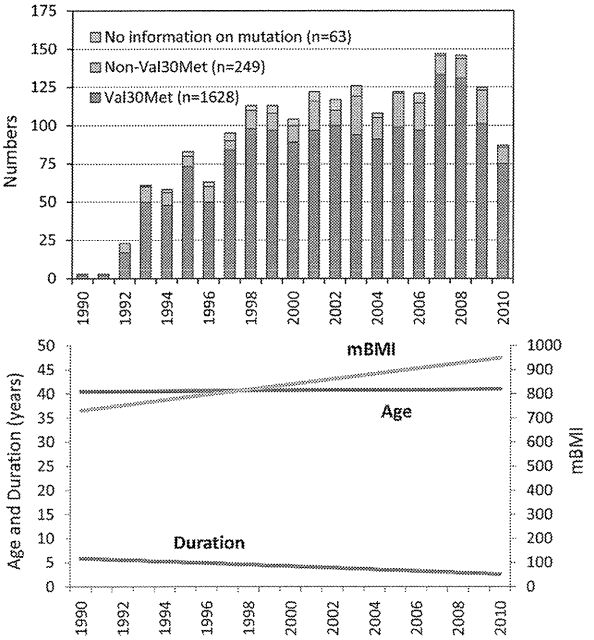

Figure 1. Number of patients with hereditary transthyretin amyloid disease transplanted annually between 1990 and 2010 and trends in age, duration, and mBMI.

performed in 170 patients. Arterial thrombosis (92/188, 48.9%) followed by primary non-function (31/188, 16.5%) were the most common reasons for retransplantation with retransplantation performed median 10 and 2 days after the initial transplantation, respectively. As a curiosity, one patient was retransplanted because of FAP in the deceased donor liver, not known at time of first transplantation. There were 33 reported transplants for combined liver and kidney transplantation, and 50 combined liver and heart transplants. Three patients were reported to have undergone combined liver, heart, and kidney transplantation. Patients undergoing combined transplantation were generally older than those only being treated with Ltx for TTR amyloidosis and carrying a non-TTR Val30Met mutation (Table 1). Overall 20-year survival after transplantation, all mutations included, was 55.3% (Figure 2). The expected mortality rate decreased on average by approximately 4% per year between 1990 and 2010. Improved survival in TTR Val30Met patients was most pronounced during the first 5-year period, whereas non-TTR Val30Met patient survival improved throughout the 20-year period. The gap in long-term survival between TTR Val30Met and non-TTR Val30Met therefore decreased over the years, but it was still significant ($P < 0.05$).

Some regional differences were seen for the most common mutation, TTR Val30Met. The highest percentage of late onset, defined as onset of clinical symptoms of TTR amyloidosis after the age of 50 years, was found in Swedish patients. Lowest age at onset of disease was seen in Brazil. The highest percentage of peripheral neuropathy (sensory loss as main initial symptoms) was reported in French and Spanish patients, whereas the highest percentage of autonomic neuropathy and/or GI dysfunction as main initial symptoms was reported from Japan. The overall highest transplantation activity was reported from Portugal.

Outcome of Multivariate Analysis

The impacts of sex, duration of disease, mBMI, early versus late onset, and TTR Val30Met versus non-TTR Val30Met mutation were examined by multivariate analysis (Table 2). The analysis revealed that high mBMI, early onset of disease, short disease duration, and presence of the Val30Met mutation were all significantly related to decreased mortality, both for the whole group of patients and for the subgroups. Female sex was related to increased survival for the late-onset patient group only.

