REVIEW

Familial amyloid polyneuropathy

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Purpose of review
Transthyretin familial amyloid polyneuropathy is the most disabling hereditary polyneuropathy of adult onset because of a point mutation of transthyretin gene. This review updates our knowledge about natural history of the disease, phenotypes, diagnosis tools for small and large fibers involvement, expert's consensus for both symptomatic and asymptomatic follow-up, and treatment's research.

Recent findings
Access to *TTR* gene sequencing permit diagnosis and first reports of the disease in nonendemic countries (EU countries, United States, China, India). Most studies showed a more severe natural history of the neuropathy in nonendemic countries. First European consensus for management has been established. New long-term results allow selection of best candidates for liver transplantation based on phenotype and cardiac involvement. Multimodal evaluation of small fiber neuropathy and resonance magnetic neurography are under development. New results are available for long-term effect of tafamidis in late-onset patients. *TTR* gene silencing drugs are subject to phase 3 clinical trials.

Summary
New methods for the evaluation of the disease are being developed. The *TTR* gene silencing strategy will be available by the end of 2017.

Keywords
amyloid polyneuropathy, small fiber neuropathy, transthyretin gene silencing, transthyretin stabilizer

INTRODUCTION

Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a severe hereditary neuropathy of adult onset, affecting the sensorimotor and autonomic function as well as other organs (heart, eyes, kidney and so on). Evolution is fatal without treatment. Better knowledge of this life-threatening disease is needed to improve diagnosis and treatment. Before 1990s', TTR-FAP was considered as a hereditary disease of early onset (<50 years) because of a single point mutation of the *TTR* gene, it is now often diagnoses in the setting of a sporadic, late onset (>50 years) disabling neuropathy with various phenotypes. Up to 100 point mutations have been identified. Availability of genetic testing has improved diagnosis in nonendemic countries. This review reflects the recent progress in TTR-FAP: a better knowledge of the disease and its natural history, it is geographical widespread, new tools to assess disease onset and progression and finally therapeutic strategies with novel therapies.

IDENTIFICATION OF TRANSTHYRETIN FAMILIAL AMYLOID POLYNEUROPATHY IN NEW COUNTRIES

TTR-FAP is now diagnosed worldwide with the availability of genetic testing: most EU countries [1▪▪], America [2▪] and Asia (China [3▪] and India [4]). This has led to the description of new variants and specificities in certain areas. Val30Met is the most common variant in the EU countries with the exception of Bulgaria: Glu89Gln variant [1▪▪] and the UK: Thr60Ala variant [5▪]. In the Turkish cohort of 17 patients from nine families, with five different variants, onset of disease was 40.4 years (range 21–66) with feet paresthesia [6]. However, two patients with the Gly53Glu variant reported regressive dysarthria and hemiparesis. A retrospective study in Palma de Majorca (Spain) of 95 patients confirmed differences [7▪] between the patients with early onset and late onset. Peripheral neuropathy was the initial symptom in late onset. Autonomic involvement was more frequent in early onset than

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KEY POINTS

- TTR-FAP is a worldwide disease.
- Tafamidis, a TTR stabilizer, is able to control disease progression at very early stage of early-onset Val30Met TTR-FAP.
- Two phase 3 clinical trials are ongoing with *TTR* gene silencing to knock down both mutant and wild type TTR; results should be available at the end of 2017.
- Tools assessing small fiber neuropathy are needed to allow early diagnosis of the disease and monitor effect of therapies.
- A European consensus for management of TTR-FAP, and carriers of TTR mutations has been elaborated to guide clinicians.

late-onset patients (26 versus 5%). During follow-up, systemic involvement was more common in late-onset patients. The characteristics of four unrelated Chinese families with genetically confirmed TTR-FAP have been reported with four different mutations [3▪]. All patients presented with a length-dependent sensorimotor polyneuropathy associated with cardiomyopathy and vitreous opacities. As of today, 18 different TTR variants have been reported among 39 families in China and two TTR variants Ala97Ser [3▪] and in Taiwan.

