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ORIGINAL ARTICLE

Real-life experience with disease-modifying drugs in hereditary transthyretin amyloid polyneuropathy: A clinical and electrophysiological appraisal

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Abstract

Introduction: New treatments have dramatically improved the prognosis for Hereditary Transthyretin Amyloid Polyneuropathy (ATTRv-PN). However, there is a lack of routine follow-up studies outside of therapeutic trials. Our aim was to report the long-term clinical and electrophysiological evolution of a cohort of ATTRv-PN patients and to determine which biomarkers are most sensitive to change.

Methods: We retrospectively collected neuropathy impairment scale (NIS), polyneuropathy disability scale (PND), overall neuropathy limitation scale (ONLS), rash built overall disability scale (RODS), electrodiagnostic data, motor unit number index (MUNIX), troponin and N-terminal pro-brain natriuretic peptide levels. Electrophysiological worsening was defined as a 20% decrease in previous values.

Results: Thirty-five patients, with a median age of 58 (interquartile ranges 42–71) years, were followed for a median of 36 (24–48) months. All patients received a transthyretin stabiliser, gene silencer or liver transplant.

Overall assessment of the cohort showed clinical, biological and electrophysiological stability. However, on an individual basis, NIS worsened in 45% of patients (14/31), ONLS in 46% (13/28), PND in 28% (9/32) and RODS in 39% (11/28) at the last follow-up. Motor amplitude sum score decreased in 33% (11/33), amplitude recorded on tibialis anterior muscle in 44% (12/27), sensory amplitude sum score in 39% (11/28) and MUNIX sum score in 27% (7/26).

Conclusions: Overall effectiveness of ATTRv-PN treatments in routine care is good. However, individual assessments show up to 40% deterioration over time. Electrophysiological measures are valuable monitoring tools but are not more sensitive to change than clinical scores. Results must be confirmed in larger cohorts.

KEYWORDS
electrophysiological biomarkers, hereditary transthyretin amyloid polyneuropathy, transthyretin

TABLE 1 Patient characteristics at enrolment.

Patient	Gender	Mutation	Portuguese Origin	Age	Follow-up (months)	PND	NIS	ONLS	RODS	CMAP sum score	SNAP sum score	MUNIX sum score
Patient 1	M	Val142Ile		72	24	1				26.8	35.95	
Patient 2	M	Val30Met	+	72	36	4	114.5	7	34	2.5		29
Patient 3	M	Val30Met	+	20	60	2	36	4		6.17	12.65	208
Patient 4	M	Glu109 Gln.		47	48	1	8	0	100	25.75	32.7	383
Patient 5	M	Glu89Gln.		48	48	1	37	1	76	6.3	7.2	103
Patient 6	F	Ser77Tyr		58	12	1	28.5	2	80	14.41	33.7	248
Patient 7	M	Val30Met		60	24	1	8	?	43	22.69	14.43	
Patient 8	M	Val30Met		55	60	2	19	2	38	3.18		86
Patient 9	M	Val30Met	+	42	48	2	28	1	73	17.25	13.9	409
Patient 10	M	Val30Met		57	24	4	84	6	69	3.94	4.15	21
Patient 11	M	Val30Met		68	48	1	6	0	100	1.41	0.92	17
Patient 12	M	Val30Met		75	24	3	83.25	6	55	25	34.35	412
Patient 13	M	Val30Met	+	32	60	1	56	3	77	17.44	3.47	
Patient 14	M	Ile107Val		51	60	1	14	0	100	32.55	89.85	335
Patient 15	F	Ala36Pro	+	57	60	2	72	4	40	4.98	4.41	59
Patient 16	M	Val30Met		74	36	3	89	3		11.25	3.3	92
Patient 17	F	Val30Met		78	48	2	53.5	6	42	5.06	0	120
Patient 18	M	Ser77Tyr		46	6	1		0	100	23.5	23.3	320
Patient 19	M	Val30Met	+	30	12	1	8	2	55	27.9	76.3	388
Patient 20	F	Val30Met	+	65	12	4	153	9	73	0.018	0	
Patient 21	F	Val30Met	+	38	24	1	0	0	100	23.75	132.5	423
Patient 22	M	Val122Ileu		40	12	1	1	0	83		16.8	415
Patient 23	M	Val30Met		66	36	2	43.5	4	56	15.4	19.4	296
Patient 24	M	Val30Met		43	60	1	36	1	100	9.95	15.55	213
Patient 25	M	Val30Met		30	36	1	6	0	93	19.87	30.6	323
Patient 26	M	Val30Met	+	28	60	1	17	1		16.6		
Patient 27	F	Glu89Gln		60	48	1	40	2	63	5.56	6.65	55
Patient 28	F	Val30Met		83	36	1	17	1	60			
Patient 29	M	Phe64leu		66	24	1	45	2	71	11.65	2.5	125
Patient 30	M	Val30Met	+	73	12	3				3.65		
Patient 31	M	Ile107Val		65	60	3	54	4	42	12.75	15.25	154
Patient 32	M	Val30Met	+	18	24	3	14	3	57	14.06	16.25	

TABLE 1 (Continued)

Patient	Gender	Mutation	Portuguese Origin	Age	Follow-up (months)	PND	NIS	ONLS	RODS	CMAP sum score	SNAP sum score	MUNIX sum score
Patient 33	M	Val30Met		64	12	2	32	5	51	5.5	10.85	30
Patient 34	F	Val30Met	+	84	24	1	23.5	3	88	11.25	19	
Patient 35	F	Val30Met		78	24	2	26.5	3	76	9.35	9.68	171
	26 M/9F	Val30Met =23	12	58 (42–71)	36 (24–48)	1 (1–2)	28.5 (14–53.5)	2.5 (0.3–4)	69 (53–85)	11.6 (5.5–19.9)	14.8 (5–28.8)	171 (59–335)

Note: Data are expressed as medians (interquartile range).

