Hereditary transthyretin amyloid neuropathies: advances in pathophysiology, biomarkers, and treatment

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Hereditary transthyretin (TTR) amyloid polyneuropathy is an autosomal dominant life-threatening disorder. TTR is produced mainly by the liver but also by the choroid plexus and retinal pigment epithelium. Detailed clinical characterisation, identification of clinical red flags for misdiagnosis, and use of biomarkers enable early diagnosis and treatment. In addition to liver transplantation and TTR stabilisers, three other disease-modifying therapies have regulatory approval: one antisense oligonucleotide (inotersen) and two small interfering RNAs (siRNAs; patisiran and vutrisiran). The siRNAs have been shown to stop progression of neuropathy and improve patients' quality of life. As none of the disease-modifying therapies can cross the blood–brain barrier, TTR deposition in the CNS, which can cause stroke and cognitive impairment, remains an important unaddressed issue. CRISPR-Cas9-based one-time *TTR* editing therapy is being investigated in a phase 1 clinical study. Identification of the earliest stages of pathogenesis in *TTR* variant carriers is a major challenge that needs addressing for optimal management.

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Introduction

Hereditary transthyretin (TTR) amyloid polyneuropathy is an autosomal dominant disease caused by pathogenic variants of *TTR*.[1] TTR protein that has formed amyloid fibrils is referred to as ATTR, and diseases dependent on amyloidosis caused by a mutation in *TTR* are referred to as amyloid TTR variant (ATTRv) amyloidosis.[2] Most cases of ATTRv amyloidosis are predominantly neuropathic (ATTRv polyneuropathy), predominantly cardiac (ATTRv cardiomyopathy), or mixed systemic amyloidosis. ATTRv polyneuropathy is a disabling neuropathy that occurs in adults and causes progressive degeneration of the axons of the somatic and autonomic peripheral nervous systems. Survival from symptom onset ranges from 6–12 years. The disease is present worldwide,[3] with an estimated prevalence of 10 000 cases.[4] Diagnosis is based on identifying a pathogenic *TTR* variant[5] and TTR-related amyloid deposits. Disease management has changed greatly in the past 5 years, thanks to the emergence of *TTR* gene silencing therapies that knockdown variant and wild-type TTR protein.[1] We review advances in the genetics and pathophysiology of ATTRv polyneuropathy, emerging biomarkers, the effects of new disease-modifying therapies, and recommendations for early diagnosis and treatment.

Genetics and pathophysiology

Genetics

ATTRv amyloidosis is an autosomal dominant condition, with symptom onset between the second and ninth decades of life.[2] *TTR* is located on chromosome 18 and includes four exons.[1] There are more than 150 reported *TTR* pathogenic variants;[5] most are associated with ATTRv polyneuropathy, ATTRv cardiomyopathy, or mixed systemic ATTRv amyloidosis, but some patients with mutations in *TTR* have ocular amyloidosis or CNS involvement. A dozen *TTR* variants are polymorphisms that are not pathogenic.[5]

The most common *TTR* variant is Val30Met, originally described in Portugal.[3,6,7] The onset of symptoms before age 50 years is typical for Portuguese and Japanese patients who have the Val30Met variant, whereas later onset is common among people with this variant in Sweden[7] and most other countries. This distinction is important because the clinical presentation and natural history are different between patients with onset before age 50 years and those with later onset. Other founder *TTR* variants include Thr60Ala, originating in northwest Ireland, and Val122Ile, found in 3·5% of African Americans in the USA. The *TTR* Val122Ile allele has been found in 10% of African Americans older than 65 years who have severe congestive heart failure.[8] Later disease onset (average 61 years) is reported for *TTR* Thr60Ala and for Val122Ile (60–80 years).[9] Very early onset (in the second decade of life) has been described for the Leu55Pro variant of *TTR*.[10] Wild-type TTR can also form amyloid fibrils, which can cause systemic amyloidosis that has a predominantly cardiac manifestation, with accumulation of wild-type TTR amyloid mainly in the heart in older people (mean age at diagnosis 73·6 years); amyloidosis associated with wild-type TTR is not a hereditary disease and it is not commonly associated with polyneuropathy. A post-mortem study reported that the prevalence of wild-type TTR amyloidosis is 22–25% in patients older than 80 years.[11]

The penetrance of pathogenic *TTR* variants varies by variant and geography. In Portugal, early-onset Val30Met penetrance is 80% at 50 years and 91% at 80 years, whereas in Sweden penetrance is 71% at 90 years.[7] Anticipation (ie, earlier onset of disease in successive generations) is well described for *TTR* Val30Met and is most prominent in men with maternal transmission.[7] The underlying mechanisms of both anticipation and maternal inheritance are not understood, despite investigation of non-coding *TTR* variants, mitochondrial DNA copy number, and large normal repeat allele expansions in various genes.[12–14]

Pathophysiology

TTR is a 55 kDa tetrameric protein with four identical subunits. Each subunit consists of 127 amino acids arranged in eight antiparallel β-sheets, and the tetramer

has a central channel containing two thyroxine binding sites. The main function of TTR is the transport of thyroxine and retinol-binding protein–vitamin A complex. TTR is made predominantly by the liver, but it is also made in the choroid plexus and retinal pigment epithelium.

ATTRv amyloidosis is a protein misfolding disease: dissociation of tetramic TTR subunits into monomers leads to misfolding and aggregation of TTR amyloid fibrils in extracellular spaces, which then form larger amyloid aggregates resulting in systemic organ dysfunction.[15] The pathophysiology of peripheral neuropathy has been clarified by ex-vivo ultrastructure studies of nerve biopsy specimens. A rupture of the blood–nerve barrier has been suggested as an initial lesion, allowing entry of circulating TTR into the endoneurial space. Amyloid fibril aggregates and non-fibrillar TTR induce Schwann cell atrophy, axon loss, and neurodegeneration attributed to the high affinity of amyloid for Schwann cells.[16]

Several transgenic mouse models of ATTRv amyloidosis have been engineered by introducing *TTR* genes with different promoters and variants. Cardiac TTR amyloid deposition in a mouse model of ATTRv expressing pathogenic variants of human *TTR* requires local plasmin generation mediated by an enzyme plasminogen activator and TTR cleavage, consistent with the mechano-enzymatic hypothesis for amyloid formation.[17] Mice with *TTR* comprising human exons and mouse introns showed that serum concentrations of ATTR and the *TTR* gene per exon were similar to each other in the liver, brain, and eyes. This mouse model might be useful in the study of new treatments, especially gene therapy.[15]

The mechanism of amyloidosis involving wild-type TTR has not been elucidated, but an age-related decrease in TTR amyloid clearance might be involved. In a transgenic mouse model, 20% of animals older than 18 months have human cardiac TTR amyloid deposition that is similar to the lesions seen in people with wild-type TTR amyloidosis, and the amyloid deposits are made of human TTR monomers.[18]

