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## Monitoring and management of hereditary transthyretin amyloidosis with polyneuropathy

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### Abstract

Our aim in this review is to discuss current treatments and investigational products for patients with hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) and to provide suggestions for monitoring disease progression and treatment efficacy. We will explore the effectiveness of existing therapies, including pharmacological interventions and gene-silencing treatments, as well as emerging therapies currently under investigation. Additionally, we will address best practices for monitoring patients, including the use of biomarkers, imaging techniques, and clinical assessments to track disease progression and evaluate treatment responses. By synthesizing the latest research and clinical guidelines, we hope to offer a comprehensive resource for healthcare professionals managing ATTRv-PN.

**Keywords:** Polyneuropathy, transthyretin, amyloid, transthyretin stabilizers, gene silencers

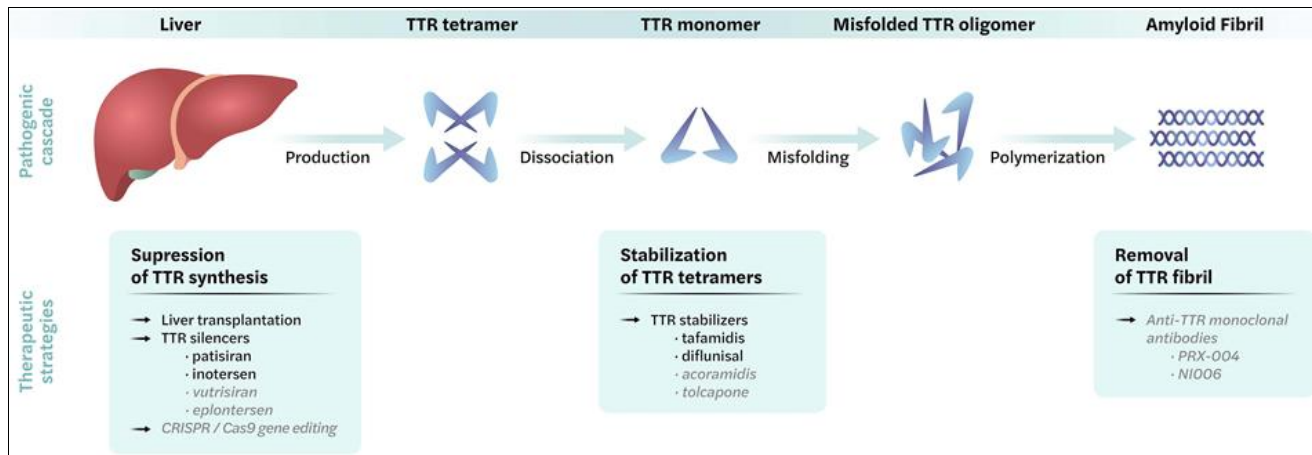
### Introduction

Hereditary amyloidogenic transthyretin amyloidosis with polyneuropathy (ATTRv-PN) is an adult-onset, autosomal dominant disease produced by mutations in the *TTR* gene, which encodes the transthyretin (TTR) protein [1]. ATTRv-PN was thought to be endemic to Portugal [2], Sweden [3], and Japan [4], however, an expanding number of cases, frequently adult-onset and sporadic, has been observed globally. According to a study from 2018, [5] there are 10,186 cases of ATTRv-PN worldwide, with a range of 5526-38,468 cases. With greater clinical knowledge of the disease and an increased use of genetic testing, especially in areas where it is not endemic, the incidence of ATTRv-PN is predicted to increase [5].

TTR, also known as prealbumin, is a homo-tetrameric carrier protein that transports thyroid hormones (Thyroxine) in the plasma and cerebrospinal fluid. It is also involved in the transport of retinol (vitamin A) by associating with retinol-binding protein [6]. The tetramer conformation is thermodynamically or kinetically destabilized by mutations in the *TTR* gene, which cause the tetramer to split into erratic monomers that misfold and clump together to form mature amyloid fibrils that lead to tissue injury by microangiopathy, cytotoxicity or direct compression [7]. Moreover, fibrillar (Monomers and oligomers) TTR might induce tissue damage through increased cytotoxicity [8]. The peripheral nervous system, heart, and kidneys are the most commonly damaged organ systems.

