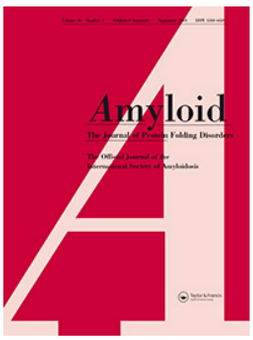

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REVIEW ARTICLE

Assessment of patients with hereditary transthyretin amyloidosis – understanding the impact of management and disease progression

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ABSTRACT

Timely diagnosis of hereditary variant transthyretin (ATTRv) amyloidosis is critical for appropriate treatment and optimal outcomes. Significant differences are seen between patients receiving treatment and those who are not, though disease progression may continue despite treatment in some patients. Healthcare professionals caring for patients with ATTRv amyloidosis therefore need reliable ongoing assessments to understand the continuing course of disease and make appropriate treatment choices on an individual basis. Various signs and symptoms experienced by patients may be evaluated as indicators of disease progression, though there is currently no validated score that can be used for such ongoing assessment. Recognizing this situation, a group of clinicians highly experienced in ATTR amyloidosis developed an approach to understand and define disease progression in diagnosed and treated patients with ATTRv amyloidosis. The suggested approach is based on the recognition of distinct phenotypes which may usefully inform the particular tools, tests and investigations that are most likely to be appropriate for individual patients. It is aimed at implementing appropriate and ongoing assessment of patients being treated for ATTRv amyloidosis, such that the effectiveness of management can be usefully assessed throughout the course of disease and management can be tailored according to the patient's requirements.

Abbreviations: 6MWT: 6-minute walk test; ATTR-CM: hereditary transthyretin amyloid cardiomyopathy; ATTR-PN: hereditary transthyretin amyloid polyneuropathy; ATTRv: variant transthyretin amyloidosis; BMI: body mass index; CMAP: compound muscle action potentials; CMR: cardiac magnetic resonance; COMPASS-31: Composite Autonomic Symptom Score 31; ECG: electrocardiography; ECV: extracellular volume; EMG: electromyography; ESC: electrochemical skin conductance; FAP-RODS: Familial Amyloid Polyneuropathy Specific Rasch-Built Overall Disability Scale; IVCM: *In vivo* confocal microscopy; LEP: laser-evoked potentials; LV: left ventricular; mNIS + 7: Modified Neuropathy Impairment Score +7; NCS: nerve conduction studies; NDS: Neurologic Disability Score; NIS: Neuropathy Impairment Score; NIS-LL: Neuropathy Impairment Score in the lower limbs; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; PND: polyneuropathy disability; PSMS: Physical Self-Maintenance Scale; QSART: quantitative sudomotor axon reflex test; QST: quantitative sensory testing; SNAP: sensory nerve action potentials; SSR: sympathetic skin response; TTR: transthyretin

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ATTR; amyloidosis; hereditary; follow-up; monitoring; progression; transthyretin

Introduction

Hereditary variant transthyretin (ATTRv) amyloidosis is a rare and devastating disease resulting from extracellular deposition of amyloid fibrils formed by transthyretin (TTR), a transport protein produced predominantly by the liver [1,2]. It is an autosomal dominant disorder with an age of onset ranging from the second to the ninth decade of life and various clinical manifestations including progressive sensorimotor and autonomic neuropathy (hereditary ATTR polyneuropathy [ATTR-PN]), infiltrative cardiomyopathy (hereditary ATTR cardiomyopathy [ATTR-CM]) [2,3], amyloid ophthalmopathy [4] and nephropathy [1,5]. More than 130 different *TTR* gene mutations associated with the disease have been identified worldwide, of which Val30Met has been the most commonly recognized to date [5].

Diagnosis of ATTRv amyloidosis is often challenging, particularly due to low awareness or understandable lack

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of suspicion in patients presenting in the general medical system and with no known family history of the disease. Timely diagnosis is, however, critical for appropriate treatment and optimal outcomes [5]. A diagnosis of active disease in individuals with a *TTR* gene mutation should be made in the presence of at least one quantified or objective symptom or sign definitively related to the onset of symptomatic ATTRv amyloidosis; or at least one probably related symptom plus one abnormal definitive or confirmed test result; or two abnormal definitive or confirmed test results in the absence of clinical symptoms [6].

Data from registries of diagnosed and treated patients, such as the Transthyretin Amyloidosis Outcomes Survey (THAOS), indicate that disease progression may variably continue despite appropriate treatment, although treatment has been shown to slow disease progression [7]. This situation demands accurate and structured monitoring of the ongoing and changing disease state in individual patients.

An understanding of the disease course will help to inform decisions on important components of physiological, pharmacological or psychological management, as well as other essential aspects of supportive care.

Various signs and symptoms experienced by patients have significant potential as ongoing indicators of disease progression. These include unintentional and continuous weight loss; new appearance or worsening of autonomic problems, such as impotence, diarrhoea or orthostatic hypotension; progression of somatic neuropathy (sensory and motor); development/progression of ocular complications (vitreous opacities/secondary glaucoma); and development/progression of cardiac manifestations.

A group of clinicians experienced in the care of people diagnosed with ATTR amyloidosis met to develop an approach to understanding and defining disease progression in diagnosed and treated patients with ATTRv amyloidosis. This multidisciplinary group included neurologists, an ophthalmologist and cardiologist and internal medicine specialists.

This publication aims to outline the suggested structured approaches agreed by the group, to help in the ongoing assessment of individual patients being treated for ATTRv amyloidosis, to better understand changes in the disease, provide a personalized approach for monitoring of disease and optimize patient care and management.