Disease presentation

Neurological features

Clinical heterogeneity among people with ATTRv polyneuropathy contributes to missed and delayed diagnoses.[1] People with symptom onset before the age 50 years typically present with a length-dependent polyneuropathy with early impairment of pain and thermal sensibilities starting in the toes and soles, in association with autonomic dysfunction and clinically significant weight loss. Other hallmarks include a progressive and insidious disease course, onset in the third decade of life, a familial condition, and a 20% rate of mortality within 7–10 years from onset. Sensory symptoms, such as shooting pain and allodynia, extend proximally to the knees and thighs. On physical examination, distal hypoesthesia for thermal and pain sensibilities precedes anaesthesia, and finally postural loss with initially preserved tendon reflexes. This initial length-dependent, small-fibre neuropathy, often with nerve conduction study results similar to those of healthy people, progresses at diagnosis to large-fibre sensory and motor involvement.[1] ATTRv polyneuropathy can also present in later decades of life as a length-dependent axonal neuropathy with less neuropathic pain than at younger ages. The condition can progress slowly, such as in patients with the *TTR* Val122Ile variant, or more rapidly, such as in patients with the Val107Ile variant, who often have early weakness and prominent disability within 2 years from the onset of disease.[19]

Neuropathy with onset in the upper limbs has been reported in 18% of patients with ATTRv polyneuropathy;[20] this type of neuropathy resembles carpal tunnel syndrome but extends into upper limbs after carpal tunnel syndrome surgery, and later into lower limbs. ATTRv polyneuropathy can also present as a predominant motor neuropathy.[1] Autonomic neuropathy is an inaugural symptom in 30% of patients with early onset peripheral neuropathy and the Val30Met *TTR* variant. Erectile dysfunction and retrograde ejaculation are early symptoms of ATTRv polyneuropathy whereas later symptoms include gastrointestinal manifestations, such as alternating diarrhoea and constipation, early satiety, and eventually urinary disorders and orthostatic hypotension.[21]

CNS manifestations are the initial symptom in patients with some *TTR* variants. In addition, CNS involvement is becoming increasingly common in individuals with variants such as Val30Met, who usually present with PNS symptoms, as patients receiving liver-targeted disease-modifying therapies can now live longer than 10 years, especially after liver transplantation.[22] TTR amyloid primarily accumulates in the leptomeninges and leptomeningeal vessels in direct contact with CSF, and later extends to meningocortical penetrating vessels and subpial cortical lesions.[23] The most common CNS manifestations are: transient focal neurological episodes (TFNEs), cerebral haemorrhage, subarachnoid haemorrhage, and cerebral infarction, all secondary to cerebral amyloid angiopathy;[24,25] auditory neuropathy; and, in later stages, cognitive impairment.[26,27] TFNEs can include aphasia, unilateral weakness or sensory disturbance, dysarthria, atypical behaviour, scintillating scotoma, seizures, and disturbance of consciousness lasting from several minutes to several hours.[24,25]

Non-neurological clinical features

Cardiac involvement in ATTRv polyneuropathy is frequent. Cardiac abnormalities are most prominent in people with late-onset polyneuropathy associated with *TTR* Val30Met or Thr60Ala, who usually have an abnormal ECG at presentation.[28] Severe cardiac conduction block requiring pacemaker implantation or atrial fibrillation is seen in 40% of patients who carry the Val30Met variants.[24] Interventricular septal thickness of more than 12 mm is reported in 70% of patients with

	Investigation	Marker for	Duration of the examination	Time to result	Routine in clinical practice?	Indications	Requirements	Limitations	Specificity
Gold -standard diagnostic biomarkers									
Variant *TTR*[5]	*TTR* gene sequencing	Genetic disease	0·25 h	From 10 days to several months	Yes	Genetic counselling: presymptomatic and prenatal	*TTR* gene testing for amyloidogenic variant	Insufficient in asymptomatic carriers to start disease-modifying therapy	+
Congo red labelling[1]	Minimally invasive biopsies: punch skin biopsy, LSGB abdominal fat pad, or nerve biopsies	Amyloid deposit	0·5 h	1 week	Yes	To confirm disease onset before starting disease-modifying therapy	Pathology laboratory expertise, Congo red, polarised microscopy	Availiability of laboratories able to provide serial sections, Congo red staining and examination to identify amyloid deposits	+
Cardiac DPD uptake[38]	99mTc-DPD; PYP; HMDP bone scintigraphy	Amyloid in myocardium	0·5 day	A few days	Yes	Cardiac amyloidosis to avoid myocardial biopsy	Nuclear medicine laboratory; no monoclonal protein to rule out light chain amyloidosis	Cannot be repeated every year; contraindicated in pregnancy	+
Large nerve fibre loss									
NIS[39]	Clinical examination	Sensory motor neuropathy	10 min	Immediately	Yes	Baseline assessment and follow-up with therapy	Training on reproducible scoring required for meaningful follow-up of disease	Not useful in small fibre neuropathy	0
Nerve conduction studies[40]	Neurophysiologial testing	Large-fibre lesion	0·5 day	Immediately	Yes	Baseline assessment and follow-up with therapy	Same examinator and same machine	Not useful in small fibre neuropathy	0
Median nerve cross-section area[41]	Nerve ultrasound	Large-fibre lesion	0·5 h	1 day	No	Carriers of *TTR* pathogenic variants	Ultrasound device operated by a trained physician	Not specific, also chronic inflammatory demyelinating polyneuropathy	0
T2w signal[38] proton spin density (r) SN calibre measured as cross-sectional area	3 Tesla magnetic resonance neurography with high-structural resolution	Large -fibre lesion	50 min	NA	No	Carriers of *TTR* pathogenic variants	High resolution protocol at 3.0 Tesla magnetic field	Expert neuroradiology team required	NA
Magnetisation transfer ratio and cross-sectional area of the sciatic nerve[42]	Magnetisation transfer contrast imaging at 3 Tesla	Nerve damage	50 min	1·5 h post-processing	No	People with ATTRv amyloidosis	3.0 Tesla magnetic resonance scanner	Expert neuroradiology team required	NA
Total fatty infiltration score[43]	Muscle MRI lower limbs	Axonal degeneration	0·5 day	A few days	No	For assessment of axonal degeneration in calves and thighs	3 Tesla scanner	Expert neuroradiology team required	0

(Table 1 continues on next page)

	Investigation	Marker for	Duration of the examination	Time to result	Routine in clinical practice	Indications	Requirements	Limitations	Specificity
(Continued from previous page)									
Efficacy of disease-modifying therapy									
Serum TTR[44-45,46]	Lab test prealbumin nephelometry	Amyloid precursor concentration	Blood test	1 day	Yes	To measure *TTR* knockdown after *TTR* gene silencing RNAi ASO	Biochemical lab before and after *TTR* gene silencing every 6 months	Does not measure ATTRv, dimers or monomers	0
Plasma NfL[47]	SIMOA	Neuronal axonal degeneration	2 h	1 week	No	For biological effect of *TTR* gene silencing RNAi on axonal degeneration	SIMOA device in laboratory	Assay in hospital lab only	0
Amyloid load[48]	Punch skin biopsy	Amyloid load	NA	NA	No	For biological effect of *TTR* gene silencing RNAi	Expert pathological laboratory	Requires analysis of repeated skin biopsies in the same laboratory	+
Gland nerve fibre density[49]	Punch skin biopsy	Sweat gland nerve fibre density	NA	NA	No	To assess effect of RNAi on small nerve fibres	Laboratories able to provide serial sections, Congo red staining, and examination to identify amyloid deposits	Requires analysis of repeated skin biopsies in the same laboratory	0

Sensivity is categoried as present (+), absent (0), or NA. ASO=antisense oligonucleotides. DPD=3,3-diphosphono-1,2-propanodicarboxylic acid. HMDP=^{99m}Tc- hydroxymethylene- diphosphonate. LSGB=labial salivary gland biopsy. NA=not available. NIS=neuropathy impairment score. NfL=neurofilament light chain. RNAi=RNA interference. PYP=technetium-99m pyrophosphate. SIMOA=single-molecule array.