PHENOTYPE VARIABILITY, VARIOUS COURSE SEVERITY

A more severe and rapid course has been reported with some variants: late-onset Val30Met, Ile107Val, and Thr60Ala with a shorter survival of 6–7 years from onset [5▪,8▪▪]. French patients with three different genotypes were compared with Portuguese Val30met patients. French, Ile107Val, Ser77Tyr, and late-onset Val30Met FAP showed more rapid and severe disease progression in comparison with Portuguese Val30Met FAP. Onset of gait disorders was three times faster and the functional impairment measured by modified Norris declined 40 times faster in Ile107Val patients. Median survival was significantly shorter in Ile107Val and in late-onset Val30Met patients [8▪▪].

A large multinational study characterized neuropathy severity and rate of progression in 283 patients with TTR-FAP. Neuropathy Impairment Scores (NIS), polyneuropathy disability (PND) scores, and manual grip strength were collected. Intercountry variation was observed, concerning TTR variants with the majority of patients from Portugal (92%) having early-onset Val30Met-FAP as well as for PND score and FAP stage. There was an association between NIS and *TTR* genotype. The estimated rate of NIS progression for a population with a median NIS of 32 was 14.3 points/year; the corresponding estimated rate for the modified NIS + 7 is 17.8 points/year [9▪].

MISDIAGNOSIS AND RED FLAGS

TTR-FAP is a rare disease and diagnosis is usually delayed by 2–5 years; we must evoke this diagnosis more often in case of progressive idiopathic polyneuropathy. In endemic countries like Portugal, early diagnosis of onset of the disease is frequent and facilitated by positive family story, genetic counselling, and periodic follow-up in the national referral center. In nonendemic countries, diagnosis is still difficult and delayed, favored by a sporadic presentation, many pitfalls and misdiagnosis because of varied inaugural symptoms [10,11▪▪] (Table 1). Chronic inflammatory demyelinating polyneuropathy is one of the major misdiagnosis [8▪▪,11▪▪], because of a sensorymotor impairment with areflexia; nerve conduction sometimes fulfilling European Federation of Neurological Societies/PNS definite criteria for chronic inflammatory demyelinating polyneuropathy in 15% [8▪▪] to 37% [11▪▪], albuminocytologic dissociation in cerebrospinal fluid in 23% [11▪▪] to 71% [11▪▪]. Other misdiagnosis are recurrent including lumbar spinal stenosis [10,11▪▪] and idiopathic axonal polyneuropathy [10], seldom motor neuron disease [12]. TTR-FAP is rarely initially suspected in late-onset TTR-FAP, and only in 23 to 33% of patients [10]. Hereditary amyloid protein transtyretin (ATTR) amyloidosis should be suspected in elderly presenting with progressive vitreous opacities of undetermined etiology [13▪].

Red flags to identify TTR-FAP have been suggested [14▪] (Table 2). TTR-FAP should be suspected when progressive peripheral sensory–motor neuropathy is associated to one or more of the following: family history of a neuropathy, autonomic dysfunction, cardiac hypertrophy, gastrointestinal disorder, unexplained weight loss, carpal tunnel syndrome, renal impairment, or ocular involvement. These red flags are frequent in early-onset Val30Met patients, but are uncommon in late-onset cases except weight loss and are thus less appropriate for nonendemic areas [15,16▪] (Table 2).