TTR Mutation and Transplantation

Over the years, an increasing number of patients with new TTR mutations underwent Ltx. In 1995, 16 different TTR mutations had been identified among patients who were undergoing Ltx. In 2010, the corresponding figure was 55 mutations. Throughout the 20-year period, TTR Val30Met was the most common mutation among TTR patients who underwent Ltx. Although pretransplant mBMI as a measurement of the patients' nutritional status gradually increased during the observation period, mean age at time of transplantation, and duration of disease before transplantation successively declined (Figure 1). In Table 1, some important differences between the TTR Val30Met patients and non-TTR Val30Met patients are shown. The proportion of male patients was smaller, and the age at transplantation indicated a younger population of patients in the TTR Val30Met group. In addition, non-TTR Val30Met patients were more likely to undergo combined transplantations. Table 3 shows the outcome of patients with the most common non-TTR Val30Met mutations, as well as their sex and age distribution and whether a combined heart-liver transplant was performed or not.

Age of Onset of Clinical Symptoms of TTR Amyloidosis

In late-onset patients, that is, onset of symptoms of disease after the age of 50 years, no differences were seen between TTR Val30Met and non-TTR Val30Met patients in the proportion of men and women, age at onset, duration of symptoms, or mBMI at transplantation. Moreover, survival after Ltx in patients with late onset was similar between TTR Val30Met and non-TTR Val30Met patients, but was significantly reduced compared to early-onset TTR Val30Met patients (Figure 2). Male late-onset patients had a markedly reduced 10-year survival compared to early-onset male patients (28% and 78%, respectively) (Table 1). The mortality rate in late-onset men was 156.9% that of late-onset women ($P = 0.014$). Early-onset patients, all mutations, had an expected mortality rate of 37.8% that of the late-onset group ($P < 0.001$). Furthermore, TTR Val30Met patients had an expected mortality rate of 61% that of non-TTR Val30 Met patients ($P < 0.001$) (Table 2).

Duration of Disease Before Transplantation

Duration of disease before transplantation had a significant impact on survival after transplantation (Table 2). Thus, a 1-year increased duration of the disease increased the mortality by 10.9% ($P < 0.001$). Different effects of duration were seen between the early- and late-onset groups: 19.1% ($P < 0.001$) increased mortality per year for the early-onset group compared to 5.1% ($P < 0.05$) for the late-onset group.

TABLE 1.

Important differences between patients who underwent transplantations due to TTR Val30Met and Non-TTR Val30Met mutations and characteristics of early- and late-onset TTR Val30Met and Non-TTR Val30Met patients

	Val30Met	Non-Val30Met	*P*
Men/women, %	55/45	66/34	<0.01
Age at transplant, y	39 ± 10	51 ± 11	<0.001
Duration of symptoms, y	3.8 ± 2.7	3.9 ± 3.4	0.582
mBMI at transplant	865 ± 219	897 ± 186	<0.05
Type of transplant			
Liver	97.9%	81.5%	<0.001
Liver + kidney	1.8%	0.4%	0.1118
Liver + heart	0.3%	17.3%	<0.001
Liver + kidney + heart	0%	0.8%	<0.05
Initial symptoms			
Neurological	83.27%	45.40%	<0.001
Cardiac	1.00%	16.09%	<0.001
GI dysfunction	14.37%	19.54%	0.0898
Carpal tunnel	0.07%	8.05%	<0.001
Ocular	0.29%	6.09%	<0.001
Other	1.00%	4.02%	<0.01

	Val30Met						Non-Val30Met					
	Early onset (≤50 y)			Late onset (>50 y)			Early onset (≤50 y)			Late onset (>50 y)		
	Men (*n* = 699)	Women (*n* = 597)	*P* value	Men (*n* = 95)	Women (*n* = 57)	*P* value	Men (*n* = 64)	Women (*n* = 40)	*P* value	Men (*n* = 47)	Women (*n* = 24)	*P* value
Age at transplantation	34.6 ± 7.0	38.3 ± 6.7	<0.001	62.0 ± 4.5	58.2 ± 4.0	<0.001	44.5 ± 8.3	41.0 ± 9.0	<0.05	60.5 ± 4.5	57.8 ± 5.4	<0.05
Age at onset	30.9 ± 6.5	34.3 ± 6.0	<0.001	58.1 ± 4.5	55.1 ± 3.7	<0.001	40.1 ± 7.1	36.9 ± 8.1	<0.05	56.9 ± 4.9	54.8 ± 5.0	0.098
Duration	3.7 ± 2.6	4.0 ± 2.9	<0.05	3.9 ± 2.3	3.2 ± 1.6	<0.05	4.4 ± 4.2	4.1 ± 3.6	0.625	3.6 ± 2.5	3.0 ± 2.4	0.313
10-yr survival	78%	75%	0.1097	28%	55%	<0.05	37%	45%	0.8177	37%	43%	0.2170