Abbreviations: CMAP, compound muscle action potential; MUNIX, motor unit number index; NIS, neuropathy impairment scale; ONLS, overall neuropathy limitation scale; PND polyneuropathy disability scale; RODS, rash built overall disability scale; SNAP, sensory nerve action potential.

INTRODUCTION

Hereditary Transthyretin Amyloid Polyneuropathy (ATTRv-PN) is an autosomal dominant inherited disease that is primarily responsible for neurological, cardiological, dysautonomic and gastrointestinal disorders [1]. The disease is potentially fatal if left untreated, with an estimated survival time of 7 to 10 years [2].

The amyloidogenic mutation of the TTR gene causes a quaternary conformational change that destabilizes the tetramer and leads to monomeric and oligomeric amyloid deposition in target organs [3]. The Val30M is the most common mutation, particularly in Portugal, where the average age of onset of the disease is 33 years old [4]. However, there are more than 150 other identified non-Val30M mutations distributed throughout the world and responsible for different clinical phenotypes [1].

In recent years, significant progress has been made in the treatment of ATTRv-PN, including liver transplantation [5] and more recently treatments that stabilise the TTR tetramer [6, 7] or that inhibit the TTR synthesis [8]. These therapies have demonstrated their efficacy in slowing disease progression and prolonging patient survival. The long-term impact of these drugs on clinical and electrophysiological parameters in real-life conditions remains to be fully understood. Current limitations of these treatments include questions about their long-term efficacy, accessibility to all patients, potential side effects, and ability to treat or completely reverse disease manifestations. In addition, the variability in response to treatment between individuals highlights the need for personalized therapeutic strategies to better understand the underlying mechanisms of the disease. It is therefore crucial to define the most relevant clinical neuropathy assessment scores and the electrophysiological parameters most sensitive to the evolution of the ATTRv-PN, to improve its management and prognosis.

The aim of this study is to describe the long-term clinical and electrophysiological evolution of a cohort of patients with ATTRv-PN treated in routine care at a referral centre. A second objective is to determine which clinical and/or electrophysiological parameters are the biomarkers most sensitive to change to measure the evolution of ATTRv-PN and guide possible therapeutic decisions.

METHOD

This is a monocentric retrospective study with collection of clinical and electrophysiological parameters in 35 symptomatic patients with TTR mutation recruited in the reference centre for neuromuscular diseases and ALS in Marseille, France, over a period from 2014 to 2023. Patients gave their consent for data collection and the study was submitted to the local ethics committee of the APHM, under the final number PADS24-115_dgr.

All clinical and electrophysiological parameters were recorded on an annual basis at inclusion and at 12, 24, 36 and 48 months of follow-up. Collected clinical data included age of onset, sex, origin,

TABLE 2 Breakdown of treatment during follow-up.

Treatments						
Months	**0**	**12**	**24**	**36**	**48**	**Last follow-up (median = 36)**
Tetramer Stabilizers	25	12	6	7	6	13
Gene Silencers	2	7	4	6	2	8
Silencers + Stabilizers	2	8	10	5	5	10
Liver transplantation	3	3	2	2	2	3

Note: Patients currently received multiple treatments for their amyloidosis and switched from one treatment to another throughout the follow-up according to disease evolution. The table shows the distribution of treatments at each time point. Tetramer stabilizer = tafamidis 20 or 61 mg/day. Gene silencer = patisiran or vutrisiran or inotersen.

TABLE 3 Changes in clinical scores cardiac outcomes during follow-up.

Months	0	12	24	36	48
Patients (*n*=)	35	32	24	21	15
PND	1 (1–2)	2 (1–2)	2 (1–2)	1 (1–2)	1 (1–2.25)
NIS	28.5 (14–53.5)	38.5 (16–59)	39.75 (16–68)	41.25 (16–56)	49.25 (15–69)
ONLS /12	2.5 (0.3–4)	4 (2–5)	3 (1–4)	2 (0.8–4.3)	4 (1–5)
RODS /100	69 (53–85)	65 (51–80)	65 (47–76)	69 (52–73)	64 (50–85)
NT-pro-BNP (pg/ml)	128 (53–320)	122 (44–528)	131 (43–377)	125 (38–449)	98 (35–513)
Troponin (ng/ml)	16 (9–30)	13 (7–31)	9 (4–22)	12 (6–23)	8 (4–22)

Note: No significant variation was observed during follow- up for all the collected measures ($p > 0.05$), except for ONLS between M0 and M12 ($p = 0.02$). Data are expressed as medians (interquartile range).

Abbreviations: NIS, neuropathy impairment scale; NT-pro-BNP, N-terminal pro-brain natriuretic peptide brain natriuretic peptide; ONLS, overall neuropathy limitation scale; PND polyneuropathy disability scale; RODS, rash built overall disability scale.

type of mutation and current specific treatment for ATTRv-PN. The course of the disease was assessed using an impairment score, the neuropathy impairment scale (NIS) [9], and disability scores, the polyneuropathy disability scale (PND) [1], the overall neuropathy limitation scale (ONLS) [10] and the rash built overall disability scale (RODS) [11].