Table 1: **The diagnosis and monitoring of people with hereditary amyloid polyneuropathies**

Figure 1: **Amyloid deposits from a leg skin biopsy obtained 10 cm proximal to the lateral malleolus in the midaxillary line**
Typical findings in a patients with ATTRv polyneuropathy. 50 µm-thick skin section stained with Congo red show staining around a sweat duct (broken arrow) and in the dermis (A, B; solid arrows) in a patient with ATTRv polyneuropathy. The section in panel B is shown in panel C under polarised light and shows birefringence confirming the presence of amyloid (green arrows). A skin section from a healthy control (D) shows no Congo red staining. Scale bar=50 µm. ATTRv=amyloid transthyretin variant.

late-onset ATTRv polyneuropathy compared with 15% of patients with early onset.[28] 24-h ECG is recommended to detect conduction disturbances. Ocular manifestations are frequent in early-onset ATTR Val30Met polyneuropathy, including amyloid deposition in the vitreous, dry eye, and secondary glaucoma.[1,29] Renal involvement might occur in late-onset ATTR Val30Met polyneuropathy, with microalbuminuria, proteinuria, and end-stage renal failure in 10% of cases.

Diagnosis

Differential diagnosis and red flags

In high-prevalence regions (ie, Japan, Portugal, and Sweden), diagnosis of ATTRv polyneuropathy is facilitated by a family history of ATTRv polyneuropathy, presentation of common symptoms, and access to specialist clinical centres. In other countries, diagnosis can be delayed owing to variable clinical presentation and lower clinical suspicion. Many patients with ATTRv polyneuropathy are misdiagnosed with idiopathic progressive neuropathy at early stages.[30]

For length-dependent small-fibre polyneuropathy, the main differential diagnoses include idiopathic axonal polyneuropathy and diabetic polyneuropathy. For generalised polyneuropathy, differential diagnoses include chronic inflammatory demyelinating polyneuropathy (CIDP), idiopathic axonal polyneuropathy,

***Panel*: Emerging biomarkers for diagnosis and monitoring of patients with transthyretin amyloid polyneuropathy**

High-resolution magnetic resonance neurography
This method can detect and localise nerve injury at the level of an individual nerve fascicles in various neuropathies. The total number of nerve-lesion voxels and signal quantification of proton density at thigh level were greater in asymptomatic carriers than in non-carriers. Sural nerve T2 signal and proton spin density were also significantly increased in asymptomatic carriers of variant transthyretin (*TTR*) compared with individuals in a control group compared with non-carriers.[50]

High-frequency nerve ultrasound
This painless method can quickly probe morphological changes in peripheral nerves to indirectly reflect the neuropathological changes of chronic neuropathies. The technique can quantify the cross-sectional area of nerves, and peripheral nerve cross-sectional area in the brachial plexus is larger in asymptomatic carriers of pathogenic variants of *TTR* than in non-carriers.[51]

Plasma neurofilament light chain
This biomarker of axonal damage is released into the circulation and discriminates asymptomatic mutation carriers from early symptomatic patients.[99] This method could eventually be used as a biomarker of nerve damage before onset of symptoms of polyneuropathy.

In-vivo laser scanning corneal confocal microscopy
This rapid and non-invasive imaging technique can be used to quantify small corneal nerve fibres. Corneal nerve fibre density was significantly lower in pre-symptomatic carriers of pathogenic variants of *TTR* than in non-carriers.[98]

Meta-iodobenzylguanidine (MiBG) scintigraphy
The sympathetic system effect involves a decrease in pre-synaptic catecholamine stores with preserved cardiac β-receptor catecholamine responsiveness, which leads to an early and striking decrease in MiBG uptake. Sympathetic cardiac denervation can be detected with scintigraphic measurement of the heart-to-mediastinum uptake ratio in MiBG scintigraphy. Early cardiac sympathetic denervation evidenced by decreased 123I-MIBG uptake in a scan precedes amyloid burden detected by 3,3-diphosphono-1,2-propanodicarboxylic acid in *TTR* variant carriers.[100]

Punch skin biopsies
This method is the gold standard for small-fibre neuropathies. Skin biopsy is performed following established procedures. A 3-mm diameter skin punch is taken from the distal leg 10 cm proximal to the lateral malleolus under local anaesthesia with 2% lidocaine. Skin biopsy sections are processed for quantifying epidermal and sudomotor innervation. Reduction of intra-epidermal nerve fibre density has been reported in 73[46]–94%[41] asymptomatic carriers of pathogenic variants of *TTR* compared with non-carriers. Quantitatively, the sudomotor cholinergic innervation (peptidergic marker) SGII(VIP) was significantly higher in asymptomatic carriers compared with symptomatic hereditaryTTR amyloid polyneuropathy.[46]

Quantitative sensory testing
This psychophysical test method investigates the functional status of the somatosensory system by calibrated stimuli and subjective perception thresholds, providing an overview of the presence of sensory plus or minus signs, such as hyperalgesia or hypoaesthesia. Cooling detection thresholds and heat pain (HP 5 and HP 0·5) modalities seem particularly useful for identifying subclinical neuropathy in carriers of pathogenic variants of *TTR*, with cooling detection thresholds showing a high sensitivity to detect early neuropathic involvement.[96]

Nerve conduction studies
By us of this method, an annual decrease of at least 25% in a sensory composite score within 2 years before symptom onset represented a 1·48 increase in the risk of conversion from asymptomatic to symptomatic stage of disease.[97]

Pittsburgh compound B-PET
This biomarker is useful for the early detection of cerebral amyloid angiopathy associated with TTR amyloidosis by imaging of systemic amyloid deposition in early-onset TTR Val30Met amyloidosis.[25]

lumbar spinal stenosis,[31] toxic peripheral neuropathy, alcoholic neuropathy, and paraproteinaemic peripheral neuropathy.[1,32] Differential diagnoses for upper limb onset neuropathy include carpal tunnel syndrome, CIDP, paraneoplastic neuropathy, and cervical radiculopathy; for motor neuropathy, the differential diagnoses include amyotrophic lateral sclerosis and motor CIDP.