A point mutation in the *TTR* gene, a four-exon gene located on chromosome 18, that results in the substitution of methionine for valine at position 30 of the mature protein causes the majority of cases of ATTRv-PN (standardized nomenclature now begins at the methionine initiation codon and the mutation is technically known as p.ATTRVal50Met, although Val30Met continues to be widely used in the literature) [9]. However, over 130 mutations have been identified in this gene, the majority of which are pathogenic [10]. ATTRv-PN manifests commonly as a progressive peripheral neuro-pathy with a predominantly sensory involvement. Autonomic neuropathy and gastrointestinal symptoms are prominent in Val30Met early-onset, whereas motor neuropathy and cardiac involvement were more common in late-onset patients [11]. Furthermore, characteristics of amyloid deposits are distinct between Val30Met early and late-onset patients [12]. The penetrance of mutations in the *TTR* gene is highly variable. In endemic regions, this can reach 100%, but outside these regions, incomplete penetrance is more common [13].

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**Fig 1:** Overview of therapeutic strategies in hereditary transthyretin amyloidosis with polyneuropathy. Top: Pathogenic process, bottom: therapeutic approaches available in clinic (black) or clinical trials (grey).

Prior to 1990, the available treatments for ATTRv-PN were to manage symptoms and the condition was traditionally considered incurable. However, in the past three decades, various disease-modifying therapies have been developed. Current treatments and investigational therapies will be described and discussed here, and suggestions for monitoring disease progression and treatment effectiveness will be provided.

To treat ATTRv-PN, the main strategies focus on one of the following (Figure 1): (1) suppression of amyloidogenic TTR synthesis (TTR silencers) and liver transplantation, (2) stabilization of TTR tetramers to prevent misfolding (TTR stabilizers), and (3) removal of existing TTR amyloid fibrils (TTR disrupters).

### Available Disease-Modifying Therapies

#### Liver Transplantation

The first liver transplantation for ATTRv-PN was performed in Sweden in 1993 [14]. Since then, thousands of patients have undergone this treatment to replace the main source of mutant TTR for a more stable wild-type variant and slow the progression of the disease, since wild type TTR is less amyloidogenic. It is well acknowledged that transplanting patients with ATTRv-PN dramatically lengthens their life expectancy [15, 16] however, neuropathy and cardiomyopathy [17], as well as ocular and central nervous system amyloidosis, can progress after liver transplantation [18-19].

A long follow-up (more than 20 years) to collect outcome data and predictors indicated that late onset (after the age of 50 years) in male patients as well as non-Val30Met patients showed a less post-transplant benefit. On the other hand, patients with < 7 years since the debut of disease had a better prognosis [16]. Nowadays, with the implementation of effective pharmacotherapy, liver transplantation for ATTRv-PN is considered exceptional.

#### TTR Silencers

##### Patisiran

Small interfering RNAs (siRNAs) are non-coding, double-stranded RNA molecules that trigger RNA-induced silencing complexes that bind to their complementary mRNA. By doing this, translation is hindered and protein synthesis is stopped.20 Patisiran (Onpattro) is a first-generation siRNA that was approved in 2018 for the treatment of ATTRv-PN, based on positive results in the Phase III trial APOLLO A that involved administering

intravenous patisiran (0.3 mg/kg) or placebo once every three weeks to 225 patients with ATTRv-PN.21 The primary endpoint was the change from baseline at 18 months in the modified Neuropathy Impairment Score + 7 (mNIS + 7),22 a variation of the Neuropathy Impairment Score (NIS) that includes quantitative sensory and autonomic items and nerve conduction studies, achieving a greater detection of disease progression [23-25]. The least-squares mean conversion was -6.0 versus 28.0 ( $p < 0.001$ ) and there were no differences between the subgroups with respect to age or variant. The majority of adverse events were mild or moderate, while the incidence of severe and serious adverse effects was similar in both arms. Other clinical assessments, including the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) questionnaire, the 10-meter walk test (10-MWT), and the COMPASS 31 autonomic score, also showed improvements from baseline.21 The open-label extension (OLE) trial included 211 subjects who had finished the phase III APOLLO study or Phase II OLE parent studies, and demonstrated a sustained improvement at 12 months [26].

Remarkably, mortality and disability remained higher in the patients who had received patisiran at a late stage of the disease, highlighting the importance of early recognition and treatment of ATTRv-PN.