The electrophysiological motor parameters of the median, ulnar, tibial and fibular nerves, and the sensory parameters of the median, ulnar and sural nerves were studied. We measured the amplitudes of the distal compound muscle action potential (CMAP), the distal motor latencies, the conduction velocities, the F-wave latencies, the duration of the distal CMAP, the sum of the motor amplitudes of the 4 limbs including the median, ulnar, posterior tibial and fibular nerves, and the sum of the motor amplitudes of the lower limbs (tibial and fibular nerves). The sensory amplitudes of the median, ulnar and sural nerves, the sum of the amplitudes of the sensory nerve action potential (SNAP) of the median, ulnar and sural nerves, and the velocities of sensory conduction were analysed.

The number and the size of the motor units were estimated using the MUNIX (Motor Unit Number Index) and MUSIX (motor unit size index) methods for the abductor digiti mini (ADM), tilbialis anterior (TA) and abductor pollicis brevis (APB) muscles on the non-dominant side. We calculated the sum scores of the MUNIX and MUSIX of the ADM, APB and TA muscles [12].

Cardiological assessment was based on the measurement of troponin and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels.

Based on previous studies, we defined a worsening as a one-point increase for the PND and the ONLS, a four-point decrease for the RODS estimated on 100 [13], a two-point increase for the NIS [6] and a 20% decrease for the CMAP sum scores, the SNAP sum scores [14] and the MUNIX sum scores [12]. These criteria were used to assess the clinical and electrophysiological evolution of patients during follow-up.

Data were expressed as medians (interquartile range) or numbers (percentage). Quantitative data were compared with a one-factor ANOVA test with a mixed analysis effect corrected by the Geisser–Greenhouse method and a Dunnett test for multiple comparisons. The percentages of patients worsened over time were compared using the Kaplan–Meier method with a log-rank statistical test. In subgroup analyses we compare patients who had at inclusion a PND score < or ≥1 and patients who received a tetramer stabilizer only and patients who also received a gene silencer. Correlations between clinical and electrophysiological data were assessed with the Spearman correlation coefficients. The intrinsic variability of biomarkers was assessed by calculating the standardised mean response (SRM = mean / standard deviation). SRM values greater than 0.50 and 0.80 are indicative of a moderate or high sensitivity, respectively, to detect a change [15]. A p value <0.05 was considered significant in bivariate analysis.