Methods

In July 2017, a dedicated team of experts in ATTR amyloidosis met to discuss the ongoing management of patients with ATTRv amyloidosis. Based on literature review, analysis of the methodologies utilized in clinical trials investigating the treatment of ATTRv amyloidosis and the experts' personal knowledge from years of real-world experience, the group aimed to identify the tests and investigations that best evaluate disease progression in diagnosed and treated patients and achieve consensus on the clinical indicators and thresholds that define disease progression and indicate a need for change in the management of such patients.

Initial monitoring considerations – diagnostic tests may not be appropriate in the treatment phase

Once a person has been diagnosed and is being treated for confirmed ATTRv amyloidosis, it is important to employ tests and assessments that are capable of revealing ongoing change rather than the existence of the disease state itself, as in the initial diagnostic work-up. Tests undertaken as part of the diagnostic process may therefore not be as useful in the long-term monitoring of the changing state of ATTRv amyloidosis. Indeed, tests and investigations that are useful for the initial diagnosis of the disease may have a "floor" or "ceiling" effect, whereby no further change in the parameter being measured occurs due to ongoing disease progression. This means that such useful diagnostic tests may have limited utility in assessing subsequent treatment outcomes or in identifying ongoing disease progression.

As an example, long-term follow-up of patients in clinical trials has shown that both change from baseline and ongoing change in the Neuropathy Impairment Score (NIS, especially in the lower limbs [NIS-LL]) have been a useful parameter for measuring early disease progression in the study setting [8,9]. However, it is acknowledged that this measure may have a rapid "ceiling" effect, particularly in sensory evaluations and may not be useful after the stages of early disease progression. The Modified Neuropathy Impairment Score +7 (mNIS + 7) may be a more useful measure for ongoing assessment [10], although it is accepted that this measure is complex and time-consuming in real-life clinical practice, often involving a degree of training and central laboratory reference values in order to be used appropriately [11].

Designing a specific approach to follow-up treated patients with ATTRv amyloidosis

ATTRv amyloidosis presents with many different clinical presentations and with considerable variation in terms of signs and symptoms, among individuals and across geographic locations [2]. There are also important differences in *TTR* gene mutations, which, in turn, are associated with different phenotypes [2]. Even for a specific *TTR* gene mutation, phenotypes may be polymorphous, even within the same family [2]. In addition, late-onset disease may be different from early-onset disease, in terms of amyloid deposition and disease course [2].

The different phenotypes seen in clinical practice (and largely associated with *TTR* gene mutation or time of disease onset) could lead to the definition of four major phenotype groups: Val30Met early onset (<50 years); Val30Met late onset (>50 years); non-Val30Met mixed phenotype and non-Val30Met cardiac phenotype (eg Val122Ile) [6] (Table 1). Recognition of these groups usefully informs the particular tools, tests and investigations that are most relevant to the long-term follow-up of specific patients. Clinical approaches will also need to address change in the individual patient as the disease progresses and specific dysfunctions or disabilities become the key impact on the individual.

It should be noted that the exact age of disease onset may be difficult to determine with certainty and an alternative approach to differentiate between the two phenotypes

Table 1. Spectrum of clinical findings at disease onset in hereditary variant ATTR amyloidosis genotype/phenotype groups.

Val30Met early onset (<50 years)	Val30Met late onset (>50 years)/ Non-Val30Met mixed phenotype	Non-Val30Met cardiac phenotype (onset >65 years) For example, Val122Ile, Ile68Leu, Leu111Met, Leu58His, Thr60Ala
• Small-fibre neuropathy • Motor neuropathy • Dysautonomia • Cardiac conduction disturbances • Gastrointestinal dysfunction • Ophthalmopathy: dry eye/vitreous opacities/secondary amyloid glaucoma	• Sensory and motor neuropathy • Subtle autonomic signs • Cardiomyopathy • Cardiac conduction disturbances • Ophthalmopathy: dry eye/vitreous opacities/ secondary amyloid glaucoma (more rarely) • Bilateral carpal tunnel syndrome	• Symptoms associated with heart failure with preserved or mildly depressed ejection fraction – no cavity enlargement and symmetrical increase in wall thickness • Cardiac conduction disturbances • Disproportionately elevated NT-proBNP • Relatively high frequency of bilateral carpal tunnel syndrome
Renal involvement has been described in a sub-group of Portuguese patients with intermediate onset and female predominance		Neuropathy and/or dysautonomia is rarely present, in contrast to other genetic variants
Diagnosis <2 years from symptom onset in endemic regions	Diagnosis >2 years from symptom onset in non-endemic regions	Patients have a prognosis of only 2.5–5 years' survival from disease onset

NT-proBNP: N-terminal pro-brain natriuretic peptide.

of Val30Met patients has previously been reported, which is based on the amyloid fibril composition (Type A or Type B) [12]. However, as not every centre diagnosing patients has the expertise or resources to perform fibril typing, we have categorized disease according to age of onset, which is currently more widely used.

Which tests and investigations will be most useful for the ongoing monitoring of treated patients with ATTRv amyloidosis?

After review of the published literature and the approach applied when assessing symptoms of disease and its progression in clinical trials [8,9,11,13–17], it was agreed that tests should be targeted at the expected phenotypical presentation for the specific mutation. For all tests, it is important to establish baseline values and repeatability of the different measurements in order to assess ongoing change in routine follow-up.