CLINICAL MEASURES AND NEW TOOLS FOR ASSESSING TRANSTHYRETIN FAMILIAL AMYLOID POLYNEUROPATHY PATIENTS

It is necessary to better quantify the evolution of TTR-FAP to manage these patients. The relationship

Table 1. Misdiagnosis of Transthyretin familial amyloid polyneuropathy

Ref	Characteristics of series	Most frequent Genotype	Incidence of misdiagnosis	Misdiagnosis	%
[11▪▪]	150 patients with ATTR diagnosed Period 1999–2013 Reference center for amyloidosis (Pavia, Italy)	Val30Met 26% Glu89Gln 19% Phe64Leu 13% Ile68Leu 9% Thr49Ala 5%	33%	CIDP $n=30$ Lumbar and sacral radiculopathy and lumbar canal stenosis ($n=11$) Paraproteinaemic peripheral neuropathy ($n=3$) AL amyloidosis ($n=3$) Wild-type ATTR amyloidosis ($n=1$) Toxic peripheral neuropathy ($n=4$) Vasculitic peripheral neuropathy ($n=1$) Motor neuron disease ($n=1$) Fibromyalgia ($n=2$) Other diagnosis ($n=2$)	(61) [22▪▪] [6] [6] [2▪] [8▪▪] [2▪] [2▪] [4] [4]
[10]	60 patients Period 2008–2010 46 French non Portuguese origin Four major phenotypes: SF-PNP, or LD all fiber PNP, and three new phenotypes: multifocal neuropathy in upper limbs, ataxic PNP (20%)	Val30Met 46 Ser77Tyr 28 Ile 107 Val 6.5%	74%	idiopathic axonal PNP ($n=11$) CIDP ($n=8$) lumbar spinal stenosis ($n=7$)	
[12]	Report of cases of ATTR amyloidosis mimicking ALS and review of cases	Val30Met Phe64Leu Ile68Leu Tyr78Phe Val93Met	$N=10$	ALS Motor neuropathy Motor CIDP	

ALS, amyotrophic lateral sclerosis; ATTR, amyloid protein transtyretin; CIDP, Chronic inflammatory demyelinating polyneuropathy; PNP, polyneuropathy.

between disease stage and NIS-lower limbs (NIS-LL) and Norfolk quality of life-diabetic neuropathy (Norfolk QOL-DN) total score was assessed in 61 patients with Val30Met-TTR-FAP and 16 healthy controls. NIS-LL and Norfolk QOL-DN scores discriminated disease stages [17▪▪]. An outcome measure at the activity and participation level has been built in FAP using Rasch methodology [18▪]. A preliminary pre-familial amyloid polyneuropathy specific Rasch-built overall disability scale (FAP-RODS) was assessed twice in 248 patients with early-onset Val30Met TTR-FAP patients enrolled in

Table 2. Proposed red flags

	EO V30M TTR	LO V30M TTR[a]
Progressive peripheral sensory-motor neuropathy with one or more of the following:		
Family history of a neuropathy	94%[a]	31%[b]–48%[a]
Autonomic dysfunction, gastrointestinal problems	40–48%[a]	10%[a]
Carpal tunnel syndrome	10%[c]	23%[b]
Unexplained weight loss	15%[b]	49%[b]
Cardiac hypertrophy	<5%	<10%
Renal impairment,	<5%	<10%
Ocular involvement	<5%	<10%
Additional alert signs:		
Rapid disease progression	NA	NA
Failure of response to prior therapies	NA	NA

EO, early onset (<50 years); LO, late onset (>50 years); NA: incidence not available; TTR, transthyretin.
[a][15].
[b][8▪▪].
[c][16▪].
Adapted with permission [14▪].

Portugal. An ordinal-based 24-item FAP-symptoms inventory questionnaire was also assessed. A final 34-item FAP-RODS was constructed fulfilling Rasch requirements and is a disease-specific interval measure suitable for detecting activity and participation restrictions in patients with TTR-FAP. The association between severity of neuropathy and disease stage, and the rate of neuropathy progression was assessed in a retrospective cross-sectional analysis of a multinational population of 283 patients with TTR-FAP [8▪▪]. NIS was associated with functional scales of locomotion, PND score, and FAP stage. There was an inverse association between right hand manual grip strength and the PND score, with an observed reduction in median grip strength from 30.8 kPa for PND score I to 6.0 for PND score IV.