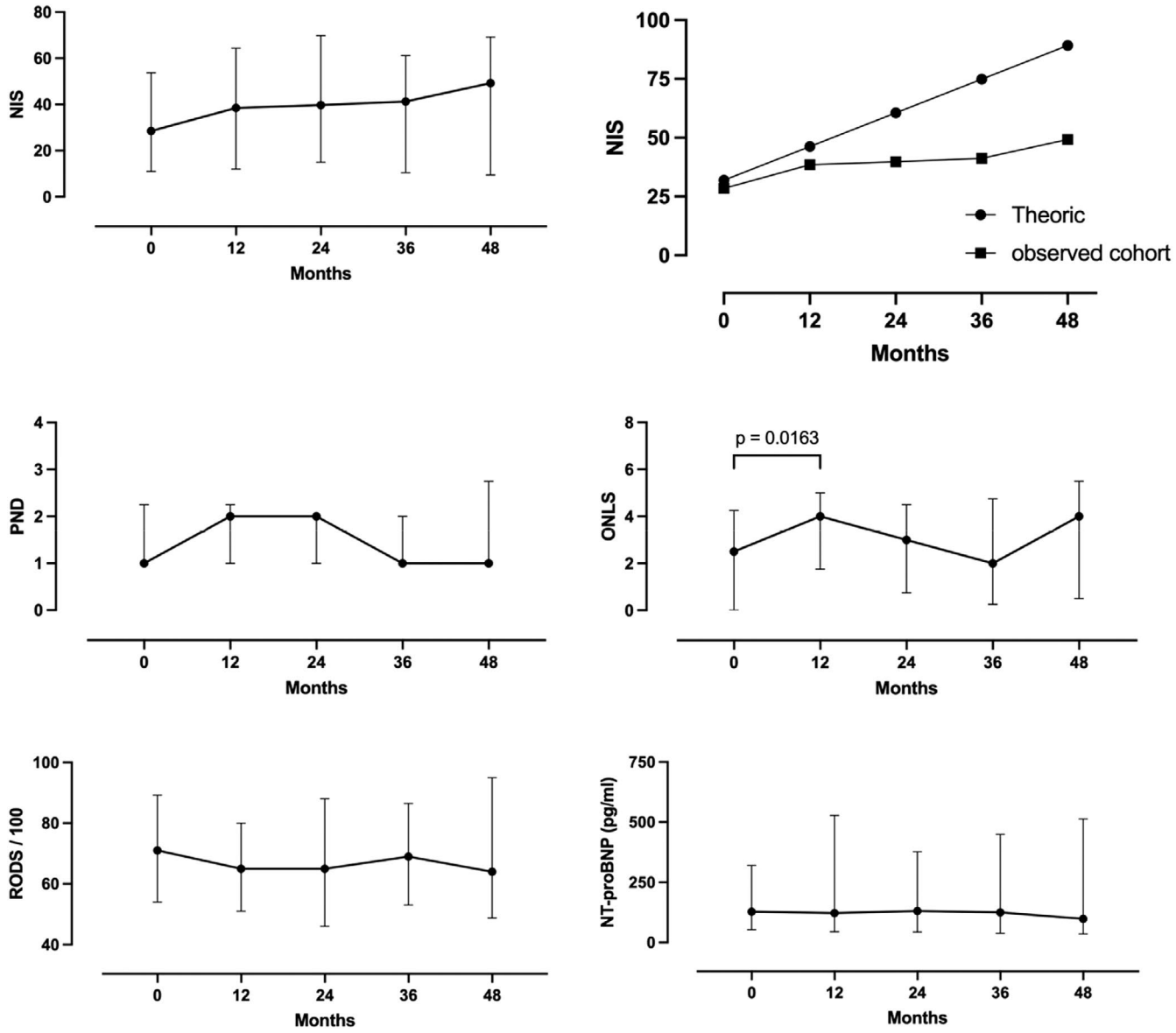

FIGURE 1 Evolution of the clinical scores and cardiac outcome. The theoretical change in the NIS score corresponds to an increase of 14.3 points per year according to Adams et al, 2015 [16]. Graphs show medians with interquartile range. No significant variation was observed during follow- up for all the collected measures ($p > 0.05$), except for ONLS between M0 and M12 ($p = 0.02$). NIS, neuropathy impairment scale; PND polyneuropathy disability scale; ONLS, overall neuropathy limitation scale; RODS, rash built overall disability scale; NT-pro-BNP, N-terminal pro-brain natriuretic peptide.

Graphs and statistical analyses were produced using Graph Pad Prism 5 (GraphPad Software, San Diego, CA, USA).

RESULTS

Description of the cohort at enrolment

Thirty-five patients, with a median age of 58 years (42–71), 26 men and 9 women, were included. Twelve patients were of Portuguese origin. Twenty-three patients carried a Val30Met mutation. All patients had an axonal polyneuropathy. Demographic, clinical and electrophysiological data are summarized in Table 1.

Overall assessment of the patients of the cohort

Median follow-up was 36 months (24–48). Thirty-two patients were followed up at 12 months, 24 patients at 24 months, 21 patients at 36 months and 15 patients at 48 months. Table 2 shows how the different treatments were distributed during the follow-up.

Patients tended to be clinically and electrophysiologically stable throughout the follow-up period. In fact, the clinical scores did not change significantly during follow-up (Table 3 and Figure 1). The initial median NIS score was 28.5. It increased by 10 points in the first year of follow-up and then by 4.25 points per year over the next 3 years, significantly less than the theoretical worsening of 14.3 points per year estimated in cohorts of untreated patients [16] (Figure 1).