In most countries where late-onset ATTRv amyloidosis is more common than early-onset forms, the main misdiagnosis is CIDP, accounting for 15–35% of patients.[1,33] Early diagnosis of ATTRv polyneuropathy can be improved by consideration of red flags for incorrect diagnoses.[30] In countries where early-onset ATTR Val30Met is common, the diagnosis should be considered in any patient with length-dependent small-fibre peripheral neuropathy, autonomic dysfunction, a family history of ATTRv polyneuropathy, unexplained weight loss, heart rhythm disorders, vitreous opacities, or renal abnormalities.[30,34,35] In other countries, diagnosis should be considered in patients with an idiopathic rapidly progressive axonal neuropathy or atypical CIDP. Clinical and electrophysiological red flags that help distinguish ATTRv polyneuropathy from CIDP include pain, dysautonomia, small-fibre sensory loss above the wrists, upper limb weakness, neurophysiologically severe motor and sensory axonal loss,[33] bilateral carpal tunnel syndrome, and cardiac hypertrophy.[30] TFNEs—the most common CNS manifestations of ATTRv polyneuropathy—

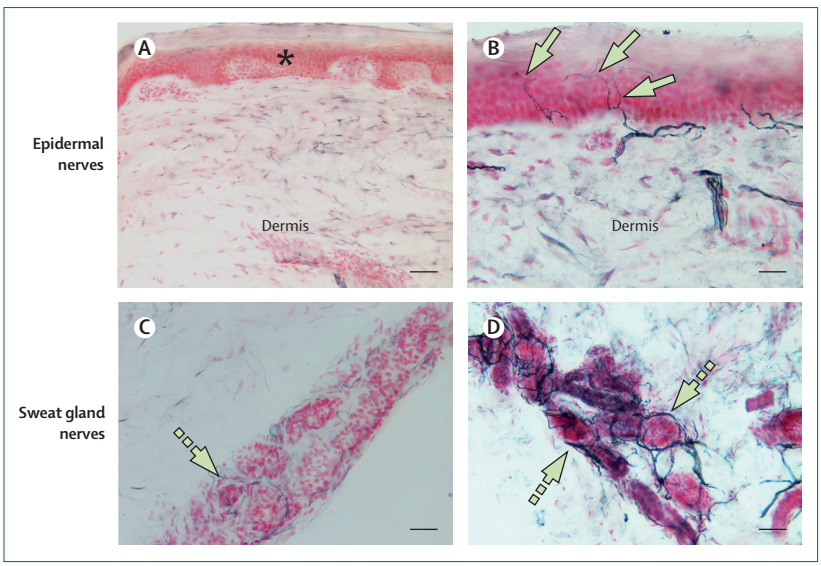


***Figure 2*: Nerve fibre density in a leg skin biopsy obtained 10 cm proximal to the lateral malleolus in the midaxillary line**

Representative 50-µm skin sections immunohistochemically stained with PGP9·5, a marker of neuron cytoplasmic protein and therefore nerve fibre density, from a patient with amyloid transthyretin variant peripheral neuropathy (A, C) and a healthy control (B, D). Panel A shows an absence of epidermal nerve fibres (*), whereas C shows a sweat gland with markedly reduced innervation (broken arrow). Panel B shows innervated epidermis (arrows) and panel D shows a densely innervated sweat gland (broken arrows).

See Online for appendix

are frequently misdiagnosed as transient ischaemic attacks. Differential diagnosis between TFNEs and transient ischaemic attacks is important because TFNEs are a risk factor for future symptomatic intracerebral haemorrhage and therefore antiplatelet or anticoagulant drugs should be avoided in people who have TFNEs.[36]

Diagnostic methods and biomarkers

Biomarkers are measured as an indicator of pathogenic processes or responses to an exposure or intervention.[37] Three main diagnostic biomarkers are used for ATTRv polyneuropathy: *TTR* gene testing, tissue biopsy, and bone scintigraphy (table 1). *TTR* gene testing and screening for pathogenic variants of *TTR*[5] should be used first in patients with idiopathic neuropathy. In a multinational study,[49] pathogenic variants were identified in 1% of participants who had idiopathic neuropathy or heart disease. *TTR* should be screened for variants in patients with suspected Charcot–Marie–Tooth disease who have late onset and initial sensory symptoms,[50] or patients with atypical CIDP,[51] especially those with pain or dysautonomia, but not in individuals who have idiopathic small-fibre neuropathy.[52]

Amyloid deposition is a key biomarker of ATTRv polyneuropathy.[53] Identifying TTR-containing amyloid is crucial in carriers of *TTR* variants to confirm a diagnosis and so that disease-modifying therapy can be initiated. Amyloid can be identified in any tissue but not in tenosynovial biopsy for carpal tunnel syndrome, which might precede onset of ATTRv polyneuropathy by 10 years. Minimally invasive biopsies, including labial salivary gland biopsy, punch skin biopsies[53,54] (figure 1), and abdominal fat pad biopsy[50] have a high diagnostic yield and are preferred to nerve biopsy.[55] Amyloid can be detected in distal leg skin biopsies in 70%–100% of symptomatic individuals,[53,54,56] with a diagnostic sensitivity of 70–85% and specificity of 100%.[54,56] The amount of amyloid in skin correlates with the severity of neuropathy.[54,56,57]

Bone scintigraphy can be used because cardiac uptake of the tracers used in bone scintigraphy can be a measure of cardiac amyloid deposition. This procedure avoids myocardial biopsies in patients who have pathogenic *TTR* variants,[38] but should be used only if the minimally invasive skin biopsies are negative (appendix).

Two measures are widely used in clinical practice to assess impairment and as sensitive indicators of progression: the neuropathy impairment score (NIS; range 0–244), which comprises scores of muscle weakness, reflexes, and sensory impairment,[39] and nerve conduction studies that measure large-fibre impairment, degree of axonal loss as sural nerve amplitude, and peroneal nerve amplitude.[40]

