

A designer drug for amyloid polyneuropathy

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There are frustratingly few specific treatments available for the 100-odd etiologies of polyneuropathy. Some notable exceptions aside (e.g., dapsone and rifampin for leprosy, IV immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy), symptomatic treatments, such as ankle-foot orthoses or drugs for neuropathic pain, form the bulk of the therapeutic armamentarium for polyneuropathy. Specific treatments are even more elusive in the genetic polyneuropathies. Recent hopes from animal models that vitamin C might be effective in type 1 Charcot-Marie-Tooth disease have been unrealized.¹ In this context, the report about tafamidis in familial amyloid polyneuropathy (FAP) in this issue of *Neurology*® is of particular interest.²

The amyloid polyneuropathies can be acquired or inherited, and they are classified according to the protein responsible for amyloid fibril formation. Proteins implicated in acquired amyloid neuropathy include immunoglobulin light chains, serum protein A, and β -2 microglobulin, whereas in the familial amyloid polyneuropathies (usually referred to as FAP) amyloid formation is a result of misfolding of mutant proteins, including transthyretin (TTR), apolipoprotein A-1, or gelsolin.³ The most common variety of FAP is due to dominantly inherited TTR gene mutations, the most prevalent of which results in substitution of methionine for valine at position 30 (p.M30V) in the 127-amino acid TTR polypeptide monomer.

TTR amyloidosis is particularly prevalent in Sweden, Japan, and the Oporto region of Portugal, although cases have been described worldwide. In endemic regions, the disease usually presents in the 30s as a distal painful sensory neuropathy followed by progressive autonomic and then motor dysfunction. Symptomatic cardiac involvement usually becomes evident within 7 to 8 years, and most patients succumb to heart failure or cardiac arrhythmias within 10 years of onset. As the mutated TTR is primarily generated in the liver, liver transplantation has been increasingly used as a treatment for TTR-

FAP. Randomized trials have not been performed, but there is a general consensus that liver transplantation does have an important and lasting benefit in this disease.⁴ However, cost, perioperative mortality, and the need for long-term immunosuppression are important drawbacks to transplantation.

TTR is a homotetrameric serum protein with binding sites for thyroxine and retinol A. Mutated TTR is unstable and dissociates into mutated TTR monomers, which readily misfold, aggregate, and deposit in tissues as β -pleated sheets of amyloid. An appreciation of this mechanism of amyloid formation led to the idea that if one could stabilize the mutated TTR tetramer, and inhibit its dissociation, this would reduce the availability of the amyloidogenic monomer, and thereby decrease amyloid formation and its deleterious consequences on peripheral nerve and heart.⁵ Tafamidis is a small molecule that occupies TTR's thyroxine binding sites and stabilizes both normal and mutated TTR tetramers, thus shifting the monomer-tetramer equilibrium away from the amyloidogenic monomers. But does this attractive biochemical hypothesis lead to improvement in human FAP?

In the trial reported in this issue of *Neurology*®, Coelho et al.² randomized 128 patients with V30M TTR-FAP to treatment with either tafamidis 20 mg daily or placebo for 18 months. Two primary outcome measures were used: the Neuropathy Impairment Score (a quantified neurologic examination) and a 35-item, patient-reported quality of life questionnaire. Using an intention-to-treat analysis, there was no significant change in either primary outcome measure in tafamidis-treated patients. The Neuropathy Impairment Score did improve, but the improvement fell slightly short of statistical significance. However, interpretation of these results is confounded by the unexpectedly high dropout rate (21%) in both the tafamidis and placebo groups due to liver transplantation (dropout patients were considered to be tafamidis nonresponders). If the transplant patients are removed from the analysis and only

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those who completed the trial are analyzed, patients treated with tafamidis experienced improvement in both primary outcome measures, which appears to be clinically meaningful. In essence, because of the high attrition rate, this otherwise meticulously conducted study proved to be underpowered. The efficacy of tafamidis in FAP is thus supported by Class II evidence, i.e., somewhat less compelling evidence than that provided by a flawless randomized controlled trial.

Looking beyond the present study, important questions about the role of tafamidis in transthyretin amyloidosis remain. What can be expected in patients treated beyond 18 months? Most importantly, what is the drug's effect on cardiac and autonomic function, impairment of which is the major cause of morbidity and mortality in most patients? Is tafamidis an alternative to liver transplantation, or should it be viewed as a temporizing measure, offering stability or even improvement of disease until liver transplantation can be performed? A clearer answer to the latter question will hopefully emerge as more long-term experience with tafamidis is gained.

Tafamidis is an important therapeutic advance, although transthyretin amyloidosis is a rare disease,

and few neurologists will have direct experience with affected patients. In a broader sense, however, the tafamidis story nicely illustrates how an understanding of polyneuropathy pathophysiology at a molecular level can lead to disease-specific therapies. More examples are sorely needed.

DISCLOSURE

The author reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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