Below, we outline the proposed tests and assessments that should be applied to monitor disease progression in treated patients with ATTRv amyloidosis.

Patient-reported aspects and quality of life measures

Patient-reported aspects are an essential component of understanding disease progression and its impact on daily living in the individual being assessed. Information on patient-reported symptoms (neuropathic [positive and/or negative], gastrointestinal, genitourinary, sexual dysfunction, severe syncope) should be collected and compared every 6 months.

Patient questionnaires can be used to measure changes in health-related quality of life. The Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire is a 35-item, self-reported questionnaire to assess patients' subjective perceptions of symptoms associated with specific nerve fibre damage. The questionnaire comprises domains for physical functioning/large-fibre neuropathy, symptoms, activities of daily life, small-fibre neuropathy and autonomic neuropathy and has been validated for use in patients with ATTRv amyloidosis as a reliable indicator of disease severity [9,16,18,19]. Indeed, in some countries, the patient's Norfolk QoL-DN score must be provided to the regulatory authorities during treatment with approved drugs.

Additionally, the Val30Met Familial Amyloid Polyneuropathy Specific Rasch-Built Overall Disability Scale (FAP-RODS) is a 34-item, disease-specific interval measure suitable for detecting activity and participation restrictions in patients with ATTRv amyloidosis [20].

The Composite Autonomic Symptom Score 31 (COMPASS-31) is another useful self-reported questionnaire designed to comprehensively evaluate the severity and distribution of symptoms and the autonomic functional capacity of patients with autonomic disorders. It has good psychometric properties in the population of patients being evaluated for small-fibre polyneuropathy [21].

For general functioning, various scales are available for assessing activities of daily living. These include the Physical Self-Maintenance Scale (PSMS), the Katz ADL Index and the Barthel ADL Index [22]. These can be used regularly to detect any changes or the emergence of new symptoms or impacts on the patient.

Neurological assessments

Neurophysiology. The assessment and progression of neuropathic symptoms in patients diagnosed with ATTRv amyloidosis can be assessed using multiple tools and scoring scales that include the polyneuropathy disability (PND) score; neuropathy symptom score; Neurologic Disability Score (NDS); total NIS and NIS-LL, each with their own advantages in measuring disease progression [2].

The PND score is a simple staging system that provides a good indication of disease staging, by categorizing patients into four stages according to their neuropathy impairment and its impact on ambulation: stage I (sensory disturbances but with preserved walking capability); stage II (impaired walking ability without need for a stick); stage III (walking only with the help of one stick (IIIA) or two sticks (IIIB)) and stage IV (wheelchair- or bed-bound) [23].

An important neurological assessment to quantify neuropathy progression across the full disease course is total NIS. NIS is a composite score derived from neurological assessment of muscle strength, reflexes and sensation in the upper and lower limbs [24]. It has been found to be positively associated with functional scales of locomotion, PND

score and disease stage [10]. Despite the "ceiling effect" observed when measuring NIS in diagnosed and treated patients with ATTRv amyloidosis, it remains a useful test that should be considered to monitor disease progression, until there are no further changes in value and the "ceiling" has been reached.

Nerve conduction studies (NCS) and electromyography (EMG) are good tools for longitudinal follow-up and assessment of change from baseline for phenotypes associated with sensorimotor polyneuropathy, although they are not sensitive methods for small-fibre involvement [25]. With NCS, sensory nerve action potentials (SNAP) and compound muscle action potentials (CMAP) can be usefully measured and monitored, being a direct measure of axonal loss [26].

Distal small-fibre neuropathy causes length-dependent involvement of both somatic and autonomic unmyelinated fibres. Electrochemical skin conductance (ESC), as measured by Sudoscan™ (Impeto Medical SAS, Paris, France), sympathetic skin response (SSR) and quantitative sudomotor axon reflex test (QSART) are the sudomotor tests most frequently used for assessment of small unmyelinated fibres (C-fibres). Quantitative sensory testing (QST) and laser-evoked potentials (LEPs) also enable the assessment of small myelinated (Aδ fibres) and unmyelinated (C-fibres) fibres [26].

From the above tests, some are available in only a few centres and are not suitable for a routine follow-up of patients with ATTRv amyloidosis. QST is a psychophysical test of sensory perception for longitudinal follow-up; however, it suffers from variability of instruments and methodological approaches for location, stimulus application and the sensation qualities examined, making its reliability questionable [26]. QSART provides a quantitative, validated assessment of post-ganglionic sympathetic cholinergic sudomotor function [26], although it can be time-consuming and complex method for routine clinical application, requiring a high degree of technical expertise, and is available in only a limited number of centres [25]. SSR and LEP have a low sensitivity and reach a rapid floor effect reflecting their limited use [25,27]. In a recent study, SSR failed to demonstrate a significant decline over time [28].

ESC measured by Sudoscan as a non-invasive, quick and reproducible test seems to be a good tool to evaluate the progression of small-fibre function impairment and a promising tool to monitor disease progression, but may be limited in its use in more advanced stages of disease due to a potential floor effect [25,28,29].

Although the above-mentioned neurophysiological tests can be promising tools to follow-up disease progression, due to the limitations described, the group agreed that, in routine clinical practice, a composite nerve conduction score comprising a sensory score and a motor score could be a useful and pragmatic tool. For the sensory score, SNAP can provide unilateral assessment of the sural plus ulnar nerves. For the motor score, CMAP can be used for the unilateral assessment of the ulnar plus peroneal nerves. From a neurophysiological perspective, an overall approach for routine clinical practice may therefore comprise a composite nerve conduction score plus the use of Sudoscan.

