

# Familial amyloidotic polyneuropathy: current and emerging treatment options for transthyretin-mediated amyloidosis

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**Abstract:** Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a fatal clinical disorder characterized by extracellular deposition of abnormal fibrils derived from misfolded, normally soluble transthyretin (TTR) molecules. The disease is most commonly caused by a point mutation within the TTR gene inherited in an autosomal dominant fashion. Over 100 of such mutations have been identified, leading to destabilization of the physiological TTR tetramer. As a result, many monomers originate with a tendency for spontaneous conformational changes and self-aggregation. The main clinical feature of TTR-FAP is progressive sensorimotor and autonomic neuropathy. In the beginning, this polyneuropathy predominantly involves small unmyelinated nerve fibers with the result of dissociated sensory loss disproportionately affecting sensation of pain and temperature. Autonomic neuropathy typically accompanies sensory deficits early in the disease course. The symptoms include orthostatic hypotension, constipation alternating with diarrhea, erectile dysfunction, anhidrosis, and urinary retention or incontinence. Later, involvement of motor fibers causes rapidly progressive weakness and gait disturbances. In addition to the peripheral nervous system, the heart and the gut are frequently affected. Onset of symptoms is bimodal, with one peak at age 33 years (early onset) and another distinct peak in the sixth decade of life (late onset). The course of TTR-FAP is uniformly progressive and fatal. Death occurs an average of 10.8 years after the onset of symptoms in Portuguese patients, and 7.3 years in late-onset Japanese patients. Common causes include cachexia, cardiac failure, arrhythmia, and secondary infections. Liver transplantation is the standard therapy for patients who are in a clinical condition good enough to tolerate this intervention because it stops progression of neuropathy by removing the main source of mutant TTR. Recently, orally administered tafamidis meglumine has been approved by European authorities for treatment of FAP. The substance has been shown to stabilize the TTR tetramer, thereby improving the outcome of patients with TTR-FAP. Various other strategies have been studied *in vitro* to prevent TTR amyloidosis, including gene therapy, immunization, dissolution of TTR aggregates, and free radical scavengers, but none of them is ready for clinical use so far.

**Keywords:** FAP, transthyretin, amyloidosis, treatment, therapy

## Introduction

Familial amyloidotic polyneuropathies (FAP) are a group of autosomal-dominantly inherited fatal neurodegenerative disorders caused by systemic extracellular deposition of amyloid. Various proteins are known to cause amyloidosis. In FAP, amyloid is composed of misfolded and fibrillary aggregated transthyretin (TTR) in the majority of cases. Rarely, genetically induced variants of apolipoprotein-A1 or gelsolin are precursors of hereditary neuropathic amyloidosis.<sup>1</sup> TTR, formerly called prealbumin, is a small soluble protein composed of 127 amino acids. Physiologically, it exists as

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a tetramer and serves, apart from thyroxine-binding globulin and albumin, as a transport protein for thyroxine in blood plasma and, with assistance of retinol-binding protein, of vitamin A. The main production site is the liver, but small amounts are also produced in the retina and the choroid plexus. Under physiological conditions, TTR already comprises eight beta-pleated sheets packed in an antiparallel, sandwich-like fashion, rendering the already native protein weakly amyloidogenic. By this way, wild-type TTR causes a condition known as senile systemic amyloidosis, or SSA. In TTR-associated FAP (TTR-FAP), a mutation in the TTR gene increases amyloidogenicity of TTR.

By now, over 100 point mutations in the TTR gene are known to cause instability of the tetramer. As a consequence, large amounts of monomers originate that are prone to unfold rapidly into a cross beta-sheet configuration.<sup>2</sup> These misfolded, beta-rich monomers, in turn, have a strong tendency for self-aggregation, leading to the formation of nonfibrillar oligomers, protofibrils, and fibrils. These fibrils are insoluble and deposit as amyloid in tissues. The process of fibril formation, rather than amyloid deposition itself, is cytotoxic and causes damage to various organs.<sup>3</sup>

## The clinical spectrum of TTR-FAP

The clinical disease most commonly starts with autonomic and peripheral nervous system symptoms. Additional organs involved in FAP include the gut, the heart, the eyes, and the kidneys. However, renal involvement is never as prominent as it is in light-chain (AL), serum amyloid A (AA) and apolipoprotein-A1 amyloidosis.<sup>4</sup> In these latter conditions, renal involvement manifesting as nephrotic syndrome is a leading feature that limits outcome. Many patients with TTR-FAP also suffer from carpal tunnel syndrome, which may be the presenting symptom with certain mutations preceding the full-blown disease by several years.<sup>5,6</sup> Very rarely, symptoms of the central nervous system may be present as the result of leptomeningeal amyloid deposition. In other patients, cardiac involvement with the result of cardiomyopathy or conduction disturbances may be a leading feature.<sup>7</sup> Such patients are often referred to as having familial amyloidotic cardiomyopathy, or FAC.