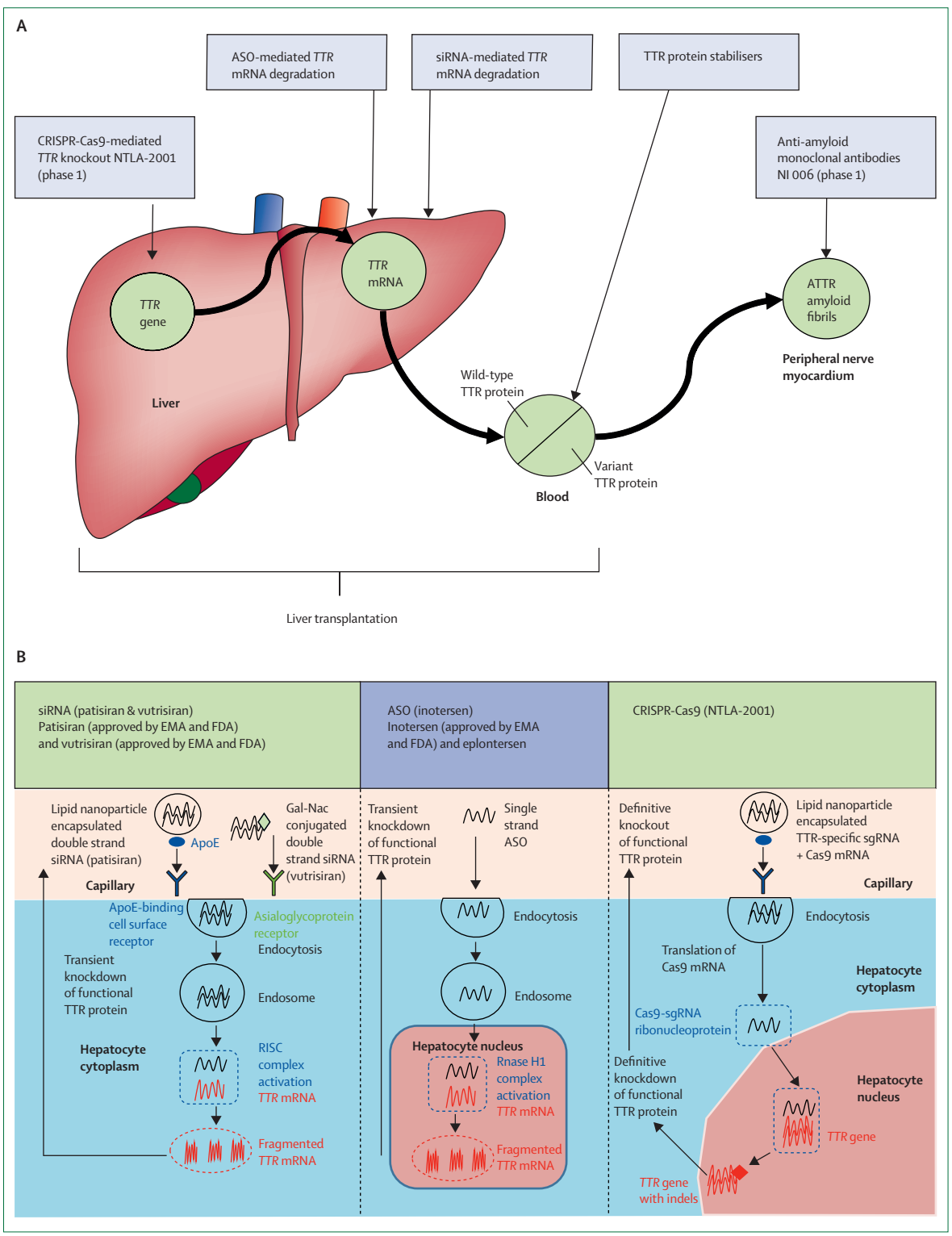
Novel nerve imaging biomarkers are emerging for large-fibre and small-fibre involvement (table 1; panel). Nerve imaging requires high-resolution magnetic resonance neurography with magnetisation transfer ratio and cross-sectional area in proximal and distal nerves[42] Nerve ultrasounds have shown differences, including nerve enlargement,[41,62] in people with ATTRv polyneuropathy compared with controls; differences from healthy individuals are also seen in CIDP.[63] Intramuscular fat quantification by muscle MRI

***Figure 3*: Approved and emerging disease-modifying therapies for hereditary transthyretin amyloid polyneuropathy**

(A) Inhibition of TTR amyloidosis. Some approaches inhibiting ATTR production are approved for clinical use whereas others are in development. Liver transplantation was the first therapy to be approved for clinical use, followed by the TTR stabiliser tafamiids (approved by the European Medicines Agency) and diflunisal and more recently *TTR* mRNA-targeted silencing by small interfering RNAs (siRNAs; eg, patisiran and vutrisiran) and ASOs (eg, inotersen). TTR stabilisers inhibit dissociation of TTR tetramers into amyloidogenic monomers. Treatments that are preliminary include CRISPR-Cas9 technology-mediated gene knockout (eg, NTLA-2001) and anti-ATTR amyloid antibodies to disrupt amyloid deposits (eg, NI 006). Green circles represent the potential targets of disease modifying therapies and black lines represent the steps from the gene to the amyloid deposits. (B) Mechanisms of *TTR* gene silencers and *TTR* gene editing. Patisiran comprises siRNAs bound to the RNA-induced silencing complex[98] to mediate the cleavage of target mRNA of both pathogenic variant and wild-type *TTR* and knockdown their production and release. A lipid nanoparticle formulation ensures hepatic delivery through vascular fenestrations and binding to ApoE receptors on hepatocytes. Vutrisiran is directed to the liver by conjugation to a triantennary N-acetyl galactosamine ligand that binds the asialoglycoprotein receptor on the surface of hepatocytes. Inotersen selectively hybridises to *TTR* mRNA, resulting in the degradation of *TTR* mRNA via RNase H1, preventing production of TTR protein. NTLA-2001 consists of the same lipid nanoparticle delivery system as patisiran, encapsulating a mRNA for Cas9 protein and a sgRNA targeting *TTR*. In the liver, endocytosis ensues, Cas9 mRNA is translated, and the Cas9-sgRNA ribonucleoprotein enters the nucleus and instigates targeted DNA cleavage. Endogenous DNA repair then provokes the appearance of indels in the *TTR* gene, leading to frameshift mutations impairing functional TTR protein production. ATTR=transthyretin protein that has formed amyloid. ASO=s antisense oligonucleotide. gRNA=single guide RNA. TTR=transthyretin.

reflects axonal degeneration[43] and is a promising method that needs to be further investigated.

Punch skin biopsy is increasingly used to assess intraepidermal (sensory) and sudomotor (autonomic) innervation and is safe and well tolerated in patients with pathogenic *TTR* variants.[56] Additionally, the same tissue can be used to identify the presence of amyloid (figure 1). Reduced intraepidermal nerve fibre density has been



observed in symptomatic patients with ATTRv compared with age-matched and sex-matched controls;[41,42,45] the reduction in nerve density is more pronounced at distal sites than proximal sites (figure 2). This pattern has been observed across many *TTR* variants. The reduction in distal leg intraepidermal nerve fibre density has been correlated with disease duration, neuropathy severity,[53,54,56] thermal pain thresholds, and autonomic function.[54] Similar patterns have been reported in sweat gland innervation and pilomotor innervation.[56,57]

Management

Overall management

ATTRv polyneuropathy requires a multidisciplinary management involving neurologists, cardiologists, genetic counselors, and, if necessary, ophthalmologists and other health-care professionals.[1] Care includes symptomatic treatment and amyloid-specific therapies (figure 3A).

ATTRv polyneuropathy can have a substantial effect on health-related quality of life, severely impairing patients and causing anxiety and depression in some asymptomatic carriers.[64] The Norfolk quality of life diabetic neuropathy score was similar in people with ATTRv polyneuropathy and people with severe diabetes complications.[65] Lower quality of life correlates with advanced disease,[64] lower polyneuropathy disability scores (indicating greater disability),[57] and longer disease duration.[44,54,66]

Disease-modifying therapy

Liver transplantation was first used to treat ATTRv polyneuropathy in 1990, and four disease-modifying therapies have been approved for ATTRv polyneuropathy in the past 10 years: the TTR stabiliser tafamidis and, more recently, three *TTR* gene silencers (figure 3A).