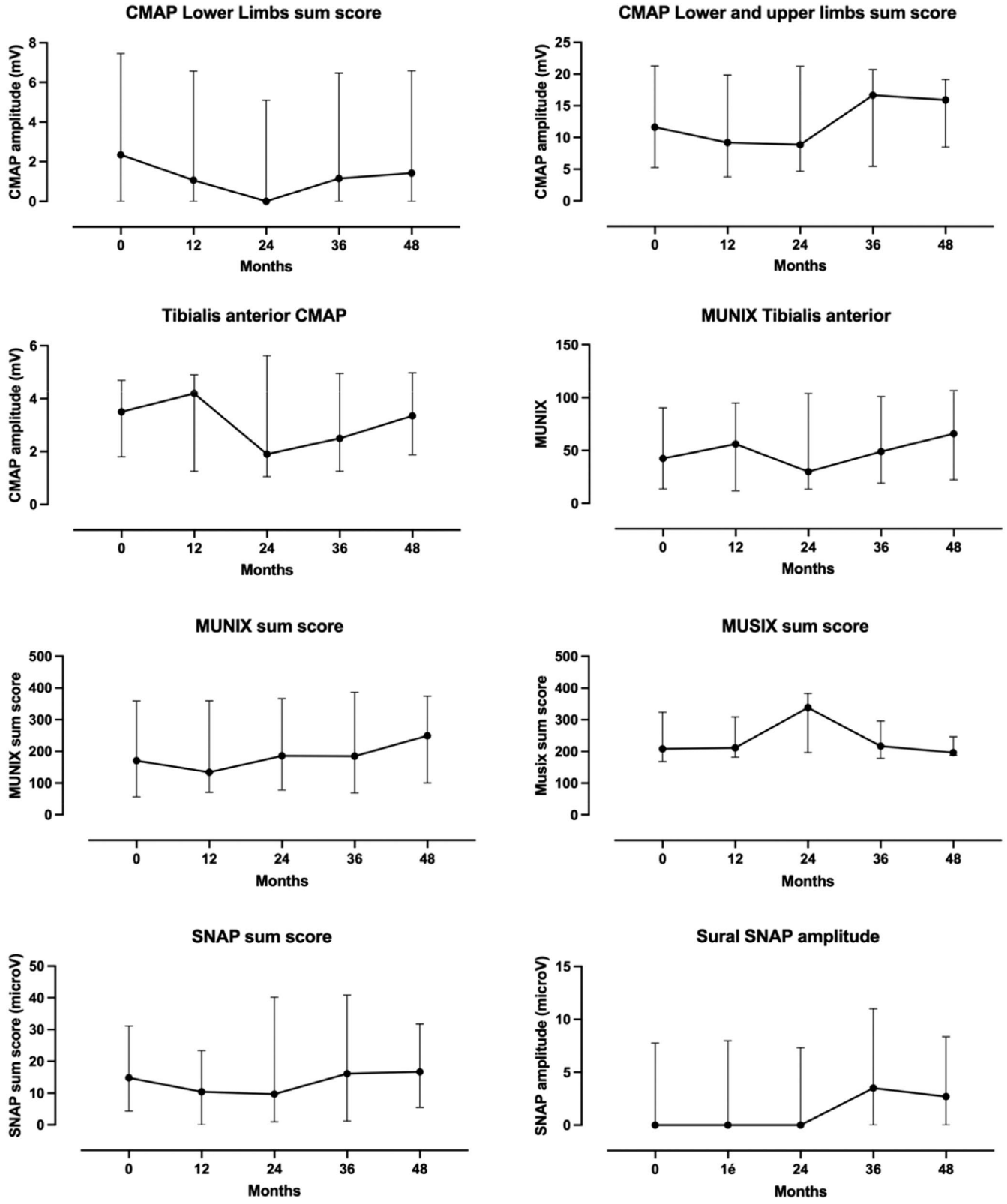

FIGURE 2 Changes in electrophysiological parameters. Graphs show medians and interquartile range. No significant variation was observed during follow-up for all the collected measures ($p > 0.05$). CMAP, compound muscle action potential; MUNIX, motor unit number index; MUSIX, motor unit size index; SNAP, sensory nerve action potential.

TABLE 4 Changes in electrophysiological data.

Months	0	12	24	36	48
Motor nerves					
Median nerve					
Amplitude mV	4.6 (2.3–7.4)	2.1 (0.9–6.7)	4.2 (1.3–8.3)	3.7 (1.5–8.3)	7.0 (4.0–8.3)
Distal latency ms	4.6 (3.9–5.2)	4.4 (3.9–5.4)	4.5 (4.0–5.2)	4.5 (4.0–5.0)	4.3 (4.0–5.0)
Velocity (m/s)	45.5 (42–51)	46.0 (42–52)	46.6 (42–51)	50 (48–54)	54.4 (53–57)
CMAP duration ms	6 (5.2–6.5)	5.7 (5.2–6.3)	5.9 (5.1–7.3)	5.6 (5.0–6.2)	5.5 (5.1–6.4)
F-wave latency ms	26.5 (24–29)	25.8 (25–28)	26.0 (23–28)	25.6 (23–26)	25.6 (24–28)
Ulnar nerve					
Amplitude mV	5.5 (3.5–7.6)	5.2 (3.1–7.7)	6.4 (2.7–7.9)	6.3 (3.5–7.4)	6.1 (3.6–7.6)
Distal latency ms	3.0 (2.8–3.5)	3.4 (3.0–3.6)	3.0 (2.7–3.3)	3.0 (2.9–3.0)	3.2 (2.9–3.7)
Velocity (m/s)	51.9 (47–55)	52.7 (49–56)	52.7 (49–54)	54.0 (51–58)	58.6 (57–60)
CMAP duration ms	6 (5.8–6.5)	6.6 (5.4–7.2)	6.4 (5.7–6.6)	6.3 (5.3–7.3)	6 (5.5–6.7)
F-wave latency ms	27.5 (25–29)	26.6 (25–28)	27.3 (26–29)	25.8 (25–26)	26.6 (25–27)
Tibial nerve					
Amplitude mV	0.5 (0–4.6)	0.4 (0–1.7)	0.2 (0–2.1)	0.1 (0–2.0)	0.4 (0–1.0)
Distal latency ms	4.3 (4.0–5.4)	4.9 (4.6–5.6)	4.3 (4.2–5.0)	4.8 (4.3–4.9)	4.4 (3.6–6.0)
Velocity (m/s)	41.6 (39–44)	39.7 (37–43)	40.2 (33–48)	40.0 (39–43)	41.8 (39–44)
CMAP duration ms	5.6 (5.1–6.6)	5.2 (4.7–6.2)	5.3 (5.0–6.1)	5.5 (4.5–6.2)	5.1 (4.4–6.4)
F-wave latency ms	52 (49–56)	49.1 (41–50)	53.0 (48–54)	48.0 (47–49)	54.5 (50–54)
Fibular nerve					
Amplitude mV	1.1 (0.0–3.0)	0.6 (0–3.8)	0.2 (0–2.3)	0.6 (0–2.4)	0.8 (0.0–3.9)
Distal latency ms	4.1 (3.4–5.3)	3.8 (3.5–5.0)	4.1 (3.6–4.6)	3.6 (3.2–4.8)	3.9 (3.3–5.0)
Velocity (m/s)	42.1 (38–46)	42.5 (39–47)	42 (38–44)	44.1 (40–45)	42 (40–43)
CMAP duration ms	6.2 (6.0–7.0)	7.0 (5.7–7.5)	6.9 (5.7–7.5)	6.6 (5.6–7.7)	7.6 (6.2–8.2)
F-wave latency ms	50.1 (46–54)	48.7 (44–50)	47 (44–53)	51.4 (48–53)	51 (46–55)
CMAP sum score	11.6 (5.5–19.9)	9.2 (4.1–18.7)	8.9 (5.3–19.9)	16.6 (5.5–20.5)	15.9 (10.2–18.4)
CMAP sum score Lower limb	2.3 (0–7.1)	1.0 (0–6.0)	0 (0–4.1)	1.1 (0–4.8)	1.4 (0.1–4.8)
Munix sum score	171 (59–335)	134 (75–339)	186 (81–340)	185 (78–376)	249 (109–370)
Musix sum score	208 (170–312)	211 (183–300)	338 (202–382)	217 (186–281)	196 (187–236)
Sensory nerves					
Median nerve					
Velocity (m/s)	46.8 (37–53)	46 (40–52)	45.6 (41–58)	45.8 (41–53)	45.6 (41–51)
SNAP amplitude	5.1 (0.8–9.5)	4.0 (0–10.15)	3.7 (0–13.7)	9.6 (0–14.0)	13.5 (3.3–18)
Ulnar nerve					
Velocity (m/s)	49.7 (43–54)	51.8 (45–56)	51.7 (48–56)	53.1 (46–59)	50.2 (46–56)
SNAP amplitude	6.4 (2.5–12)	5.1 (0–12.9)	4.8 (0.4–15.7)	6.7 (2.6–14)	10.2 (6–17.8)
Sural nerve					
Velocity (m/s)	45.4 (40–54)	47.6 (44–58)	45.8 (42–55)	47.4 (45–49)	40.7 (34–46)
SNAP amplitude	0 (0–7.1)	0 (0–6.1)	0 (0–5.6)	3.5 (0–10.0)	2.7 (0–8.3)
SNAP sum score	14.8 (5–28.8)	10.4 (1–22.8)	9.7 (1.3–36)	16.1 (3–37.4)	16.7 (5.6–30)