Polyneuropathy in FAP is of the length-dependent ascending type and typically starts with sensory disturbances in the toes, moving rapidly upwards to more proximal parts of the legs. By the time the knees are reached, the hands usually become involved. At the very beginning, sensory disturbances often show predilection for small unmyelinated fibers, which has been demonstrated by skin biopsy and

quantitative sensory testing.<sup>8,9</sup> As a consequence, sensation of pain and temperature is reduced, while light touch sensation and proprioception are relatively preserved. In addition, patients may have painful dysesthesias. In this early clinical stage, neurography and clinical examination, including tendon reflexes and vibration sense, may be normal or only slightly impaired. Autonomic disturbances are also present in early stages of the disease. Symptoms include diarrhea alternating with constipation, postprandial vomiting, orthostatic hypotension, sweating abnormalities, and bladder symptoms. In men, erectile dysfunction is an early feature. Eventually, large sensory and motor fibers are affected, and FAP is a pan-modality neuropathy resulting in progressive invalidating weakness and atrophy. Motor deficits also progress in a length-dependent manner, making walking increasingly difficult. Progression of motor deficit symptoms is rapid; within a few years, patients need walking assistance and use wheelchairs. Later on, they become malnourished and confined to bed. In patients with the Ala97Ser mutation, the chronic progressive course of FAP may be superimposed by episodes of rapid deterioration within weeks.<sup>9</sup> In advanced stages of FAP, muscle weakness and atrophy, weight loss, and orthostatic hypotension are cardinal clinical features. Death is reported to occur an average of roughly 10 years after onset of symptoms of FAP in various populations, and is usually due to cachexia or cardiac disturbances. However, disease duration onset to death may be as short as 7.3 years in late-onset Val30Met patients from nonendemic areas in Japan.<sup>10</sup>

A peculiar finding in FAP is bimodal onset of symptoms even with the same mutation. Portuguese patients with the common TTR-Val30Met mutation usually show first symptoms between the ages of 25 and 35 with a mean of 33.7 years. By contrast, in Swedish patients with the same mutation, symptoms start in the sixth or seventh decade. The oldest patient so far reported was 83 years old at the time of diagnosis.<sup>11</sup> The reason for the very different age of onset in Swedish and Portuguese patients is unknown. Different composition of amyloid fibrils, with fibrils composed of full-length TTR in the early-onset phenotype and presence of TTR fragments in the amyloid of late-onset patients, may be an explanation.<sup>12</sup> Subtle analyses revealed differences in the clinical picture between early- versus late-onset patients. Patients with late-onset may show less prominent autonomic features, more frequent cardiac involvement, lower penetrance, and a family history in only one third of patients.<sup>13,14</sup> Both misleading findings and phenotypical heterogeneity are frequent causes of misdiagnosis in late-onset FAP.<sup>6</sup> Detecting subclinical cardiac involvement may lead to the correct diagnosis.<sup>15</sup> Several

mutations apart from TTR-Val30Met typically present with late-onset FAP.<sup>1,9</sup> In such patients it is not unusual that they present as seemingly sporadic cases, despite the autosomal dominant trait of the mutation.

## Therapy

### Liver transplantation

Liver transplantation was introduced for treatment of TTR-FAP in 1990 to prevent amyloid formation.<sup>11</sup> It now has become standard therapy for FAP. The rationale for this intervention is that it removes the main source of variant TTR (vTTR). As a consequence, serum vTTR levels decline shortly after liver transplantation, and progression of FAP stops.<sup>16</sup> Survival is substantially prolonged in transplant patients compared to nontransplant patients.<sup>17</sup> Since FAP livers are functionally normal except for production of vTTR, they are often used for a subsequent graft in a patient in need of a liver transplantation. This procedure is called sequential or domino liver transplantation. By December 2010, a total of 1900 liver transplant recipients were recorded in the FAP World Transplant Registry with an actual rate of 110–120 transplantations per year.<sup>11</sup> According to this registry, the outcome is substantially better when liver transplantation is done early on in the course of the disease, for example in patients with a good body mass index and short time of symptoms.<sup>11</sup>