##### Inotersen

Inotersen (Tegsedi) is an antisense oligonucleotide designed to bind to TTR mRNA, triggering its degradation through nuclear ribonuclease H1 (RNaseH1) and resulting in a decreased protein expression. It was approved in 2018 for the treatment of ATTRv-PN based on a phase III trial (NEURO-TTR) that included 172 patients who had been randomized to receive intravenous inotersen (300 mg) weekly or placebo [27]. The primary goals of improvements in the NIS and quality of life measurements were achieved. The difference in the least-squares mean change from baseline to week 66 between the two groups was -19.7 points.

The most frequent serious adverse events in the inotersen group were glomerulonephritis in three patients (3%) and severe thrombocytopenia in four patients (4%), with one caused by an intracranial hemorrhage associated with profound thrombocytopenia. Four more deaths occurred in the treated arm (vs 0 deaths in the placebo arm) that were related to disease progression. Thereafter, treatment with

inotersen has required ongoing laboratory monitoring of these adverse effects [27].

## TTR Stabilizers

### Tafamidis

Tafamidis is a selective TTR stabilizer that binds to one of the thyroxine-binding sites at the TTR tetramer, therefore inhibiting the first dissociation step of the amyloidogenic cascade. A phase III clinical trial with 125 Val30Met-related ATTRv-PN patients randomized to tafamidis (20 mg daily) or placebo for 18 months did not show statistically significant differences in the two primary outcome measures, the Neuropathy Impairment Score in the Lower Limbs (NIS-LL) and the Norfolk QOL-DN total score, in the intent-to-treat (ITT) population. However, in an “as treated” analysis, significantly more patients on tafamidis than those on placebo were NIS-LL responders (60.0% vs 38.1%;  $p = 0.041$ ), with significant differences in most secondary endpoints, including changes in neurological function, nutritional status, and TTR stabilization that favored tafamidis [28]. Based on these data, tafamidis was approved for the treatment of ATTR-PN in Europe, Asia and South America; however, it was rejected by the Food and Drug Administration (FDA) of the United States of America. In an observational study, the response to tafamidis in Val30Met Portuguese patients was evaluated after 6 years of treatment, beholding that patients with early disease, specially female patients, presented the best response to treatment (NIS 10) [29].

The Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT) was a phase III study that had enrolled 441 patients with transthyretin amyloidosis with cardiomyopathy (ATTR-CM) who had been randomized to receive 80 mg, 20 mg, or placebo by mouth daily. Patients with ATTR-CM can be further classified into variant (ATTRv-CM) or wild-type (ATTRwt-CM) disease according to the presence of genetic mutations in the TTR gene; in this study both ATTR-CM and ATTRwt-CM patients were included. At 30 months, patients treated with tafamidis demonstrated a 13.4% absolute reduction in all-cause mortality when compared to those on placebo, as well as fewer cardiovascular-related hospitalizations, a lower decline in functional capacity, and a lower decline in quality of life. Based on these favorable results, tafamidis was ratified to treat both ATTRwt-CM and ATTRv-CM [30].

### Diflunisal

Diflunisal, a non-steroidal anti-inflammatory drug (NSAID), is a salicylic acid-derived medication that was developed as an analgesic. It stabilizes TTR by interfering with the binding site at the dimer-dimer interface of TTR tetramers. A randomized, placebo-controlled, double-blind, multicenter, international study conducted on 130 patients with ATTRv-PN showed a reduction in disease progression (Measured as the progression scores on the NIS + 7 nerve tests and the NIS score at 2 years after treatment) in patients who received diflunisal compared to those who received placebo. However, 52% of the patients had discontinued treatment as a result of disease progression and liver transplantation, suggesting that this TTR stabilizer is insufficient to stop rapid progression.31 The study excluded patients who were at an increased risk with NSAID therapy, including those with severe congestive heart failure, renal

insufficiency, and ongoing anticoagulation, which are common in this pool of patients in clinical practice.