SMALL FIBER NEUROPATHY INVOLVEMENT

New tools must be found for earlier diagnosis. Sudomotor function failure is one of the autonomic neuropathy manifestations of TTR-FAP. A study investigated the pathology and clinical significance of sudomotor denervation among 28 patients with Ala97Ser TTR and late-onset disabling neuropathy [19▪▪]. Autonomic symptoms were present in 22 patients (78.6%). Skin biopsies were performed on the distal leg of TTR-FAP patients. Sudomotor innervation was stained with two markers: protein gene product 9.5 (PGP 9.5), and vasoactive intestinal peptide, a sudomotor nerve functional marker. The sweat gland innervation index for PGP 9.5 (PGP 9.5) and vasoactive intestinal peptide of TTR-FAP patients were significantly lower than those of age and sex-matched controls. Patients with orthostatic hypotension or absent sympathetic skin response at palms were associated with lower sweat gland innervation index PGP 9.5.

The diagnostic value of a new 3 min and noninvasive sudomotor test (SUDOSCAN by Impeto Medical, Inc.; Paris, France) was assessed in TTR-FAP [20▪]. In total, 133 TTR-FAP Val30Met carriers, divided in asymptomatic and symptomatic stage 1 were compared with 37 healthy controls. The right sural sensory nerve action potential (SNAP), the plantar sympathetic skin response, and the electrochemical skin conductance (ESC) measured by Sudoscan in both hands and feet were analyzed. All neurophysiological measures were significantly worse in the symptomatic patients. Feet ESC was the only test distinguishing symptomatic patients with autonomic dysfunction from those without, and both groups from asymptomatic carriers and healthy controls. Feet ESC showed 76% sensitivity and 85% specificity for detection of dysautonomia.

EARLY SKIN DENERVATION IN TRANSTHYRETIN FAMILIAL AMYLOID POLYNEUROPATHY

To assess early skin denervation in TTR-FAP, intraepidermal nerve fiber density (IENFD), and clinical findings were investigated in 32 patients with TTR-FAP, 11 asymptomatic mutation carriers, and 23 healthy volunteers. IENFD values were reduced in patients with the V30M mutation, patients with non-V30M mutations, compared with healthy controls. Skin denervation also occurred in presymptomatic V30M mutation carriers. The IENFD was correlated with disease duration and various peripheral neuropathy parameters such as sensory impairment in the Kumamoto clinical score, heat-pain detection threshold, and SNAP. IENFD may thus be useful for early diagnosis and may serve as a biomarker in clinical trials for TTR-FAP [21▪▪].

CONFOCAL CORNEAL MICROSCOPY TO ASSESS SMALL FIBER DENERVATION

A prospective, single-center, cross-sectional controlled study determined the correlation of small fiber neuropathy with in-vivo confocal microscopy (IVCM) of the corneal nerves, a rapid noninvasive technique in patients with TTR-FAP [22▪▪]. Fifteen patients with TTR-FAP underwent a complete neurologic examination, including NIS-LL, hand grip strength, and evaluation of autonomic dysfunction, as well as nerve conduction and ESC studies, and IENFD quantification. They underwent complete ophthalmologic assessment, including IVCM. The corneal nerve fiber length (CNFL) was shorter in patients than controls. There was a correlation between CNFL and the severity of small fiber neuropathy and sensorimotor neuropathy according to NIS-LL. Patients with altered SNAP and IENFD had a shorter CNFL. The CNFL could be measured in all patients thus avoiding the floor effect seen with other neuropathy measures such as SNAP ($n = 11$) and IENFD ($n = 4$).