Liver transplantation

More than 2000 liver transplantations have been done in patients with ATTRv polyneuropathy worldwide since 1990.[67] Independent predictors of longer survival after transplant are earlier age of symptom onset, shorter disease duration before transplantation, carrying the Val30Met *TTR* variant, and high BMI.[67] Disease progression and poor survival after transplantation can occur in patients with late onset polyneuropathy caused by wild-type amyloid TTR. Liver transplantation is more effective in individuals with the Val30Met variant of *TTR* who have early-onset ATTRv polyneuropathy than in those who have late onset or other variants.[67,68]

TTR stabilisers

TTR stabilisers are small molecules that bind strongly to the unoccupied thyroxine-binding sites within TTR, thereby inducing kinetic stability, limiting tetramer dissociation, and limiting amyloidogenesis. Tafamidis is the only TTR stabiliser approved by the European Medicines Agency (EMA) for ATTRv polyneuropathy. A study of long-term effectiveness of tafamidis in 210 patients with early-onset *TTR* Val30Met peripheral neuropathy[69] showed that patients with a low median NIS of six and a high neurophysiological score at baseline were significantly more likely to respond to tafamidis treatment with fully stabilised neuropathy and weight, than patients with a median NIS of 14 and low neurophysiological score, who were more likely to worsen or to progress.

20 mg and 80 mg tafamidis doses were compared with placebo in the phase 3 Transthyretin Amyloidosis Cardiomyopathy Clinical Trial.[70] 441 patients were enrolled, including 24% with pathogenic variants in *TTR* and 76% with wild-type *TTR*. All-cause mortality was lower in the groups treated with tafamidis than in those treated with placebo. The long-term extension study[71] of this trial has provided evidence in favour of tafamidis 80 mg compared with 20 mg for people who have cardiomyopathy associated with amyloid TTR. Benefits of tafamidis seem to be the greatest for early-onset patients. Tafamidis (61 mg) has marketing authorisation for ATTR cardiomyopathy from the EMA and US Food and Drug Administration (FDA).

Diflunisal, another TTR stabiliser, reduced disease progression by 60% compared with placebo in a 24-month randomised, placebo-controlled, double-blind, international study including 130 patients with ATTRv polyneuropathy; 52% of patients discontinued treatment as a result of disease progression and liver transplantation,[72] which was the only other treatment option at the time of the study. The long-term effect of diflunisal is unknown.[64]

TTR gene silencers

The aim of *TTR* gene silencing is to degrade mRNA of both variant and wild-type *TTR* alleles in hepatocytes to limit liver TTR production. The mechanisms of *TTR* RNA interference (RNAi) by patisiran and vutrisiran and the antisense oligonucleotide inotersen in the liver are detailed in figure 3.

In a phase 3 trial (APOLLO-A),[45] 225 patients with ATTRv polyneuropathy and a wide range of disease severities were randomly assigned to receive intravenous patisiran or placebo once every 3 weeks (table 2). The primary endpoint was the change in the modified NIS+7 score, a validated 304-point composite measure,[39] at 18 months. The study was positive: the least-squares mean change from baseline deteriorated by 28·0 (SD 2·6) points with placebo at 18 months but improved by 6·0 (SD 1·7) points with patisiran. 83 (56%) of 148 participants in the patisiran group improved from baseline, whereas three (4%) of 77 improved with placebo. Timed 10 m walk test and COMPASS 31 autonomic score questionnaire results improved from baseline in the patisiran group and the Rasch-built overall disability scale remained stable. In the patisiran group, serum TTR concentrations were reduced by 81% over 18 months. Adverse events that were more frequent in the patisiran group included peripheral oedema and infusion-related reactions.

	Patisiran	Vutrisiran	Inotersen
Phase 3 trial	APOLLO-A, Adams et al (2018)[45]	Helios-A, Adams et al (2023)[46]	NEURO-TTR, Benson et al (2018)[44]
Category	RNAi therapy	RNAi therapy	ASO therapy
Dose	0·3 mg/kg every 3 weeks	25 mg, every 3 months	300 mg, once per week
Administration	Intravenous	Subcutaneous	Subcutaneous
Duration of trial (months)	18	9 and 18	15
Randomisation ratio	2:1 patisiran to placebo	3:1 vutrisiran to patisiran	2:1 inotersen to placebo
Participants (n)	225	164	172
FAP stage	1 and 2	1 and 2	1 and 2
Primary endpoint	Change from baseline in mNIS+7	Change from baseline in mNIS+7 at 9 months*	Change from baseline in mNIS+7 and Norfolk QOL-DN at 15 months
Secondary endpoints	Change from baseline in Norfolk QOL-DN, 10M-WT, mBMI, R-ODS, and compass 31	Change from baseline in Norfolk QOL-DN and gait speed 10-MWT at month 9* and mNIS+7, Norfolk QOL-DN, 10-MWT, mBMI, and R-ODS score at 18 months*	Change from baseline in Norfolk QOL-DN symptoms domain score physical functioning or large fibre neuropathy domain score, TTR, and mBMI
Characteristics of patients at baseline			
Age (years), median (range), or mean (SD)			
Placebo	63 (34–80)	63 (SD 15)†	59·5 (SD 14·0)
Drug	62 (24–83)	60 (SD 20)	59·0 (SD 12·5)
TTR variants (n)	39	25	27
mNIS+7 at baseline mean (SD)			
Placebo	74·6 (37·0)	74·6 (37·0)	74·8 (39·0)
Drug	80·9 (41·5)	60·6 (36·0)	79·2(37·0)
FAP stage 1; FAP stage 2			
Placebo	37/77 (48%); 39/77 (51%)	37/77 (48%); 39/77 (51%)	42/60 (70%); 18/60 (30%)
Drug	67/148 (45%); 81/148 (55%)	94/122 (77%); 28/122 (23%)	74/112 (66%); 38/112 (34%)
Results			
Participants who completed the study, n (%) of N			
Active drug	138/148 (93%)	117/122 (96%)	87/112 (75%)
Placebo	55/77 (71%)	55/77 (71%)†	52/60 (87%)
Primary endpoints			
Least squares mean changes from baseline (SE)*	mNIS+7	mNIS+7 9 months	mNIS+7
Placebo	+28·0 (2·6)	+14·76 (2·00)	+25·5 (2·7)
Drug	−6·0 (1·7)	−2·24 (1·43)	+5·8 (±2·13)
Least squares mean difference medicine *vs* placebo, intention-to-treat population	−34·0 (SD 3·0; 95% CI −39·9 to −28·1); p<0·001	−17·00 (95% CI −21·78 to −12·22); $p=3{\cdot}54\times10^{-12}$	−19·7 (95% CI −26·4 to −13·0); p<0·001
Secondary endpoint least squares mean change from baseline (SD)*	QOL-DN	mNIS+7 18 months	QOL-DN‡
Placebo	+14·4 (SD 2·7)	+28·09 (SD 2·28)	+12·7 (SD 2·67)
Medicine	−6·7 (SD 1·8)	−0·46 (SD 1·60)	+1 (SD 2·2)
Precautions	Patisiran administration requires premedication with steroids anti H1, and anti-H2	None	Check platelet count before injection
Main adverse events	Infusion-related reaction, peripheral oedema	Transient injection site reactions 4·1%	Thrombocytopenia, glomerulonephritis
Biological monitoring in the trial	None	None	Platelet count every 2 weeks
Improved mNIS+7 in active drug; versus placebo	83/148 (56%); 3/77 (4%)	59/122 (48·3%); 3/77 (3·9%) at 18 months*	40/112 (36%); 11/60 (19%)
Marketing authorisation	EMA and FDA	EMA and FDA	EMA and FDA