Note: No significant variation was observed during follow- up for all the collected measures ($p > 0.05$). Data are expressed as median (interquartile range).

Abbreviations: CMAP, compound muscle action potential; MUNIX, motor unit number index; MUSIX, motor unit size index; SNAP, sensory nerve action potential.

TABLE 5 Proportion of patients with clinical or electrophysiological worsening.

Months	12	24	36	48	Last follow-up (median = 36)
Patients (n=)	32	24	21	15	35
% of patients with worsened clinical biomarker					
PND	9%	17%	17%	32%	28% (9/32)
NIS	29%	40%	40%	57%	45% (14/31)
ONLS	35%	40%	46%	46%	46% (13/28)
RODS	25%	29%	41%	49%	39% (11/28)
% of patients with worsened electrophysiological biomarker					
CMAP LL sum score	27%	27%	32%	52%	39% (13/33)
CMAP UL + LL sum score	26%	26%	35%	41%	33% (11/33)
CMAP TA	23%	34%	54%	63%	44% (12/27)
SNAP sum score	8%	20,8	32%	55%	39% (11/28)
Sural SNAP	11%	15%	15%	26%	17% (5/29)
MUNIX sum score	12%	21%	21%	44%	27% (7/26)
MUNIX TA	23%	33%	33%	50%	33% (9/27)

Abbreviations: CMAP, compound muscle action potential; LL, lower limb; MUNIX, motor unit number index; NIS, neuropathy impairment scale; ONLS, overall neuropathy limitation scale; PND polyneuropathy disability scale; RODS, rash built overall disability scale; SNAP, sensory nerve action potential; UL, upper limb.

Regarding electrophysiological data, no significant variation was observed during follow- up for all the collected data: distal motor amplitudes of each nerve, CMAP sum scores, conduction velocities, F-wave latencies, CMAP durations, sensory amplitudes, SNAP sum score, sensory conduction velocities, MUNIX and MUSIX sum scores (Figure 2, Table 4).

Troponin and NT-pro-BNP remained stable throughout the study (Table 3 and Figure 1).

Individual assessment of the patients of the cohort

Table 5 and Figure 3 show the proportion of patients who worsened over time for each clinical and electrophysiological parameter.

At the last follow-up, PND, NIS, ONLS and RODS scores worsened in 28%, 45%, 46% and 39% of patients respectively. Kaplan–Meier curves show (Figure 3) that the proportion of worsened patients are comparable over time for the scores RODS, ONLS and NIS. However, the NIS and ONLS scores detected more deteriorated patients than the PND score ($p = 0.03$, Figure 3). Calculation of the SMR confirms the sensitivity of the ONLS score to change, with a result of 0.63. The SMR were not so good for the other clinical scores: 0.57 for the PND, 0.48 for the NIS and 0.40 for the RODS.

At the last follow-up, the CMAP sum scores of the lower limbs, of the 4 limbs and of the fibular nerve recorded on the TA muscle were worsened in 39%, 33% and 44% of patients respectively. SNAP sum score and sural nerve amplitudes were reduced in 39% and 17% of patients respectively. The MUNIX sum score and the MUNIX of the TA muscle were reduced in 27 and 33% of patients respectively. The proportions of worsened patients were comparable for all the electrophysiological data, except for the distal motor amplitude recorded on the TA muscle, which was more frequently deteriorated than the distal sensitive amplitude of the sural nerves ($p = 0.03$, Figure 3). The SRM were low overall for the electrophysiological data: 0.27 for the distal motor amplitude of the fibular nerve recorded on the TA muscle; 0.31 for the MUNIX of the TA muscle; 0.13 for the MUNIX sum score; 0.11 for the SNAP sum score; 0.28 for the sensory amplitude of the sural nerve; 0.44 for the CMAP sum score of the lower limbs and 0.35 for the CMAP sum score of the 4 limbs.

If we compare the changes in the clinical and electrophysiological scores, the analysis of the distal motor amplitude of the CMAP recorded on the TA muscle is more sensitive in detecting deterioration than the PND clinical score ($p = 0.04$). On the other hand, the RODS, ONLS and NIS clinical scores detected as much deterioration as all the electrophysiological analyses.

Subgroup analysis based on disability and treatments

The various parameters were compared between patients with moderate disability (PND <1) and more severe disability (PND >1) and between patients who had received tetramer stabilisers only and patients who had received stabilisers and gene silencers. No significant differences were observed between these different groups.