Confocal microscopy for small-fibre nerve assessment. *In vivo* confocal microscopy (IVCM) of the corneal nerves is useful for both early detection and assessment of progression of small-fibre neuropathies [26,30]. It is a simple, rapid, non-invasive, reiterative and cost-effective approach for quantifying small-nerve fibre loss [31], making it suitable for ongoing follow-up. Normative reference values are available [32], although there is great variability and standard deviations are wide, even within age and sex classes. Thus, with available analytic tools, it may still be difficult to use IVCM as a routine diagnostic test. However, with a baseline recorded, it may be useful for ongoing assessment of change in an already diagnosed patient [33]. It seems to provide sensitive results, as it may be altered in patients with asymptomatic small-fibre polyneuropathy [31], and also allows demonstration of re-innervation [34].

Some preliminary results in ATTRv amyloidosis have shown that corneal fibre length, assessed using IVCM, was correlated with clinical and paraclinical parameters of sensorimotor and autonomic neuropathy, as well as functional impairment stage [35]. Reliable automated analysis of IVCM scans using software integrated into IVCM machines will help to develop this non-invasive and rapid technology [36].

Altogether, IVCM represents a promising approach that may be useful for monitoring patients with ATTRv amyloidosis, once data from longitudinal studies to assess the capacity of IVCM to detect changes in corneal nerve fibre length over time are available [35].

Exploratory neurological assessments

Magnetic resonance imaging. Less frequently used and described in the literature, magnetic resonance neurography is magnetic resonance imaging dedicated to the peripheral nerves. It detects and localizes nerve injury at the level of individual nerve fascicles [37]. Although in early stages of use for monitoring disease progression, this imaging modality has been shown to detect and quantify lower limb nerve injury *in vivo* at the microstructural level in patients with symptomatic ATTR-PN, as well as in asymptomatic carriers of a *TTR* mutation. It thus has potential for early monitoring of microstructural nerve injury [37].

Skin biopsy. Skin biopsy can lead to a reliable quantification of somatic and autonomic small nerve fibres using both bright-field immunohistochemistry and indirect immunofluorescence approaches. Intraepidermal nerve fibre density is a consistent and stable measure [27], making it useful for assessing disease progression when compared with a baseline assessment. Skin biopsy is more accurate than nerve biopsy, although may be limited in clinical practice owing to logistical aspects and degree of availability.

Cardiac-specific assessments

Cardiac assessments should include clinical examination using the New York Heart Association (NYHA) staging system, electrocardiography (ECG), echocardiography, the 6-minute walk test (6MWT) and laboratory tests, such as

N-terminal pro-hormone brain natriuretic peptide (NT-proBNP), in each case.

NYHA functional class and NT-proBNP plasmatic concentration remain the most useful measures to longitudinally monitor disease progression and should be repeated every 6–8 months in stable patients. Changes in the overall functional capacity can also be accurately evaluated by 6MWT (as documented in the ATTR-ACT trial) [38].

A 12-lead ECG to detect rhythm, QRS duration, QRS voltage, cQT, Q waves and ST abnormalities should be repeated on at least an annual basis. An annual Holter ECG should be used to search for rhythm and conduction disturbances and for the assessment of heart rate variability (in selected cases). The most relevant clinical implications are associated with the possible appearance of paroxysmal atrial fibrillation or advanced atrioventricular block. Echocardiography plays a major role in the non-invasive diagnosis of cardiac amyloidosis due to its assessment of structure and function. Myocardial thickness, biventricular systolic and diastolic circumferential and longitudinal function, parietal strain and strain rate can be easily evaluated at basal level and during follow-up. Nevertheless, variations in clinical status are rarely paralleled by changes in myocardial thickness. A restrictive transmitral Doppler pattern is a marker of disease severity, and its disappearance can be considered as a sign of haemodynamic improvement. Left ventricular (LV) ejection fraction is not a reliable marker of disease progression or regression in ATTR-CM. A recent prospective trial using tafamidis indicated that changes in LV strain measurements can parallel clinical improvements [38]. In a separate clinical trial using patisiran, improvements were observed in cardiac manifestations of ATTRv amyloidosis, as measured by LV strain, in a prespecified cardiac subpopulation with mixed phenotype [19].

Cardiac magnetic resonance (CMR) can provide detailed functional and morphological information. The advantage of CMR is its unique ability to enable tissue characterisation through the extension of late gadolinium enhancement on late gadolinium imaging and elevated native T1 and extracellular volume (ECV). T1 mapping, a relatively new and quantitative technique, with native T1 and ECV, has the potential to longitudinally monitor disease progression [39]. Nevertheless, the real possibility of CMR to assess the response to disease modifying treatments remains to be established.

Although myocardial scintigraphy with bone avid tracers has high sensitivity and specificity for ATTR-CM, even in cases with initial involvement, its capability of assessing longitudinal changes in amyloid burden has not been demonstrated [40]. New amyloid-specific positron-emission tomography tracers are interesting but not yet accurately studied for evaluating amyloid burden and longitudinal changes.