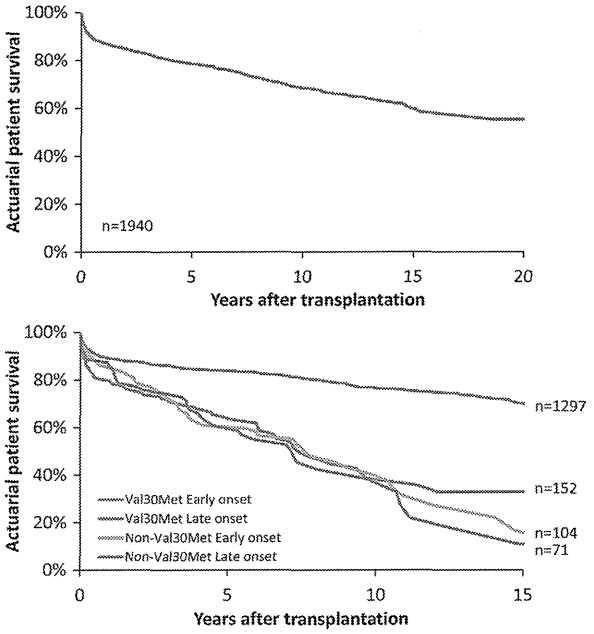

Figure 2. Overall actuarial patient survival between 1990 and 2010. For all patients (above), and according to TTR Val30Met/non-TTR Val30Met mutations and early or late onset of disease (below).

Nutritional Status at Time of Transplantation

Because low mBMI at transplantation has been shown to be associated with worse posttransplantation survival in FAP patients, we analyzed survival outcome in patients using 4 different mBMI levels, less than 600, 600–699, 700–799, 800–899, and 900 or higher, respectively. A log rank test was run to determine if there were differences in the survival distribution for the different levels of mBMI. The survival distributions for the five levels of mBMI were statistically significantly different ($\chi^2(4) = 28.827$, $P < 0.0001$). In all patients, for each 100-unit increase in mBMI at transplantation, mortality was reduced to 89.1% that of the expected mortality ($P < 0.001$) (Table 2).

Causes of Death

A total of 561 patient deaths were reported. In 22% of these patients, the cause of death was reported as secondary to septicaemia. Cardiovascular-related deaths occurred in 22% of the cases, and liver-related complications resulted in death in 14%. Intraoperative death represented 3%. When these main causes of death were compared with the European Liver Transplant Registry (ELTR), the causes were comparable, except for cardiac-related deaths: FAPWTR 22% versus ELTR 9%.

Risk Associated With Domino Donation

The 1064 h-TTR amyloidosis patients who donated their liver for domino transplantation had a survival that was similar to that of the 660 patients from the same time period who did not donate.

DISCUSSION

Since the introduction of LTx for h-TTR amyloidosis, the number of cases reported to the registry increased rapidly up until 2000. Thereafter, it remained relatively stable, with an apparent increase in 2007 to 2008 and then a decline; the latter may have been related to the approval, by the European medical product agency, of tafamidis for the treatment of early-stage (able to walk without support) neuropathic TTR amyloidosis. Because tafamidis is prescribed to patients in the early stages of the disease, it will take considerable time before an improvement in survival associated with tafamidis treatment can be proven.

In the present analysis, a 20-year survival rate of more than 50% was found after transplantation in h-TTR amyloid patients; this is a considerable improvement compared to that of previous reports on the natural history of the disease, in which the survival from onset of disease was approximately 10 to 15 years.[16–18] Considering the difference between

TABLE 2.