## Strategies under Development

### TTR Silencers

#### Second-Generation Gene Silencers

Vutrisiran (Previously ALN-TTRsc02) is a second-generation RNA interference (RNAi) therapeutic that targets a sequence within the TTR mRNA, inhibiting the formation of TTR. Conjugation of vutrisiran with a triantennary GalNAc ligand allows subcutaneous dosing at a lower frequency of administration compared to patisiran treatment [32]. Two Phase III, randomized, open-label studies are currently being conducted to estimate the safety and efficacy of vutrisiran in 164 patients with ATTRv-PN (projected finalization date in May 2024) and 665 patients with ATTRv-CM (estimated completion date in June 2025), who have been randomized to receive either vutrisiran or patisiran [33, 34]. Based on the Phase I trial with vutrisiran that demonstrated a safe profile in 80 healthy patients [32], the FDA has granted fast-track designation to vutrisiran as a potential therapy for ATTRv-PN.

Eplontersen is a subcutaneously administered single-stranded antisense oligonucleotide with the addition of a receptor ligand protein that allows direct binding to hepatocytes, leading to decreases in the amount of dose and interval of administration (every 4 weeks compared with previous weekly dosing) as well as reductions in adverse effects and dose increment. The estimated primary completion date of the study assessing the safety and efficacy of eplontersen is in July 2024 [35].

### CRISPR/Cas9 Gene Editing

Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) gene editing cuts DNA and lets natural DNA repair processes take over, disrupting, deleting, or inserting a specific DNA sequence. With this therapy, the *TTR* gene can be actually knocked out in those patients with ATTRv-PN after one single administration. In a phase I study conducted on patients with ATTRv-PN, NTLA-2001, and the first systemically delivered CRISPR/Cas9 therapy, was well tolerated and reached a drop in TTR levels [36].

### TTR Stabilizers

#### Acoramidis

Acoramidis (previously known as AG10), is a highly selective TTR stabilizer. Is orally bioavailable and was designed to mimic the structure of the protective Thr119Met mutation, which prevents tetramer dissociation by promoting hydrogen bond formation between serine residues [37]. In a randomized, double-blind, placebo-controlled, multicenter phase II clinical trial in 49 patients with symptomatic ATTRv-CM and ATTRwt-CM, acoramidis was well tolerated, with no clinically significant safety concerns [38]. Moreover, there was a statistically significant increase in the mean serum TTR concentration, a prognostic indicator of survival, in patients treated with acoramidis compared to those on placebo [38]. An Open-Label Extension and Safety Monitoring Study with acoramidis in patients with symptomatic ATTRv-CM is being carried out, with the estimated study completion date being in May 2028 [39].

**Tolcapone**

Tolcapone, a well-known drug approved for the treatment of Parkinson’s disease, stabilizes TTR tetramers by binding both thyroxine-binding pockets of the TTR tetramer [40]. An open-label, phase IIA proof-of-concept study in asymptomatic ATTR amyloidosis patients (ATTRwt, N = 6; Val30Met ATTRv, N = 11) demonstrated TTR stabilization, suggesting a potential role for tolcapone in ATTR amyloidosis [40]. Moreover, tolcapone can cross the blood-brain barrier, thus, it could be an option for the treatment of leptomeningeal manifestations of ATTRv amyloidosis [41]. A proof-of-concept study that evaluated tolcapone efficacy to stabilize TTR in the cerebrospinal fluid and plasma of leptomeningeal ATTRv patients was finished in 2019 [42], but the results are not available yet. Therapy with tolcapone requires extensive monitoring for potential hepatotoxicity; therefore, the indication for treatment with this drug will have to be carefully evaluated.

**TTR Disrupters**

**Monoclonal Antibody Therapy**

Monoclonal antibodies can selectively target dissociative monomers, oligomers or TTR aggregates to suppress fibrillo-genesis and further aggregation or they can target amyloid deposits to trigger their removal by phagocytic mechanisms, sparing the normal tetrameric TTR [43]. In a phase I clinical trial, PRX004, a potential therapeutic monoclonal antibody targeting the TTR epitope comprising residues 89-97, was well-tolerated and safe at all dose levels. In this study, 21 patients received PRX004 intravenously once every 28 days for up to three infusions. All the evaluable patients experienced an improvement or slower progression versus the natural history of disease, at month 9 [44]. NI006 is another human antibody targeting TTR amyloid deposits that is currently being evaluated in a phase I trial in patients with hereditary or wild-type ATTR-CM [45].