Correlation between clinical and electrophysiological data

At enrolment, some electrophysiological parameters correlated with disease severity. CMAP sum score of the lower limbs was correlated with the NIS ($r = -0.51$, $p = 0.01$) and the ONLS ($r = -0.44$, $p = 0.03$) scores. CMAP sum score of the four limbs was related to the ONLS score ($r = -0.48$, $p = 0.01$). SNAP sum score was correlated with the NIS ($r = -0.49$, $p = 0.02$) and the ONLS ($r = -0.48$, $p = 0.02$) scores.

Electrophysiological data at enrollment were not associated with clinical worsening at last follow-up. The variations of the electrophysiological data at the first and last assessments were not correlated with the variations of the various clinical scores. Electrophysiological worsening at 1 year was also not associated with clinical worsening at last follow-up.

Side effects

No significant side effects were reported for both TTR stabilizers and gene silencers therapies.

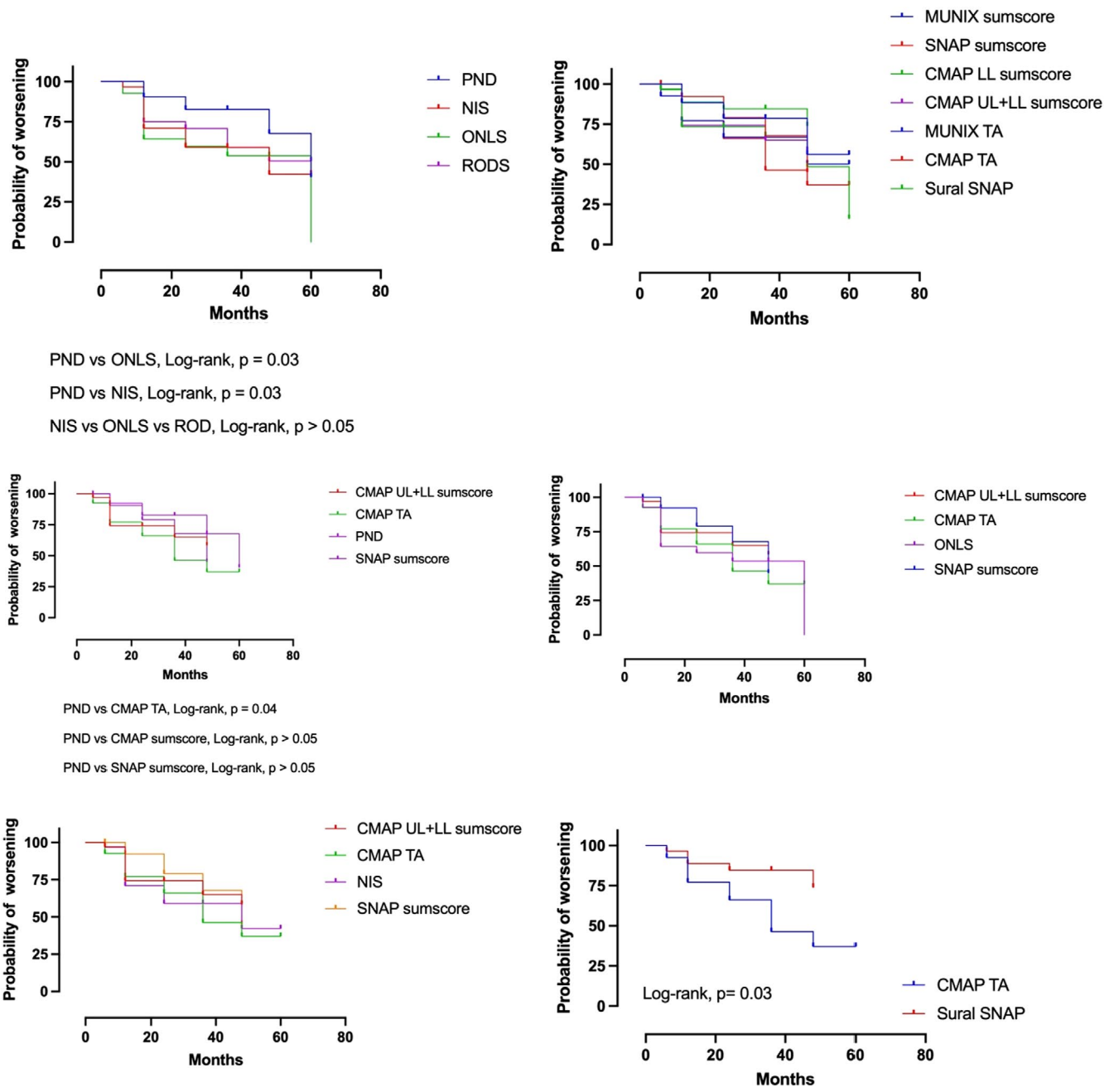

FIGURE 3 Kaplan–Meier curves showing the evolution of patients according to clinical scores and electrophysiological data. NIS, neuropathy impairment scale; PND polyneuropathy disability scale; ONLS, overall neuropathy limitation scale; RODS, rash built overall disability scale; CMAP, compound muscle action potential; MUNIX, motor unit number index; SNAP, sensory nerve action potential; TA, tibialis anterior muscle.