IN-VIVO DETECTION OF LARGE NERVE INJURY IN TRANSTHYRETIN FAMILIAL AMYLOID POLYNEUROPATHY BY MAGNETIC RESONANCE NEUROGRAPHY

Lower limb nerve injury in TTR-FAP was assessed and quantified *in vivo* by high-resolution magnetic resonance neurography (MRN) [20▪]. Twenty study participants with *TTR* gene mutation were investigated: 13 patients with polyneuropathy and seven asymptomatic carriers and compared to age and sex-matched controls. MRN (3T) was performed with large longitudinal coverage in lower limbs by using

axial T2-weighted and dual echo turbo spin echo 2D sequences with spectral fat saturation. Precise manual segmentation of lower limbs nerves was performed on each slice. Histogram-based normalization of nerve–voxel signal intensities was performed using the control group as normative reference. Nerve–voxels were subsequently classified as lesion voxels if a threshold of 41.2 (normalized signal intensity) was exceeded. The total number of nerve–lesion voxels (cumulated from proximal-to-distal) was significantly higher in symptomatic patients versus asymptomatic carriers and controls. It was also higher in asymptomatic carriers compared to controls. Lower limb nerve injury could be detected and quantified *in vivo* on microstructural level by MRN in both symptomatic TTR-FAP and in yet asymptomatic carriers.

DETECTION OF AMYLOID DEPOSIT IN THE SKIN BY ABDOMINAL FAT ULTRASONOGRAPHY

Abdominal fat ultrasonography (AFUS) was assessed as a noninvasive screening method for TTR-FAP. Quantitative analysis of ultrasound B-mode imagery demonstrated a significant increase in mean echogenicity and a loss of the normal structure of the layers of fat tissue in 19 patients with TTR-FAP. The ultrasound features of the fat tissue and the degree of amyloid deposition seen histopathologically were significantly correlated. These results suggest that AFUS may be a valuable method for screening for TTR-FAP [23▪].

FIRST EUROPEAN CONSENSUS FOR DIAGNOSIS, MANAGEMENT, AND TREATMENT OF TRANSTHYRETIN FAMILIAL AMYLOID POLYNEUROPATHY

The European Network for TTR-FAP (ATTReuNET) including delegates from 10 European countries, including nine National Referal Centers proposed a consensus on strategies for diagnosis and management of TTR-FAP. A structured approach to ongoing multidisciplinary care for the patient was also elaborated [24▪]. A consensus recommended strategies for presymptomatic genetic testing and management of individuals at risk for TTR-FAP [25▪]. ATTReuNET experts concluded that genetic counselling for diagnosed individuals and at-risk family members is mostly beneficial and should be carried out with care by trained professionals. Systematic and regular monitoring of asymptomatic carriers is necessary to detect early signs of TTR-FAP. At least two related symptoms and positive biopsy findings for amyloid deposits are required to confirm diagnosis of TTR-FAP, and to initiate antiamyloid therapy [26▪].

PATHOGENESIS OF TRANSTHYRETIN FAMILIAL AMYLOID POLYNEUROPATHY NEUROPATHY

To better understand pathophysiology of peripheral neuropathy in TTR-FAP patients, the morphology of Schwann cells and endoneurial microvessels was examined with electron microscopy [27▪▪]. Sural nerve biopsy specimens from 49 patients with Val30Met TTR-FAP were assessed, including 11 early-onset cases from endemic foci and 38 late-onset cases from Japan. Loss of nerve fibers with or without neighboring amyloid deposition was a common feature. The amount of amyloid deposition was greater relative to the extent of nerve fiber loss in early onset than late-onset cases. The Schwann cells, particularly of nonmyelinating type, that were close to amyloid fibrils appeared to be more atrophied in early onset than late-onset cases. The numbers of endothelial cell nuclei, endothelial cell profiles, and occluded microvessels were significantly increased in patients with TTR-FAP compared with 37 controls with neuropathy. Findings suggestive of the disruption of blood–nerve barriers were also found more frequent in patients with FAP, regardless of the presence of amyloid deposition. These findings suggest that amyloid fibrils can cause Schwann cell damage, resulting in the predominant loss of small fiber axons characteristic of early-onset cases and that vasculopathy may participate in the pathogenesis of neuropathy, as in late-onset cases.