(Table 2 continues on next page)

	Patisiran	Vutrisiran	Inotersen
(Continued from previous page)			
Indication	ATTRv polyneuropathy FAP stages 1 and 2	ATTRv polyneuropathy FAP stages 1 and 2	ATTRv polyneuropathy FAP stages 1 and 2
Open-label extension	Adams et al (2021)[69]	NA	Brannagan et al (2022)[70]
Number of patients enrolled (completed) the open-label extension	186 (164 [88%])	NA	135 (27 [20%])§
Duration of open-label extension	12 months	NA	36 months

FAP stages: 1=walking unaided; 2=walking with aid (once or two crutches); 3=wheelchair bound or bedridden. ATTRv polyneuropathy=hereditary transthyretin amyloid polyneuropathy. ASO=antisense oligonucleotide. Compass-31=composite autonomic symptom score 31. EMA=European Medicines Agency. FAP=familial amyloid polyneuropathy. (FDA=US-Food and Drug Administration. mBMI=modified body-mass index. mNIS+7=modified neuropathy impairment score +7. 10-MWT=10 m walk test. Norfolk QOL-DN=Norfolk quality of life-diabetic neuropathy. RNAi=RNA interference therapeutic. R-ODS=Rasch-built overall disability scale. TTR=transthyretin. *Positive value indicates worsening of the disease, whereas negative value shows improvement. †Score compared with the placebo group of the APOLLO study (external placebo group). ‡Coprimary endpoint. §43 patients switched to an approved commercial drug.

Table 2: **TTR gene silencers; results of phase 3 trials and open label extension studies**

Vutrisiran is a second-generation N-acetylgalactosamine siRNA for the treatment of ATTRv amyloidosis given subcutaneously every 3 months (figure 3B).[46] The Helios-A phase 3 trial[46] evaluated the safety and efficacy of vutrisiran in patients with ATTRv polyneuropathy. Participants were randomly assigned to receive vutrisiran or patisiran in the ratio 3 (vutrisiran):1 (patisiran). The placebo group of the APOLLO-A study was an external comparator for the efficacy endpoints. Vutrisiran met the primary endpoint change from baseline in the modified NIS+7 at month 9 and all secondary efficacy endpoints. Serum TTR reduction with vutrisiran was similar to reduction with patisiran at 18 months.

The NEURO-TTR[44] was a pivotal randomised, double-blind, placebo controlled, phase 3 trial of inotersen in patients with ATTRv polyneuropathy and biopsy-proven amyloid deposits (table 2). 172 patients were randomly assigned to receive weekly subcutaneous injections of inotersen or placebo. Both primary endpoints (the change in the modified NIS+7 score and in the Norfolk QOL-DN score) diverged between the inotersen and placebo groups at week 66.[44] On average, patients who received placebo had an increase in the modified NIS+7 from baseline of 25·5 points versus an increase of 5·8 points with inotersen. 40 (36%) of 112 patients in the inotersen group had an improved or stable modified NIS+7 score versus 11 (19%) of 60 with placebo. In the inotersen group, reductions in circulating TTR were sustained at the nadir of 74% until 66 weeks. Three patients developed severe thrombocytopenia, including one with a fatal cerebral haemorrhage, and three patients developed glomerulonephritis.

Gene silencing was also studied in 23 patients with progression of ATTRv polyneuropathy after liver transplantation in a phase 3b, open-label trial evaluating safety and efficacy of patisiran,[67] with a median reduction in serum TTR concentrations of 91% (95% CI 86·1%–92·3%) and improved neuropathy at 12 months.[76] Adverse events were mild. Nine patients were treated with inotersen for a median of 12 months after liver transplantation in the extended access programme. The NIS remained stable and five (56%) of nine patients stopped treatment due to thrombocytopenia or liver rejection, which was reversed when inotersen was discontinued.[77]

Patisiran, vutrisiran, and inotersen received approval by the EMA and FDA for patients with ATTRv polyneuropathy at familial amyloid polyneuropathy (FAP) stage 1 (walking unaided) and stage 2 (walking with an aid). Patients receiving gene silencing need daily vitamin A oral supplementation to avoid eye disease. Treatment with patisiran requires premedication to avoid infusion-related reactions. Inotersen treatment requires platelet count assessment every 2 weeks, and assessment of urine protein creatinine ratio and estimated glomerular filtration rate every 3 months.

Open-label extension studies have confirmed the biological effects and clinical benefits of patisiran and inotersen.[74,75] However, delayed patisiran introduction had a negative effect on survival,[74] compared with earlier treatment. Close platelet and renal monitoring were effective in reducing the risk of severe adverse events in the open-label extension study of inotersen.[75] Real-word data are also available for patisiran: nine patients with ATTRv amyloidosis, with five *TTR* variants and various disease stages, benefited from patisiran treatment over 2 years.[78] In an retrospective study of 23 people with ATTRv polyneuropathy who started inotersen during the early-access programme, five patients stopped treatment and dosing frequency was reduced as a result of thrombocytopenia in seven patients.[79]

In most cases, there is no reason to combine tafamidis with gene-silencing drugs if the gene-silencing agent eliminates 90% of circulating TTR. However, as 90% suppression does not always occur, the combination of drugs needs to be considered on a case by case basis.

Follow-up of treated patients

Two biological biomarkers can be used to assess the efficacy of disease-modifying therapies for ATTRv polyneuropathy or amyloidosis (table 1): serum TTR

knockdown, which assesses the biological efficacy of *TTR* gene silencing,[44,45] and plasma neurofilament light chain, which is a marker of axonal degeneration. Plasma neurofilament light chain increased in the placebo group but showed a significant and sustained decline in the patisiran-treated group relative to baseline at 18 months.[47]

Amyloid deposition would be an ideal biomarker to assess drug effects in people with ATTRv anyloidosis but requires specific equipment and measurement methods. A reduction in cardiac uptake of 3,3-diphosphono-1,2-propanodicarboxylic acid, a marker of amyloid deposition, was seen in 15 (94%) of 16 patients with ATTRv cardiomyopathy and various TTR variants who received patisiran during 12 months of study.[17] A significant decrease in dermal amyloid burden was shown in the lower limbs over 24 months in a phase 2 open-label extension study of patisiran after repeated punch skin biopsies.[48] According to 2022 guidelines, the evaluations to monitor progression of ATTRv polyneuropathy include NIS, peripheral neouropathy disability, walking tests, COMPASS 31 questionnaire, and the Rasch-built overall disability scale.[80]

