). These therapies have demonstrated significant

reductions in circulating TTR levels and improvements in neuropathy and functional outcomes (Adams et al., 2017; Adams et al., 2022). Despite their effectiveness, they require lifelong administration and are associated with potential adverse effects, including thrombocytopenia, nephrotoxicity, and liver-related concerns (Ioannou et al., 2023). Additionally, their high cost presents a major barrier to access with patisiran and inotersen both priced at approximately $450,000 per year, making accessibility difficult (Institute for Clinical and Economic Review, 2018).

Liver transplantation was historically considered a treatment option for hereditary ATTR by eliminating the primary source of mutant TTR production (Casasnovas et al., 2023). While it can slow disease progression, it does not remove existing amyloid deposits and carries significant risks, including surgical complications, lifelong immunosuppression, and limited donor availability (Herlenius et al., 2004; Carvalho et al., 2015). As a result, it is no longer considered a first-line therapy.

Emerging Innovations

Recent advances in therapeutic development have introduced several emerging strategies aimed at overcoming the limitations of current ATTR treatments. One promising approach is CRISPR-based gene editing, which targets the transthyretin (TTR) gene directly in hepatocytes to reduce or eliminate production of the misfolded protein. In vivo CRISPR therapies have demonstrated reductions in circulating TTR levels, with early studies reporting reductions of over 85-90% following a single administration (Tahir et al., 2026). Similarly, newer CRISPR systems such as CRISPR-Cas3 have shown the ability to induce targeted gene deletions in experimental models of transthyretin amyloidosis, further supporting the potential for long-term or permanent therapeutic effects (Ishida et al., 2026). These findings suggest that gene editing may provide a one-time, disease-modifying treatment rather than requiring lifelong therapy.

In addition to gene editing, emerging research has explored targeted protein degradation strategies such as lysosome-targeting chimeras (LYTACs). These molecules are designed to bind extracellular protein aggregates and direct them toward lysosomal degradation pathways (Liu et al., 2023). Recent studies have demonstrated that LYTAC-based systems can selectively recognize and degrade extracellular amyloid fibrils through receptor-mediated endocytosis and lysosomal trafficking (Liu et al., 2023). Although current research has primarily focused on amyloid-? plaques in Alzheimer's disease, this approach may have broader applications in diseases such as ATTR that involve pathological protein deposition.

Conclusion

Transthyretin amyloidosis is a complex and progressive disease characterized by protein misfolding and systemic amyloid deposition, leading to significant morbidity and mortality. While current therapies such as TTR stabilizers and gene silencing agents have improved disease

management, they are limited by high cost, accessibility issues, and an inability to remove existing amyloid deposits. In addition, delayed diagnosis and systemic barriers to care contribute to ongoing mismedicine in ATTR. Emerging therapeutic strategies, including gene-editing approaches such as CRISPR-based therapies and targeted protein degradation strategies such as LYTACs, offer promising potential to address these limitations. Future advancements in treatment and earlier diagnosis will be critical in improving patient outcomes and reducing the burden of disease. In this context, continued innovation paired with earlier diagnosis, improved affordability, and more equitable access to care may also play an important role in reducing mismedicine by addressing systemic gaps that contribute to delayed recognition and treatment of ATTR.

Key Questions & Answers

What is transthyretin amyloidosis (ATTR)?

ATTR is a progressive disease caused by the misfolding of transthyretin (TTR) proteins, which form amyloid fibrils that deposit in organs like the heart and peripheral nerves, leading to organ dysfunction.

What are the main types of ATTR?

There are two main types: hereditary ATTR (hATTR), which is caused by mutations in the TTR gene, and wild-type ATTR (wtATTR), which occurs without mutations and is mainly associated with aging.

Why is ATTR often misdiagnosed?

ATTR is often misdiagnosed because its symptoms overlap with more common conditions such as heart failure or peripheral neuropathy, which can delay diagnosis and treatment.

What are the current treatment options?

Current treatments focus on stabilizing the TTR protein or reducing its production. These include TTR stabilizers like tafamidis and gene silencing therapies such as patisiran, vutrisiran, and inotersen.

What are some emerging therapies for ATTR?

Emerging therapies include CRISPR-based gene editing, which aims to reduce TTR production long-term, and LYTACs, which are being explored as a way to help remove existing amyloid deposits.

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