DISCUSSION

This study shows an overall stability of our cohort, regardless of the treatments used, in line with published results from therapeutic trials [6, 17–19]. Treatment of ATTRv-PN modifies the course of the neuropathy and improves patients' quality of life. In our study, the rate of progression of the NIS score under different treatments was 4.25 points/year, compared with 9.96/year with inotersen [20] and 14.3 without treatment [16]. A recent study by Ueda et al [2] focused mainly on analysing the survival time of ATTRv-PN patients with and without treatment. It showed a significant improvement in survival in patients at different stages of the disease and no significant difference between the therapies. These results are consistent with the data from our study and demonstrate the overall efficacy of ATTRv-PN treatments in routine care.

Our results also show that there is heterogeneity in response to treatment, as 40% of patients continue to deteriorate at individual follow-up. This highlights the need for regular clinical and electrophysiological

assessment to improve the treatment strategy [14]. These results are in line with previous studies. Luigetti et al [20] followed 18 patients treated with inotersen for 18 months. The NIS score increased from 77 to 90. Two patients worsened in terms of FAP stage and 4 worsened in terms of PND score. As in our study, the worsening occurred in the first few months, probably while the treatment was taking effect. The study by Lozeron et al [21] followed 13 patients on tafamidis. The NIS score deteriorated in 38% of patients and disability scores in 55% at one year's follow-up. Gentile et al [19] observed 46 patients on patisiran therapy, 9 of whom experienced a worsening of their PND score during a maximum follow-up of 48 months. This deterioration could be due to several factors, including genetic variability, individual comorbidities, disease stage at the start of treatment and the treatment used first. All these factors are rarely considered exhaustively in clinical trials. There is a lack of follow-up studies of patients outside therapeutic trials. Most of our patients were firstly treated with tafamidis, the only treatment initially available apart from liver transplantation. New drugs that inhibit the synthesis of TTR are now available, but it is not yet certain whether they will improve the long-term course of the disease if prescribed as first-line therapy. At the moment, there are only indirect comparisons between the different treatments [22].

Through this study we also aimed to highlight the clinical and electrophysiological parameters that are most sensitive for detecting worsening in patients with ATTRv-PN treated in routine care. The NIS score is the most commonly used scale for assessing ATTRv-PN. Its main drawback is sometimes its lack of clinical relevance. Can we consider a deterioration of this score by two points as clinically significant in current practice [23], knowing that this change may only correspond, for example, to the transition from weak Achilles reflexes to abolished Achilles reflexes? The ONLS score seems more relevant, as an increase of 1 point is associated with a real deterioration in functional ability. This score was first developed to evaluate autoimmune neuropathies [13]. It has not yet been validated in the assessment of ATTRv-PN, but it is already used as a primary endpoint in clinical trials concerning other hereditary neuropathies such as CMT1A [24]. Its SMR of 0.63 confirms that its sensitivity is more important than other clinical parameters in detecting clinical deterioration. The PND score appears to be the least sensitive to change over time. The RODS score showed a progressive worsening concordant with the different assessments. The initial aggravation of the clinical scores during the first year of follow-up is probably related to the time required to achieve therapeutic efficacy [20, 23].

In this study, the electrophysiological scores remained relatively stable over time. Measurement of distal motor amplitudes appears to be the most robust monitoring parameter. Measuring the amplitude of the CMAP recorded on the TA muscle is an easy parameter to measure. It is more sensitive to change than other electrophysiological data, such as the sensory amplitude of the sural nerve, or than the clinical score PND. The sensory and motor amplitudes of the lower limbs nerves are usually too reduced to be useful as follow-up criteria. On the other hand, all electrophysiological data including motor unit counts were no more sensitive than the clinical scores NIS and ONLS for detecting deterioration in FAP.

Unlike in clinical trials, the management of our patients was not homogeneous, but this reflects their clinical course in a real-life routine care. Further research is needed to better understand the mechanisms and effects of different therapies on disease progression. It would be interesting to complete this study on a larger sample of patients and to include the evaluation of other assessments. Serum neurofilament light chain reflect the severity of the disease and decreased with efficient treatment [25]. Magnetic resonance imaging and ultrasound can be used to analyse the nerves and muscles of patients [26–30]. The quantified imaging data are correlated with disease severity and separate symptomatic from asymptomatic TTR gene mutation carriers. Longitudinal studies appear promising for CMT1A [31] but are still lacking for ATTRv-PN. These complementary approaches could provide a more holistic view of the disease, enabling better management of ATTRv-PN.

ATTRv-PN treatments represent a major advance for patients. In routine care, the overall population of patients remains stable from a clinical and electrophysiological point of view. However, there is significant heterogeneity in response to treatment, hence the crucial importance of rigorous clinical and electrophysiological monitoring. Electrophysiological assessments, such as CMAP sum scores, are good monitoring tools but are not more sensitive to change than clinical scores. These results must be confirmed in a larger cohort of patients.

AUTHOR CONTRIBUTIONS

Hadia Rebouh: Data curation; formal analysis; writing – original draft. **Annie Verschueren:** Conceptualization; supervision. **Etienne Fortanier:** Data curation; validation. **Aude-Marie Grapperon:** Data curation; supervision. **Ludivine Kouton:** Data curation; investigation. **Emmanuelle Salort-Campana:** Supervision; validation. **Shahram Attarian:** Supervision; validation; visualization. **Emilien Delmont:** Conceptualization; writing – review and editing; data curation; methodology.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available on demands.

ETHICS STATEMENT

This study has been approved by the ethics committee of Assistance Publique des Hôpitaux de Marseille (Agreement number PADS24-115_dgr.) and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

CONSENT

All persons involved in this study gave inform consent for participation and publication.

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