GENETIC FACTORS CAN MODULATE AGE AT ONSET IN TRANSTHYRETIN FAMILIAL AMYLOID POLYNEUROPATHY

Val30Met TTR-FAP shows a wide variation in age at onset between clusters, families and generations, and also between sexes in Portugal. Genes found to be associated with FAP Val30Met ATTR pathways may act as age at onset modifiers. A recent study explored the role of amyloid P component, serum (APCS) and retinol binding protein 4 (RBP4) genes studying the involvement of sex-linked genetic modifiers androgen receptor (AR) and 17β-hydroxysteroid dehydrogenase (HSD17B1) genes in age at onset variation in Portuguese families. DNA from 318 patients was collected. A total of 18 tagging single nucleotide polymorphisms (SNPs) from APCS, RBP4, AR and HSD17B1 and five additional SNPs from APCS and RBP4 previously studied were genotyped. Findings were that APCS and RBP4 were associated with late age at onset. In addition,

rs11187545 of the RBP4 was associated with an early age at onset. For the AR, in the male group three SNPs were associated with an early age at onset, whereas in the female group four were associated with both an early and later age at onset [28▪]. Sixty-two tagging SNPs from nine genes were analyzed in the same cohort of patients. Variants from six genes were significantly associated with early and/or late onset. A strong synergistic interaction between neutrophil gelatinase associated lipocalin and matrix metalloprotease-9 genes was confirmed. These findings showed that different genetic factors can modulate differently the onset of disease's symptoms with clinical implications in the genetic counseling and follow-up of mutation carriers [29].

THERAPY: BETTER SELECTION OF CANDIDATES FOR LIVER TRANSPLANTATION

LT was evaluated in a 20-year retrospective analysis of the FAP World Transplant Registry composed of 1940 patients, among which 1379 are alive. Overall, 20-year survival after LT was 55.3%. Multivariate analysis revealed modified body mass index, early onset of disease, disease duration before LT, and TTR Val30Met versus non-TTR Val30Met mutations as independent significant survival factors [30▪]. Prediction of long-term survival after LT for TTR-FAP was also assessed in a monocentric cohort of 215 consecutive patients largely investigated to assess neuropathic and cardiac involvement who underwent LT between 1993 and 2011 [31▪▪]. Over a median follow-up of 5.9 years after LT, 84 patients died, and cardiac events were the leading cause of death. The significant pejorative factors for death were PND score at least III, orthostatic hypotension, New York Heart Association (NYHA) functional class more than I, QRS duration at least 120 ms, thickened interventricular septum. The risk prediction model proposed in this study accurately estimated the individual risk of death after LT for patients with TTR-FAP, with an online calculator [31▪▪]. The identification of high-risk patients should lead to consider alternative therapies. In the same 215 consecutive TTR-FAP transplanted patients, evaluation of cardiac dysautonomia following LT is a valuable asset for predicting survival: 123-MIBG scintigraphy and heart rate response to atropine had better prognostic accuracy [32▪]. Ocular manifestations of Val30Met TTR-FAP are not influenced by liver transplantation in a meaningful way [33▪].

ANTIAMYLOID MEDICINE

There are actually two innovative therapeutic approaches: TTR tetramer stabilizer and *TTR* gene silencing in clinical trials [34▪]

TTR stabilizer tafamidis is proposed as first-line antiamyloid therapy in stage 1 TTR-FAP [24▪]. It obtained marketing authorization for delaying the neuropathy in Europe and other countries with good results in early onset V30M TTR-FAP. Early intervention with tafamidis provides long-term (5.5-year) delay of neurologic progression in TTR-FAP. Mean changes from baseline in NIS-LL was 5.3 points at 5.5 years [35▪]. Three open-label studies assessed the long term effect of tafamidis (20 mg daily) on late-onset TTR-FAP on functional progression and safety [36] (Table 3). In one study which

Table 3. Long-term course of transthyretin familial amyloid polyneuropathy patients on tafamidis