**Monitoring Response to Therapy**

Careful monitoring of the multiple signs of disease progression is necessary to address the challenges associated with the initiation and adjustment of disease-modifying therapies. The monitoring of a patient should begin immediately after diagnosis to establish a baseline assessment. Thereafter, periodic assessments of peripheral neuropathy symptoms, including sensory-motor and

autonomic manifestations, as well as the monitoring of ocular and central nervous system involvement should be performed [46]. Common symptomatology of peripheral neuropathy includes pain, paresthesia, walking difficulties, balance disorders, and difficulties with fine dexterity. The NIS, combining motor function, sensory function, and tendon reflexes, has been used in clinical trials in patients with ATTRv-PN [31, 47] and reflects the severity of the neuropathy [48, 49]. Others composite scales based in NIS as the mentioned mNIS+7 are often avoided in clinical practice due their complexity and time consumption.

The polyneuropathy disability (PND) score, as well as the six-minute walk test (6-MWT) and the timed 10-MWT, evaluates the impact of neuropathy on ambulation. Furthermore, 6MWT and 10MWT are functional exercise-based tests that correlate with the cardio-pulmonary function and provide prognostic information in patients with cardiac involvement [50]. Other relevant neurological tests include nerve conduction studies in the four extremities to examine large, myelinated nerve fibers, which are mandatory in mild and moderate neuropathy. Investigations of unmyelinated and small nerve fibers, like the assessment of laser-evoked potentials, temperature quantitative sensory testing or silent period for small fiber sensory neuropathy assessment, are recommended when available [51].

Autonomic manifestations are present in 75% of patients [52], therefore, a systematic clinical screening should be performed. The COMPASS 31 questionnaire, provides a broad assessment of the severity and extent of a range of autonomic symptoms, including vasomotor, secretomotor, gastrointestinal, and bladder dysfunction. It has shown efficacy in monitoring longitudinal changes in autonomic function [53]. Additional assessments include sudomotor function tests, postural hypotension tests, heart rate variability tests, and the modified body mass index (mBMI), which can be used as an indirect marker of gastrointestinal dysautonomia [52].

Finally, the Rasch-built Overall Disability Scale (R-ODS) can be used to assess disability, since it measures the effect of the disease on activities of daily living in patients with peripheral neuropathy [54]. Table 1 summarizes the common minimum set of evaluations that should be used to monitor the progression of neuropathy [46, 55]. The recommended frequency of assessment in general is every 6 or 12 months, depending on the disease course, the severity of the polyneuropathy, and the response to treatment [52].

**Table 1:** Recommended Set of Evaluation to Monitor Progression of Neuropathy<sup>a</sup>

Assessment	Indicator of Progression
NIS	A change of 7-16 points over 12 months or worsening of the score on 2 consecutive consultations 6 months apart
NCS	Decrease of 20% amplitude in several nerves over 12 months
Jamar Hand Dynamometer	Reduction of grip strength of 4-6 kilos over 12 months
PND score	Change in disease stage
6-MWT or 10-MWT	Change in gait speed 0.05-0.10 m/s or an increase of 30% over 12 months in the time to walk 10 m
Compass-31 questionnaire	Increase by 1 point in a year
Sudomotor testing	Using Sudoscan®, a reduction on 2 consecutive examinations of the feet (Rarely performed)
Heart rate deep breathing	A change from an age-adjusted normal value to abnormal value
Orthostatic vital signs	New onset of orthostatic hypotension or syncope (Typically manifests in later stages of disease)
R-ODS	Worsening of R-ODS score by 3-8 points over 12 months or worsening of the score on 2 consecutive consultations 6 months apart

**Note:** <sup>a</sup>Data from Ando *et al.* [52] and Adams *et al.* [46]

**Abbreviations:** 6-MWT, six-minute walk test; 10-MWT, 10-meter walk test; COMPASS-31, composite autonomic symptom score-31; NIS, neuropathy impairment score; NCS, nerve conduction study; PND, polyneuropathy disability; R-ODS, Rasch-built Overall Disability Scale.

## Conclusions

ATTRv-PN is a progressive and lethal disease in which early therapeutic intervention is key for better patient outcomes. Recently approved disease-modifying therapies have changed the course of the disease, highlighting the need for guidance on managing ATTRv-PN. To monitor the disease course, clinicians should undertake detailed assessments of the multiple symptoms and signs of neuropathy at baseline and during follow-up.

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