Advantages and Emerging Problems of Novel Treatments for Transthyretin Cardiac Amyloidosis

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Transthyretin (TTR) cardiac amyloidosis (TTR-CA) is primarily caused by the accumulation of misfolded transthyretin in the heart and is of 2 types: hereditary transthyretin amyloidosis (hATTR), which develops through mutations in TTR; and wild-type transthyretin amyloidosis (wtATTR) without mutations, which occurs secondary to age-related protein misfolding. hATTR is also known as familial polyamylloid neuropathy (FAP), and it primarily presents with peripheral nerve numbness. Liver transplantation as well as TTR tetramer stabilizers are considered effective treatments. Currently, 20 mg tafamidis (Vyndaqel®; Pfizer) and patisiran (Onpattro®; Alnylam Pharmaceuticals) are available under insurance coverage in Japan. In contrast, wtATTR is also known as senile systemic amyloidosis because amyloid deposition in a variety of organs accelerates with aging and is more common in the elderly. It is commonly complicated by carpal tunnel syndrome and spinal canal stenosis. Because there was no effective treatment for this disease in the past, many physicians hesitated to diagnose wtATTR. In recent years, treatments that stabilize TTR have been reported to improve the survival rate of patients with TTR-CA and are attracting attention as novel treatment strategies. In line with these advances, more aggressive and accurate diagnosis has become necessary.

The pathophysiology of ATTR amyloidosis is shown in the Figure. Hepatocytes produce TTR monomers that are...
eventually synthesized into tetramers by the transcription of TTR mRNA. Tetramers dissociate into misfolded monomers that form insoluble ATTR amyloid fibrils. These amyloid fibrils are deposited in various organs such as the kidney, liver, tongue, intestine, and nerves, causing organ dysfunction. They also accumulate strongly in the heart, resulting in cardiac dysfunction and TTR-CA. The development of various therapeutic agents for TTA-CA is progressing, with the targets being the key processes involving in the pathogenesis.\textsuperscript{11,12} Small interfering RNA (siRNA)-based agents such as patisiran and inotersen bind to conserved sequences on TTR mRNA, leading to a decrease in TTR expression. Agents such as tafamidis, difunisal, tolcapone, and AG10 contribute to TTR tetramer stabilization, while doxycycline combined with taurourso-deoxycholic acid (TUDCA) and the monoclonal antibody PRX004 potentially remove ATTR deposits.

Of the aforementioned treatments, tafamidis and patisiran are the most common clinically studied drugs in humans. With regard to tafamidis, a phase 3, multicenter randomized controlled trial (ATTR-ACT) found that all-cause mortality and cardiovascular hospitalization rates were lower in the tafamidis group than in the placebo group.\textsuperscript{13} Furthermore, tafamidis delayed a decline in exercise capacity, evaluated on 6-min walk distance, and in quality of life (QOL), evaluated on Kansas City Cardiomyopathy Questionnaire-Overall Summary. On subanalysis, tafamidis was found to result in improvements in all-cause mortality and cardiovascular hospitalization in all subgroups (TTR genotype, baseline New York Heart Association [NYHA] class, and tafamidis dose) except in the NYHA III subgroup, in which the rate of cardiovascular hospitalization was not improved.\textsuperscript{13} Another phase 3, multicenter randomized controlled trial (APPOLO) that assessed the efficacy and safety of patisiran for patients with hATTR (FAP) showed that QOL and clinical neuropathy scores were significantly improved in the patisiran group.\textsuperscript{14} Furthermore, patisiran decelerated disease progression. On cardiac subgroup analysis, N-terminal pro B-type natriuretic peptide was significantly reduced in the patisiran group. More interestingly, patisiran significantly improved natriuretic peptide was significantly reduced in the patisiran group. Additionally, patisiran significantly improved cardiac quality of life (QOL), evaluated on Kansas City Cardiomyopathy Questionnaire-Overall Summary. On subanalysis, patisiran showed that QOL and clinical neuropathy scores were significantly improved in the patisiran group.\textsuperscript{14}

The aforementioned drugs have entered the clinical setting as innovative treatments for TTR-CA, which, previously, has had no effective treatment. They are remarkably expensive, however,\textsuperscript{15} and not very cost-effective, particularly for patients with wtATTR, many of whom are elderly. If the patient or family desires treatment, and if there are no reasonable contraindications other than the high cost, the attending physician may not hesitate to treat even a very elderly patient. The decision to proceed with treatment, however, can be made only on a case-by-case basis, and there are no uniform guidelines.\textsuperscript{15} Prescribing physicians are therefore certified on the basis of their experience in treating TTR-CA. Even an experienced physician, however, cannot easily decide on whether to introduce the drugs. Furthermore, the decision to treat involves several ethical considerations, and multiple physicians may be required to discuss the risks and benefits of introducing these drugs in each case.

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