References	*N*	TTR variant	Stage at baseline	Mean age at baseline (years)	Mean NIS	Patients followed for 18 months or more	Progression criteria	Results	Mean change of NIS score at 18 months
[35▪]	53	Val30Met	Stage 1	38	NIS-LL: 4.1	53	Change from baseline of NIS-LL		NIS-LL 5.3
[37▪▪]	61	Val30Met 17 (28%) Phe64Leu 16 (26%) Glu89Gln 14 (23%)	Stage 1: 72%	62	53	34	Change of FAP Stage Change of PND score Increase of NIS >2 points	7/21 (33 50 65%	15.6 points
[36]	10	Val30Met (90 Ser77Tyr (10%)	Stage 1: 60%	61	31	8	Increase of NIS score Ambulatory status	Worsening in 4	10 points
[38▪]	43	Val30Met (47%)	PND ≥II :47%	59	34	28	Increase of NIS >4 points Increase of mPND score	9% mPND 1 à +	13 points

NIS: including sensory score in the big toe and index finger; reflex loss and weakness in the 4 limbs.
Stage 1 for FAP: walking unaided.
PND, polyneuropathy disability; NIS-LL, neuropathy impairment score in lower limbs; TTR, transthyretin.

enrolled 10 Japanese TTR-FAP patients, biochemical TTR stabilization was achieved in eight out of 10 patients at 1.5 years. The percentage of NIS-LL responders (increase from baseline in NIS-LL <2) was 40.0% (and mean NIS-LL change from baseline was 3.3 at 1.5 years) [36]. In a multicenter Italian observational study on 34 symptomatic TTR-FAP patients, Tafamidis was not able to prevent functional progression of the disease in 23 (43%) study participants, including altered locomotion ($n=16$) and progression in NYHA score ($n=12$) during follow-up period; the autonomic function progressed in 22 (56%) patients [37▪▪]. In another monocentric study, the effect of Tafamidis in 43 TTR-FAP patients did not prevent the steady progression of the neuropathy in the long term. Deterioration of the neuropathy correlated to an older age at disease onset or treatment initiation and to poor clinical status at baseline. Body weight preservation was an important favorable prognostic factor [38▪]. Tafamidis was otherwise well tolerated in all studies. Close follow-up of late onset TTR-FAP on tafamidis is required.

ONGOING CLINICAL TRIALS: TRANSTHYRETIN GENE SILENCING

TTR gene silencing is a new approach to antiamyloid treatment. Two important phase 3 clinical trials are ongoing in TTR-FAP using *TTR* gene silencing strategy; results will be available at the end of 2017. RNA silencing (SiRNA) was identified and encapsulated in lipid nanoparticle formulations targeting a conserved sequence in three untranslated regions of nonmutant and mutant mRNA in TTR, thereby affecting production of both mutant and wild-type TTR. SiRNA treatment was administered by intravenous infusion, it suppressed the production of both mutant and wild-type TTR by hepatocytes, thus establishing proof of concept, in humans, for an RNAi therapeutic targeting mRNA transcribed from a disease-causing gene [39]. Phase II administration of ALN-TTR02 (patisiran) in six patients led to rapid, dose-dependent, and durable knockdown of TTR, with the maximum effect seen at a dose of 0.3 mg/kg; levels of mutant and wild-type TTR were reduced to a similar extent with a mean level of knockdown of 85% after the second dose. Patisiran was generally well tolerated in FAP patients [40]. The primary objective of the ongoing phase II OLE study was to evaluate the safety of patisiran. Secondary objectives include patisiran's effect on TTR levels, QOL, and mNIS + 7 neurologic score [41]. Twenty-seven patients were enrolled in the study. Patisiran was generally well tolerated, six patients experienced serious adverse events unrelated to study drug. Sustained mean serum TTR lowering of ~80% was achieved for more than 24 months. 24-month data suggested improvement in neuropathy with a mean 6.7 point decrease in mNIS + 7 ($n=24$) and a significant increase in sweat gland nerve fiber density in the distal leg [41]. A phase III multicenter, multinational, randomized, double-blind, placebo-controlled study is now ongoing to evaluate the efficacy and safety of siRNA ALN-TTR02 in TTR-FAP [42▪] (Table 4). Primary outcome measures are the difference between the ALN TTR02 and