Ophthalmological assessment

Ocular manifestations of ATTRv amyloidosis are common, some of them potentially blinding, and mainly include keratoconjunctivitis sicca, secondary glaucoma, vitreous deposits and retinal angiopathy [4,41]. Ophthalmological examination, including best-corrected visual acuity, intraocular pressure, slit lamp examination (including fluorescein staining of the ocular surface) and dilated fundus examination, should be performed to assess dry eye, anterior and posterior chamber amyloid deposits, as well as amyloid retinal angiopathy [4,41]. Vitreous opacities should be monitored using fundus photography and classified according to the modified Koga classification [42]. Structural and functional assessment of the optic nerve, by the measurement of the retinal nerve fibre layer using optical coherence tomography and automated visual field, should be performed in case of elevated and/or significant increase in intraocular pressure. Fluorescein angiography should be performed in case of retinal haemorrhages suggestive of amyloid retinal angiopathy [42].

Renal assessment

Monitoring of renal function (serum creatinine, glomerular filtration rate, proteinuria/microalbuminuria) is important, as kidney impairment and proteinuria are clinical features of ATTRv amyloidosis [43]. Microalbuminuria can precede the onset of neuropathy [43] and therefore may be a useful parameter to assess in the early stages of disease.

Among Portuguese patients with the Val30Met *TTR* mutation, a subgroup was identified with renal disease characterized by early microalbuminuria turning into proteinuria and progressive renal failure [44]. Following the onset of neuropathy, dialysis is generally required within 10 years [43].

Other assessments

Another useful assessment to detect disease progression includes the measurement of body mass index (BMI). Gastrointestinal symptoms are common in patients with ATTRv amyloidosis and have a significant negative impact on their nutritional status and health-related quality of life [45]. The modified BMI, in which the BMI (kg/m^2) is multiplied by serum albumin (g/L) to compensate for possible oedema, appears to be well suited to monitoring disease progress [46]. Grip strength tests, for which normal values by age and gender are available [47], are also simple and useful in ongoing assessment and may be a good indicator of change over time.

Strategy for clinical practice

Considering the usefulness of the various tools available to assess disease progression in patients with ATTRv amyloidosis, we propose a structured follow-up tailored to individual patients, using tests and investigations dependent on the genotype/phenotype of the individual (Tables 2 and 3). The proposed structure aims to provide a personalized approach to monitoring and management of the disease. It is important to note, however, that a necessary amount of time on treatment is needed before benefit on disease can be seen and this should be considered before adjusting the patient's treatment regime [48].

Identifying the thresholds that indicate disease progression in treated patients with ATTRv amyloidosis

Using the suggested clinical indicators of change, the group discussed potential thresholds that could indicate significant disease progression with an associated need for consideration of change in therapeutic and clinical intervention. It was emphasized that detailed dialogue with each patient is a crucial component of understanding change and the impact of specific aspects of disease progression on the individual.

Standardizing any approach is challenging due to the clear evidence that not all *TTR* variants will produce the same pattern and course of disease, including rate of progression. In addition, it is unlikely that the progression of the different clinical factors will be linear, making the time since the onset of disease another confounding factor. The specific mutation and resulting patient phenotype are therefore an important consideration in our conclusions.

Treatments are available for the management of ATTRv amyloidosis and, as such, the group suggested useful thresholds for change which could be indicative of significant disease progression. (Table 4). This is increasingly important with the availability of more treatment choices and the need

Table 2. Useful assessments to assess disease progression in diagnosed and treated patient with neuropathic or mixed phenotype of hereditary variant ATTR amyloidosis.

	Val30Met early onset (<50 years)	Val30Met late onset (>50 years) / Non-Val30Met mixed phenotype
Patient-reported questionnaires (yearly)	• SIQ/SFN • COMPASS-31 (autonomic symptom score) • Norfolk QoL-DN	• Same as early onset, with increased emphasis on sensory and motor impact • Modified Norris test
Clinical (6-monthly)	• NIS • mBMI • BP (orthostatic) • PND score	• Same as early onset, with increased emphasis on physical impact • Grip test • 6MWT
Neurophysiology (yearly)	• Composite Nerve Conduction Score • Sudoscan	
Heart (6-monthly in cases of dysfunction)	• ECG/Holter • ECHO • Additional involvement of cardiological assessments for "cardiac" phenotypes	
Kidney/laboratory (6-monthly)	• Proteinuria • Albuminuria/microalbuminuria • Serum creatinine/calculated GFR • NT-proBNP • Troponin • Haemogram	
Eye (yearly in Val30Met and 3- to 6-monthly if pathologies present)	• Dry eye/glaucoma/vitreous opacities • Confocal microscopy (needs further validation)	

6MWT: 6-minute walk test; BP: blood pressure; CMAP: compound muscle action potential; ECG: electrocardiography; ECHO: echocardiography; NIS: Neuropathy Impairment Score; NT-proBNP: N-terminal pro-brain natriuretic peptide; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy; PND: polyneuropathy disability; SFN: small-fibre neuropathy; SIQ: Symptoms Inventory Questionnaire; SNAP: sensory nerve action potential.

Table 3. Useful assessments to assess disease progression in diagnosed and treated patients with cardiac phenotype of hereditary variant ATTR amyloidosis.