However, although liver transplantation improves the outcome of FAP patients, it has several major drawbacks. First, it is not feasible in older patients or those with advanced disease. Second, the outcome of liver transplantation is not as favorable in patients with non-Val30Met mutations compared with those with the Val30Met mutation,<sup>11</sup> and in patients with the Val30Met mutation, it does not prevent life-threatening arrhythmias.<sup>18</sup> Third, in some patients, the disease progresses after liver transplantation. The reason for this unexpected finding may be that wild-type TTR accumulates to pre-existing amyloid.<sup>19</sup> Likewise, ocular amyloidosis is known to progress after liver transplantation, presumably due to the fact that the retinal pigment epithelium continues to synthesize vTTR even after liver transplantation.<sup>20</sup> The risk of progression of both ocular and cardiac amyloidosis increases with age.<sup>20</sup> Fourth, it has become increasingly clear that de novo amyloidosis may occur after domino liver transplantation.<sup>21</sup> Finally, liver transplantation is a major surgical procedure requiring longstanding immunosuppression and medical surveillance. Thus, a medical treatment that can be administered in older patients, in patients with non-Val30Met variants, and in patients not eligible for transplant surgery, is

highly desirable and would allow treating patients who are not candidates for liver transplantation.

### Oral therapy – TTR-stabilizers

Since tetramer dissociation is the rate-limiting step in TTR amyloidosis, agents that stabilize TTR tetrameric structure can be expected to reduce amyloid production and, as a consequence, prevent or improve clinical disease.<sup>22</sup> To date, numerous substances that stabilize the TTR native state in vitro are known.<sup>3</sup> The strategy to prevent TTR amyloidogenesis by small molecules is referred to as small molecule kinetic stabilization.<sup>23</sup> For clinical use, only tafamidis meglumine has been approved by European regulative authorities, after a randomized, placebo-controlled, double-blind study had shown that neuropathy did not progress in 60% of FAP patients able to walk without assistance receiving this substance, versus 38% in the placebo group.<sup>23</sup> Tafamidis meglumine binds to the T4-binding sites of the tetramer, thereby preventing its dissociation into monomers. Diflunisal, a nonsteroidal anti-inflammatory drug already licensed, has also been shown to increase serum TTR stability beyond the levels of normal controls.<sup>24</sup> Two randomized multi-center clinical trials are underway to determine whether diflunisal will alter progression of TTR amyloidosis. Preliminary data also indicate that the combination of oral doxycycline 100 mg bid and tauroursodeoxycholic acid 250 mg tid stabilizes the disease for at least one year in the majority of patients with an acceptable toxicity profile.<sup>25</sup> Other nonsteroidal anti-inflammatory drugs bind to the T4 binding site of TTR as well, but there are concerns about achieving therapeutic serum concentrations, toxicity, and the pharmacologic profile for human application.<sup>3,26</sup>

### Other treatments

Gene therapy has been attempted with single stranded oligonucleotides to repair genomic DNA,<sup>27</sup> small interfering RNAs,<sup>28</sup> antisense oligonucleotides,<sup>29</sup> or cleavage by ribozymes.<sup>30</sup> Gene therapy is considered a promising future strategy for treatment of TTR amyloidosis; however, many considerations must be addressed before it can be applied clinically.<sup>3</sup>

Another approach is immunization with selected TTR mutants. In transgenic mice carrying the most common FAP variant, Val30Met, immunization with the highly destabilized Tyr78Phe TTR variant showed significantly reduced TTR deposition compared to age-matched controls.<sup>31</sup> Unfortunately, immunization-related inflammation precluded clinical application of this method so far.

4'-iodo-4'-deoxorubicin binds to several types of amyloid and introduces catabolism of amyloid deposits.<sup>32</sup> It has been shown to dissolve TTR amyloid in vitro,<sup>33</sup> but in vivo efficacy and tolerance has not been studied. Suhr et al attempted free radical scavenger therapy by administering 300 mg of N-acetylcystein, 300 mg of tocopherol, and 500 mg of vitamin C for 6 months. This regimen had no effect in non-transplanted TTR patients, but showed a slight increase in the nutritional status of transplanted patients.<sup>34</sup>

In conclusion, TTR-FAP is an autosomal-dominantly inherited fatal multi-system disease leading to death approximately 10 years after the onset of symptoms. Liver transplantation has become standard therapy for patients in a good clinical condition. Recently, tafamidis meglumine has been approved by European authorities for treatment of patients with polyneuropathy who do not require permanent use of crutches or a wheelchair. A variety of other treatment options have been proposed or experimentally studied. Two clinical trials are underway for the nonsteroidal anti-inflammatory drug, diflunisal.

## Disclosure

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