ATTR-CM Management: Evolution from Symptomatic to Disease-Modifying

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> Amyloid transthyretin cardiomyopathy (ATTR-CM) historically presented a significant clinical challenge, with management largely confined to symptomatic relief and supportive care. The immediate takeaway for clinicians is that the landscape has fundamentally changed, with specific therapies now available that address the underlying pathophysiology, offering improved patient outcomes.

KEY TAKEAWAYS

- The Pivot: ATTR-CM management has transitioned from symptomatic treatment to disease-modifying therapies targeting transthyretin stabilisation or degradation.
- The Data: Early intervention with TTR stabilisers has demonstrated reductions in all-cause mortality and cardiovascular-related hospitalisations.
- The Action: Clinicians should pursue early diagnosis of ATTR-CM and consider initiating disease-modifying therapies in eligible patients.

ATTR-CM is a progressive and often fatal cardiomyopathy caused by the misfolding and extracellular deposition of transthyretin (TTR) protein as amyloid fibrils in the myocardium. This deposition leads to restrictive cardiomyopathy, heart failure, and arrhythmias. Historically, treatment focused on managing the symptoms of heart failure, such as diuretics for fluid overload and antiarrhythmics for dysrhythmias. However, these approaches did not address the root cause of the disease, leading to a poor prognosis with a median survival of approximately 2 to 6 years from diagnosis, depending on the subtype (wild-type or hereditary).

Evolution of ATTR-CM Therapy

The understanding of ATTR-CM pathophysiology has advanced significantly, leading to the development of therapies that target the production or stability of the TTR protein. The first major therapeutic breakthrough involved TTR stabilisers. These agents bind to circulating TTR, preventing its dissociation into monomers, which is a prerequisite for misfolding and amyloid fibril formation. This mechanism reduces the deposition of new amyloid fibrils and can slow disease progression. Clinical trials evaluating these stabilisers demonstrated a reduction in all-cause mortality and cardiovascular-related hospitalisations compared to placebo. For example, a pivotal study showed a 30% reduction in the composite of all-cause mortality and cardiovascular-related hospitalisations (HR 0.70, 95% CI 0.58-0.83, P 0.001) over 30 months in patients with ATTR-CM.

Following the introduction of TTR stabilisers, further advancements emerged with gene-silencing therapies. These treatments target the messenger RNA (mRNA) responsible for TTR production in the liver, thereby reducing the synthesis

of both wild-type and mutant TTR protein. By significantly lowering circulating TTR levels, these therapies aim to halt or even reverse amyloid deposition. Studies of these agents have shown substantial reductions in serum TTR levels, leading to improvements in neurological function in patients with ATTR polyneuropathy, and are being investigated for their cardiac benefits in ATTR-CM. The efficacy of these agents in reducing TTR production has been demonstrated with reductions of up to 80-90% in circulating TTR levels.

The current therapeutic landscape for ATTR-CM therefore includes both TTR stabilisers and gene-silencing agents. The choice of therapy often depends on the specific subtype of ATTR-CM (hereditary versus wild-type), the predominant organ involvement (cardiac versus neurological), and patient comorbidities. Early diagnosis is increasingly recognised as critical, as initiating disease-modifying therapy before extensive amyloid deposition occurs is associated with better long-term outcomes. Diagnostic pathways have also improved, with non-invasive techniques such as technetium-99m pyrophosphate (PYP) scintigraphy now widely used to diagnose ATTR-CM without the need for endomyocardial biopsy in many cases, particularly in the absence of a monoclonal gammopathy.

CLINICAL IMPLICATIONS

The shift in ATTR-CM management from palliative care to disease modification represents a significant advancement for patients. For years, clinicians were limited to managing the symptoms of a relentlessly progressive disease, often leading to frustration for both the patient and the care team. The availability of TTR stabilisers and gene-silencing therapies means that for the first time, we can intervene in the disease process itself, offering the prospect of improved quality of life and extended survival. This necessitates a heightened awareness among general practitioners and specialists to consider ATTR-CM in patients presenting with unexplained heart failure with preserved ejection fraction (HFpEF), particularly those with concomitant carpal tunnel syndrome, spinal stenosis, or peripheral neuropathy.

From an industry perspective, the development of these targeted therapies highlights the value of understanding disease pathophysiology at a molecular level. The investment in rare disease research, while often high-risk, has yielded substantial clinical benefits in this area. The competitive landscape among pharmaceutical companies developing ATTR-CM treatments is driving further innovation, with ongoing research into novel mechanisms of action, including amyloid fibril degradation. This competition, while beneficial for patients, also places a responsibility on guideline bodies and healthcare systems to ensure equitable access to these often high-cost therapies.

The impact on patients is profound. Where once a diagnosis of ATTR-CM carried a grim prognosis with limited options, there is now genuine hope. Patients can expect a more proactive approach to their care, with therapies that aim to preserve cardiac function and prevent further deterioration. However, the complexity of diagnosis and the need for specialised follow-up underscore the importance of multidisciplinary care teams. Ensuring that patients are referred to centres with expertise in amyloidosis remains paramount to optimise treatment initiation and long-term management.

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