	Non-Val30Met cardiac phenotype (>65 years) For example Val122Ile, Leu111Met, Leu58His, Thr60Ala
Frequency of assessments	• Stable patient – twice per year • Rapidly progressing patient – at least every 2 months (for supportive treatment)
Clinical	• mBMI • Heart rate • Blood pressure (including orthostatic) • Jugular venous pressure • Assess for cardiac murmurs and diastolic tones • Assess for pulmonary congestion and pleural effusion
ECG	• 12-lead ECG (rhythm, QRS duration, QRS voltage, cQT, Q wave and ST-T abnormalities) • Holter ECG aimed at searching for atrial fibrillation or conduction disturbances (if sinus rhythm on standard ECG) every 6 months
ECHO	• 2D, M-mode Doppler ECHO: standard measurements (IVS and LPW thickness, LV diameters and volumes, LVEF, SV, CO, LV myocardial fraction), TAPSE, estimated RV systolic pressure, estimated RA pressure, S wave on TDI, E/E', search for restrictive LV filling pattern, longitudinal strain and strain rate, semiquantitative or quantitative evaluation of MI and TR, pericardial effusion (Y/N and degree), pleural effusion • X-ray in selected cases
Laboratory	• NT-proBNP • Troponin • Serum creatinine/calculated glomerular filtration rate • Haemoglobin
Cardiovascular magnetic resonance	• At least once (in selected cases it can be repeated) • Not yet validated to evaluate the response to disease-modifying treatment

2D: two dimensional; BMI: body mass index; CO: cardiac output; ECG: electrocardiography; ECHO: echocardiography; IVS: interventricular septum; LPW: left posterior wall; LV: left ventricular; LVEF: left ventricular ejection fraction; mBMI: modified body mass index; MI: mitral incompetence; NT-proBNP: N-terminal pro-brain natriuretic peptide; RA: right atrial; RV: right ventricular; SV: stroke volume; TAPSE: tricuspid annular plane systolic excursion; TDI: tissue Doppler imaging; TR: tricuspid regurgitation; Y/N: yes/no.

Table 4. Proposed criteria to define normal and potential change in disease course in diagnosed and treated patients with hereditary variant ATTR amyloidosis.

Test/investigation	Frequency	Quantitative measures of disease	Qualitative assessment of disease	Typical rate of progression expected with effective treatment	Signs of disease progression more than expected with treatment
Patient-reported symptoms	Every 6 months	Positive neuropathic symptoms (pain, paraesthesia) 1. Mild 2. Moderate 3. Severe Negative neuropathic symptoms (sensory loss) 1. Mild 2. Moderate 3. Severe Gastrointestinal symptoms 1. Constipation/diarrhoea < 2x/week 2. Constipation/diarrhoea > 2x/week 3. Constipation/diarrhoea > 3x/week 4. Diarrhoea every day 5. Nausea and vomiting Genitourinary symptoms 1. Urinary retention 2. Effort urinary incontinence 3. Permanent urinary incontinence Sexual dysfunction 1. Mild 2. Moderate Orthostatic hypotension 1. Asymptomatic 2. Dizziness with orthostatism 3. Syncope with orthostatism	Patient questionnaires: Norfolk QoL-DN FAP-RODS COMPASS-31 PSMS Katz ADL Index Barthel ADL Index Findings from consultation Observations from patients	Improvement or stabilisation	Worsening by at least 1 stage of quantitative measure Need for symptomatic treatment of hypotension or worsening from 1 to 3
Neurological evaluation	Every 6 months	Total NIS PND score	N/A	Stabilisation	Increase >10 points Increase in PND score
Neurophysiology	Yearly	Nerve conduction studies CMAP (ulnar + peroneal)+SNAP (ulnar + sural) Sudomotor assessment by Sudoscan sum score (ESC feet + ESC hands)	N/A	<50% decrease in amplitude from baseline per year <25% decrease in ESC	>50% decrease in amplitude from baseline (composite score motor and sensory) per year >25% decrease in ESC (sum score feet + hands)
Heart	Twice per year in stable patient	ECG / Holter (6 monthly when dysfunction present) ECHO 6MWT NT-proBNP level Troponin level	Echocardiographic features	Decrease in NT-proBNP Increase in walked distance at 6MWT Disappearance of transmitral restrictive filling pattern Disappearance/reduction of pericardial effusion	Increase in NT-proBNP ≥30% and ≥300ng/L Decrease in walked distance at 6MWT Appearance of transmitral restrictive filling pattern Appearance/increase of pericardial effusion
Kidney	Yearly	Proteinuria, albuminuria/microalbuminuria levels Creatinine clearance	N/A	Improvement or stabilisation	Proteinuria in the nephrotic range (>3.5 g/d, predominantly albumin) Decrease in GFR >50% from baseline NB: A decline in creatinine clearance with an increase in BUN is a significant progression of disease
Eye	Yearly	Intraocular pressure Vitreous opacities classification Corneal fibre length on confocal microscopy	Ocular amyloid deposits	N/A	Significant elevation of intraocular pressure >20% and/or 5 mmHg Progression by 1 stage (modified Koga classification) (irrespective of time)

6MWT: 6-minute walking test; ADL: activities of daily living; BUN: blood urea nitrogen; ECG: electrocardiography; ECHO: echocardiography; ESC: electrochemical skin conductance; FAP-RODS: Familial Amyloid Polyneuropathy Specific Rasch-Built Overall Disability Scale; NT proBNP: N-terminal pro-brain natriuretic peptide; PSMS: Physical Self-Maintenance Scale; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy.

to consider the necessary time required for the therapy to demonstrate benefit for the patient before adjusting the treatment regime. Interventions can therefore be targeted and altered at the appropriate point in disease progression. Newer treatment options are still to determine the time required to show benefit; however, data for tafamidis have shown that at least 1 year of administration is needed before a benefit to disease can be seen [48], with greater efficacy when administered early in the disease course [9,49]. In the ATTR-ACT trial, the effect on overall survival in patients with ATTR-CM emerged after approximately 18 months of treatment with tafamidis [38], suggesting a possible longer time to benefit for cardiac endpoints. This is likely owing to ventricular remodeling, which can take months to achieve. These findings would encourage continuing treatment with tafamidis until at least after these timepoints.