Guidelines for therapy

Expert consensus guidelines for ATTRv amyloidosis therapy have been proposed.[80] Patients with ATTRv polyneuropathy with no cardiac involvement should be treated either with tafamidis in early FAP stage 1, or patisiran or inotersen in stages 1 and 2.[80] Vutrisiran was not included in the guidelines as it was approved after the guidelines were issued. People with mixed ATTRv polyneuropathy and cardiomyopathy or ATTRv cardiomyopathy can be treated with tafamidis, which is the only drug approved for cardiomyopathy,[80] or with a gene silencer. Indications for liver transplantation have narrowed since 2010, due to the inability of this procedure to halt disease progression in people who have late-onset ATTRv polyneuropathy associated with Val30Met and non-Val30Met variants.[80,81]

Genetic counselling

Genetic counselling has become crucial since the advent of disease-modifying therapies, especially for at-risk family members, who need to be informed about the disease and treatment options. Genetic counselling covers diagnostic testing, information on reproductive options, including antenatal and preimplantation diagnosis, and presymptomatic testing for relatives. Natural history studies have highlighted the importance of pre-symptomatic testing to allow early treatment.[82]

Country-specific guidelines for TTR-related genetic counselling consider which variants predominate in that particular country.[83–85] Anticipation and sex need to be considered, especially for individuals with the Val30Met variant.[86] Most countries suggest that counselling for reproductive options and presymptomatic testing is done through genetic services, whereas counselling for diagnostic testing is often done by a specialist in TTR amyloidosis diagnosis.[87]

Conclusions and future directions

The identification of various clinical presentations, and red flags, and simple assays are facilitating early diagnosis of ATTRv amyloid polyneuropathy. Phase 3 trials have validated *TTR* gene silencers, including RNAi therapy and antisense oligonucleotides. Symptomatic patients should have access to disease-modifying therapies to stop disease progression. Patients in FAP stage 3, who are wheelchair bound, do not have approved pharmacological options. We suggest treating these patients to preserve maximum of autonomy and functions in the upper limbs via compassionate use. Ongoing trials will assess whether disease-modifying therapy is efficacious for ATTRv cardiomyopathy.

New therapeutic options are in development. Acoramidis, a highly selective TTR stabiliser, showed good stability in ex-vivo tests in serum and plasma samples after oral administration in patients with symptomatic ATTRv cardiomyopathy in a phase 1 study,[88] and a good safety profile in a phase 2 study.[89] A phase 3, randomised, double-blind, placebo-controlled study of acoramidis (ATTRibute-CM trial; NCT03860935) ended in May, 2023, with positive results.[90] Eplontersen is an ASO conjugated to an N-acetylgalactosamine ligand that allows specific liver targeting. Monthly subcutaneous administration is being evaluated in an open-label multicentre phase 3 study.[91] The recombinant human anti-ATTR antibody NI006 binds to wild-type ATTR and ATTRv fibrils with the aim of eliminating amyloid deposits.[92] A phase 1 double-blind trial of NI006 in 40 patients showed weak evidence of a reduction of cardiac tracer uptake on bone scintigraphy, and also reduction of extracellular volume on cardiovascular MRI.[93] The drug was well tolerated. A phase 3 trial is in the pipeline.[93]

The hope for a single treatment that permanently reduces serum TTR is based on CRISPR-Cas9 technology, which involves delivery of Cas9 mRNA either with a unique TTR-targeted guide RNA encapsulated in lipid nanoparticles (NTLA-2001) or with an adeno-associated virus vector that can deliver a gene-editing meganuclease.[94] This method has been shown to be effective in vitro, in transgenic mice, and in a non-human primate, with a 94% inactivation capacity maintained over a 12-month period.[94,95] In a phase 1 trial, NTLA-2001 was administered to six patients with ATTRv polyneuropathy in a single intravenous dose. At day 28, the mean reduction in serum TTR protein from baseline was 87% and adverse events were rare and mild;[91] however, unexpected future adverse events are a potential concern.

Future perspectives include: the combination of disease-modifying therapies; the development of

Search strategy and selection criteria

We searched MEDLINE, Embase, and the Cochrane databases for articles published between Jan 1, 2018, and June 30, 2023. We used the search terms "transthyretin amyloid neuropathy", "hereditary amyloid neuropathy", "transthyretin amyloidosis", and "transthyretin polyneuropathy". No language restrictions were applied. We also used older articles (when more recent papers with similar scientific relevance were unavailable) and articles from our personal records. The final reference list was generated based on relevance to the topics covered in this Review.

therapies for ocular amyloidosis[96,97] and CNS leptomeningeal amyloidosis with TTR stabilisers able to cross the blood–brain barrier, such as tolcapone;[98] and *TTR*-silencing agents targeting the choroid plexus.[99]

The development of new biomarkers for earlier detection of disease onset and monitoring of disease progression in the PNS or of ATTR-type cerebral amyloid angiopathy is also crucial. Imaging biomarkers, punch skin biopsy, nerve imaging, and neurophysiological tests seem to be less specific than the current methods, such as amyloid detection by biopsies including nerve biopsy, labial salivary gland biopsy, or bone scintigraphy, but could be useful to detect subclinical nerve damage in pathogenic *TTR* mutation carriers, which could allow initiation of disease-modifying therapies at an even earlier stage of the disease.[61,100]

Contributors

DA conceptualised the manuscript. MMR, YS, IC, MW-C, AE-L, and MP searched and selected the references. DA, MMR, YS, MW-C, AE-L, and MP wrote the first draft and all authors wrote the second draft of the manuscript. All authors revised the manuscript and wrote the final draft.

Declaration of interests

DA was a consultant for Alnylam, Bridgebio, Pfizer, and AstraZeneca; and received support for travel from Alnylam. MMR was a consultant for Alnylam, Akcea; received a research grant from Alnylam and honoraria for chairing a symposium for the company; and declared consultancy compensation for being on a steering committee of Eidos Therapeutics. YS received compensation for consulting activities from Alnylam and Pfizer; received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, and educational events from Alnylam and Pfizer; and declares receiving research grants Alnylam and Pfizer. MP received compensation for consulting work from Pfizer, Alnylam, Vertex, Intellia, AstraZeneca, and Ionis. IC was a consultant for Alnylam and Pfizer; received honoraria for lectures, presentations, speakers bureaus, manuscript writing, and educational events from Pfizer, Sobi, and Alnylam; received financial support for meetings and travel from Pfizer and Alnylam; and declares receiving research funding from Pfizer. MW-C was a consultant for Ionis, Para Tu Consulta, Alnylam, Pfizer, Prothena, and AstraZeneca; and received support for attending meetings and for travel Pfizer, Ionis, and PTC. AE-L was a consultant for Alnylam; was supported by Alnylam and Pfizer to travel to attend meetings; declares receiving honoraria for lectures, presentations, speakers bureaus, manuscript writing, and educational events from Alnylam and Pfizer; and received payment for participation in a data safety monitoring board for Intellia.

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