Table 4. Ongoing phase III clinical trials for transthyretin gene silencing. Clinicaltrialgov identifier reference NCT01960348 NCT01737398 Medicine SiRNA patisiran (ALNTTR02)

N° Clinical Trial Gov identifier	Medicine	Dose /way of adminis-tration	Ratio active drug versus placebo	Study duration	inclusion criteria	exclusion criteria	Primary endpoint	Population *N*=	Estimated completion Date
NCT01960348	SiRNApatisiran (ALN-TTR02)	0.3 mg 3 weeks intravenously	2/1	18 months	TTR-FAP Symptomatic Neuropathy NIS – total 10–100 Amyloid deposit on biopsy not mandatory	NYHA >2 >PNDIIIb Age >85 years Other cause of peripheral neuropathy	Change from baseline of modified Neuropathy Impairment Score+7 (mNIS +7)	*N*=200	September 2017
NCT01737398	ISIS-TTR Rx	300 mg 3/week 1st week than 1/week SC	2/1	65 weeks (15 months)	TTR-FAP Symptomatic NIS-total : 10–100 Stage 1 and Stage 2 FAP patients with the following: Ability to walk unaided or with the use of no more than one stick/cane Documented transthyretin variant by genotyping Documented amyloid deposit by biopsy	NYHA >2 >PND IIIa Age >82 years NIS >100	Change from baseline of the modified Neuropathy Impairment Score +7 (mNIS +7) Change from baseline in the Norfolk Quality of Life Diabetic Neuropathy questionnaire	*N*=195	May 2017

TTR-FAP, transthyretin familial amyloid polyneuropathy; NIS, neuropathy impairment scores; NYHA, New York Heart Association; SiRNA, RNA silencing. Adapted with permission [34▪], [42▪], and [44▪].

placebo groups in the change from baseline of mNIS + 7 [42▪]. Final results will be available at the end of 2017.

ANTISENSE OLIGONUCLEOTIDES

IONIS-TTRRx (IONIS 420915) is a 2nd generation 2′-O-(2-methoxyethyl) modified '2′-methoxyethyl antisense oligonucleotide (ASO) that targets the TTR RNA transcript and reduces the levels of the TTR transcript through an RNaseH1 mechanism of action, leading to reductions in both mutant and wild-type TTR protein. The activity of IONIS-TTRRx to decrease TTR protein levels was studied in transgenic mice bearing the Ile84Ser human TTR mutant, in cynomolgus monkeys and in healthy human volunteers. Robust (>80%) reductions of plasma TTR protein were obtained in all three species treated with IONIS-TTRRx. These effects were dose-dependent and lasted for weeks postdosing. In a Phase 1 healthy volunteer study, treatment with IONIS-TTRRx for 4 weeks was well tolerated. TTR protein reductions up to 96% in plasma were observed [43▪]. There is ongoing Phase 3 randomized, double-blind, placebo-controlled study development of IONIS-TTRRx to assess the efficacy and safety of ASOs, IONIS, in FAP patients which began in 2013 [44▪]. In total, 300 mg IONIS-TTRRx are administered subcutaneously three times the first week and once weekly for the next 63 weeks. Efficacy of IONIS-TTRRx is assessed by change from baseline in the mNIS + 7 IONIS' score, which correlated with disability and health scores [45▪] and in the Norfolk QOL-DN questionnaire (Table 4).

CONCLUSION

TTR-FAP is a ubiquitous disease, new tools have emerged to better assess the disease, including the quantification of small fibers. The panel of antiamyloid therapies is developing with a TTR stabilizer in the early stages, generic TTR drugs are being tested in Phase 3 clinical trials. Results will be available by the end of 2017.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

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