Conclusions

A structured and personalized approach to the monitoring of patients with ATTRv amyloidosis is needed, with ongoing and frequent assessment of treated patients to inform management decisions. No validated approach to such monitoring has been developed to date, and new techniques and a combination of tests (composite scores) need to be incorporated into routine clinical practice. This paper is an initial attempt in this direction, based on clinical experience and emerging evidence and data.

When considering a structured approach, different phenotypical groups may be usefully recognized to address each with specific tests and investigations, suggesting a more individualized approach dependent on the specific *TTR* mutation involved. This paper suggests that, in routine clinical practice, it may be useful to consider patients within the following categories: Val30Met early onset (<50 years), Val30Met late onset (>50 years) and non-Val30Met mixed phenotype, and non-Val30Met cardiac phenotype.

Multiple organ systems need to be assessed through a collaborative and multidisciplinary approach, including the assessment of the nerves, heart, eyes and kidneys, as well as patient-reported symptoms and health-related quality of life as evaluated from self-reported questionnaires, such as Norfolk QOL-DN and COMPASS-31. Magnetic resonance neurography is also a promising diagnostic and follow-up tool for the future.

The proposed approach should ensure structured, appropriate and ongoing assessment of individual patients being treated for ATTRv amyloidosis, such that interventions can be targeted and adjusted at the appropriate point in disease progression. It should also help healthcare professionals to consider the necessary time for individual therapies to demonstrate benefit to the patient initiated on treatment, before adjusting their treatment regime.

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References

[1] Benson MD, Kincaid JC. The molecular biology and clinical features of amyloid neuropathy. Muscle Nerve. 2007;36:411–423.

[2] Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013;8:31.

[3] Conceição I, González-Duarte A, Obici L, et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. J Peripher Nerv Syst. 2016;21:5–9.

[4] Rousseau A, Kaswin G, Adams D, et al. [Ocular involvement in familial amyloid polyneuropathy]. J Fr Ophtalmol. 2013;36:779–788.

[5] Sekijima Y, Ueda M, Koike H, et al. Diagnosis and management of transthyretin familial amyloid polyneuropathy in Japan: red-flag symptom clusters and treatment algorithm. Orphanet J Rare Dis. 2018;13:6.

[6] Conceição I, Damy T, Romero M, et al. Early diagnosis of ATTR amyloidosis through targeted follow-up of identified carriers of *TTR* gene mutations. Amyloid. 2019;26:3–9.

[7] Mundayat R, Stewart M, Alvir J, et al. Positive effectiveness of tafamidis in delaying disease progression in transthyretin familial amyloid polyneuropathy up to 2 years: an analysis from the Transthyretin Amyloidosis Outcomes Survey (THAOS). Neurol Ther. 2018;7:87–101.

[8] Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. Neurology. 2012;79:785–792.

[9] Coelho T, Maia LF, da Silva AM, et al. Long-term effects of tafamidis for the treatment of transthyretin familial amyloid polyneuropathy. J Neurol. 2013;260:2802–2814.

[10] Adams D, Coelho T, Obici L, et al. Rapid progression of familial amyloidotic polyneuropathy: a multinational natural history study. Neurology 2015;85:675–682.

[11] Adams D, Suhr OB, Dyck PJ, et al. Trial design and rationale for APOLLO, a Phase 3, placebo-controlled study of patisiran in patients with hereditary ATTR amyloidosis with polyneuropathy. BMC Neurol. 2017;17:181.

[12] Suhr OB, Lundgren E, Westermark P. One mutation, two distinct disease variants: unravelling the impact of transthyretin amyloid fibril composition. J Intern Med. 2017;281:337–347.

[13] Keohane D, Schwartz J, Gundapaneni B, et al. Tafamidis delays disease progression in patients with early stage transthyretin familial amyloid polyneuropathy: additional supportive analyses from the pivotal trial. Amyloid. 2017;24:30–36.

[14] Merlini G, Planté-Bordeneuve V, Judge DP, et al. Effects of tafamidis on transthyretin stabilization and clinical outcomes

in patients with non-Val30Met transthyretin amyloidosis. J Cardiovasc Trans Res. 2013;6:1011–1020.
[15] Barroso FA, Judge DP, Ebede B, et al. Long-term safety and efficacy of tafamidis for the treatment of hereditary transthyretin amyloid polyneuropathy: results up to 6 years. Amyloid. 2017;24:194–204.
[16] Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. N Engl J Med. 2018;379:22–31.
[17] Suanprasert N, Berk JL, Benson MD, et al. Retrospective study of a TTR FAP cohort to modify NIS + 7 for therapeutic trials. J Neurol Sci. 2014;344:121–128.
[18] Vinik EJ, Vinik AI, Paulson JF, et al. Norfolk QOL-DN: validation of a patient reported outcome measure in transthyretin familial amyloid polyneuropathy. J Peripher Nerv Syst. 2014;19:104–114.
[19] Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med. 2018;379:11–21.
[20] Pruppers MH, Merkies IS, Faber CG, et al. The Val30Met familial amyloid polyneuropathy specific Rasch-built overall disability scale (FAP-RODS(©)). J Peripher Nerv Syst. 2015;20:319–327.
[21] Treister R, O'Neil K, Downs HM, et al. Validation of the composite autonomic symptom scale 31 (COMPASS-31) in patients with and without small fiber polyneuropathy. Eur J Neurol. 2015;22:1124–1130.
[22] Mlinac ME, Feng MC. Assessment of activities of daily living, self-care, and independence. Arch Clin Neuropsychol. 2016;31:506–516.
[23] Hawkins PN, Ando Y, Dispenzeri A, et al. Evolving landscape in the management of transthyretin amyloidosis. Ann Med. 2015;47:625–638.
[24] Coelho T, Vinik A, Vinik EJ, et al. Clinical measures in transthyretin familial amyloid polyneuropathy. Muscle Nerve. 2017;55:323–332.
[25] Castro J, Miranda B, Castro I, et al. The diagnostic accuracy of Sudoscan in transthyretin familial amyloid polyneuropathy. Clin Neurophysiol. 2016;127:2222–2227.
[26] Cazzato D, Lauria G. Small fibre neuropathy. Curr Opin Neurol. 2017;30:490–499.
[27] Conceição I, Costa J, Castro J, et al. Neurophysiological techniques to detect early small-fiber dysfunction in transthyretin amyloid polyneuropathy. Muscle Nerve. 2014;49:181–186.
[28] Castro J, Costa J, de Castro I, et al. Electrochemical skin conductance in hereditary amyloidosis related to transthyretin V30M – a promising tool to assess treatment efficacy? Amyloid. 2018;25:267–268.
[29] Lefaucheur JP, Zouari HG, Gorram F, et al. The value of electrochemical skin conductance measurement using Sudoscan® in the assessment of patients with familial amyloid polyneuropathy. Clin Neurophysiol. 2018;129:1565–1569.
[30] Cruzat A, Qazi Y, Hamrah P. In vivo confocal microscopy of corneal nerves in health and disease. Ocul Surf. 2017;15:15–47.
[31] Pritchard N, Edwards K, Russell AW, et al. Corneal confocal microscopy predicts 4-year incident peripheral neuropathy in type 1 diabetes. Diabetes Care. 2015;38:671–675.
[32] Tavakoli M, Ferdousi M, Petropoulos IN, et al. Normative values for corneal nerve morphology assessed using corneal confocal microscopy: a multinational normative data set. Diabetes Care. 2015;38:838–843.
[33] Edwards K, Pritchard N, Dehghani C, et al. Corneal confocal microscopy best identifies the development and progression of neuropathy in patients with type 1 diabetes. J Diabetes Complications. 2017;31:1325–1327.
[34] Lewis EJ, Perkins BA, Lovblom LE, et al. Effect of omega-3 supplementation on neuropathy in type 1 diabetes: A 12-month pilot trial. Neurology. 2017;88:2294–2301.
[35] Rousseau A, Cauquil C, Dupas B, et al. Potential role of in vivo confocal microscopy for imaging corneal nerves in transthyretin familial amyloid polyneuropathy. JAMA Ophthalmol. 2016;134:983–989.
[36] Chen X, Graham J, Dabbah MA, et al. An automatic tool for quantification of nerve fibers in corneal confocal microscopy images. IEEE Trans Biomed Eng. 2017;64:786–794.
[37] Kollmer J, Hund E, Hornung B, et al. In vivo detection of nerve injury in familial amyloid polyneuropathy by magnetic resonance neurography. Brain. 2015;138:549–562.
[38] Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med. 2018;379:1007–1016.
[39] Barison A, Aquaro GD, Pugliese NR, et al. Measurement of myocardial amyloid deposition in systemic amyloidosis: insights from cardiovascular magnetic resonance imaging. J Intern Med. 2015;277:605–614.
[40] Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation. 2016;133:2404–2412.
[41] Beirão JM, Malheiro J, Lemos C, et al. Ophthalmological manifestations in hereditary transthyretin (ATTR V30M) carriers: a review of 513 cases. Amyloid. 2015;22:117–122.
[42] Rousseau A, Terrada C, Touhami S, et al. Angiographic signatures of the predominant form of familial transthyretin amyloidosis (Val30Met mutation). Am J Ophthalmol. 2018;192:169–177.
[43] Lobato L, Rocha A. Transthyretin amyloidosis and the kidney. Clin J Am Soc Nephrol. 2012;7:1337–1346.
[44] Lobato L, Beirão I, Silva M, et al. Familial ATTR amyloidosis: microalbuminuria as a predictor of symptomatic disease and clinical nephropathy. Nephrol Dial Transplant. 2003;18:532–538.
[45] Wixner J, Mundayat R, Karayal ON, et al. THAOS: gastrointestinal manifestations of transthyretin amyloidosis - common complications of a rare disease. Orphanet J Rare Dis. 2014;9:61.
[46] Suhr O, Danielsson A, Holmgren G, et al. Malnutrition and gastrointestinal dysfunction as prognostic factors for survival in familial amyloidotic polyneuropathy. J Intern Med. 1994;235:479–485.
[47] Wang YC, Bohannon RW, Li X, et al. Summary of grip strength measurements obtained in the 2011-2012 and 2013-2014 National Health and Nutrition Examination Surveys. J Hand Ther. 2018;pii: S0894-1130:30389–7. [Epub ahead of print]
[48] Cortese A, Vita G, Luigetti M, et al. Monitoring effectiveness and safety of Tafamidis in transthyretin amyloidosis in Italy: a longitudinal multicenter study in a non-endemic area. J Neurol. 2016;263:916–924.
[49] Waddington Cruz M, Amass L, Keohane D, et al. Early intervention with tafamidis provides long-term (5.5-year) delay of neurologic progression in transthyretin hereditary amyloid polyneuropathy. Amyloid. 2016;23:178–183.