Outcome of multiple cox regression analysis of mortality risk for the whole group of transplanted patients and for the early- and late-onset subgroups

Factor	Coefficient	Hazard/Odds ratio	*Z* Statistic	*P*
Whole group				
Early vs late onset	−0.972831	0.3780114	−8.152	<0.0001
Val30Met vs non-Val30Met	−0.493938	0.6102189	−3.473	0.0005
mBMI at Ltx per 100-unit increase	−0.11560	0.89083	−4.312	<0.0001
Duration of disease	0.103359	1.1088898	7.704	<0.0001
Gender (male vs female)	0.0543786	1.0558843	0.530	0.59604
Early-onset subgroup				
Val30Met vs non-Val30Met	−1.0525922	0.3490318	−5.610	<0.0001
mBMI at Ltx per 100-unit increase	−0.10641	0.899059	−3.162	<0.0016
Duration of disease	0.1747060	1.1908960	8.721	<0.0001
Sex (male vs female)	−0.0966947	0.9078331	−0.769	0.442
Late-onset subgroup				
Val30Met vs non-Val30Met	−0.052046	0.949286	−0.276	0.7825
mBMI at Ltx per 100-unit increase	−0.1324	0.87599	−2.853	0.0043
Duration of disease	0.049714	1.05097	2.210	0.0271
Sex (male vs. female)	0.45074	1.569473	2.458	0.0140

From the figures, it can be estimated that for early-onset patients, for each year Ltx is delayed, the hazard of dying increases by 19%; similarly, it can be seen from the figures that the hazard of death for early-onset TTR Val30Met patients is 35% that of non-TTR Val30Met patients.

TABLE 3.

The most common non-TTR Val30Met mutations

Most common non-TTR Val30Met mutations					
TTR mutation	***n***	**Liver (n)/Liver and heart (n)**	**Liver/Liver and heart 10-Y Survival, %**	**Men, %**	**Age at transplantation, y**
Ser77Tyr	38	32/6	41/44	76	57.3 ± 5.7
Thr60Ala	23	14/9	36/55	96	59.5 ± 4.9
Tyr114Cys	15	15/0	53/—	47	48.6 ± 6.7
Leu111Met	12	5/7	100[a]/71	58	48.0 ± 4.7
Ser50Arg	12	11/1	28/0	50	41.1 ± 6.6
Val71Ala	11	11/0	82/–	55	37.5 ± 10.6
Leu58His	11	11/0	76/–	73	60.3 ± 3.6
Val30Met	1628	1624[b]/4	73/100	55	39.0 ± 10.2

[a] 8 y.
[b] Includes 30 liver + kidney transplants.

calculating survival from onset of disease and from time of transplantation, as was used in this investigation, the improvement in survival is even more impressive. In our analysis, all patients with h-TTR amyloidosis, irrespective of mutation, were included, as were those with advanced disease and/or poor nutritional status. The majority of these types of patients are no longer readily accepted for transplantation, as shown by the successively shorter disease duration, increased mBMI, and decreased age of the transplanted patients observed in the registry during the observation period. This optimization of selection criteria is also reflected in the rapidly improved outcome for early-onset TTR Val30Met patients, in whom the 15-year survival rate was close to 80%. During this 2 decade study period, several modifications to immunosuppressive protocols were of course implemented, which may have contributed to the observed improved survival. This variable could, however, not be analyzed because data on immunosuppression is not reported to the FAPWTR.

Improved survival during the study observation period was observed for non-TTR Val30Met patients. This may be related to patient selection, based on the knowledge of post-transplant development of amyloid cardiomyopathy observed in many patients with non-TTR Val30Met mutations, for which a combined liver and heart transplantation may be a viable alternative.[2-4,19,20] However, the steadily increasing number of different mutations in the registry and a gradual improvement in the survival of patients with these mutations also points to the influence of a learning curve for the different transplant centers because non-TTR Val30Met patients are often reported from centers outside the endemic TTR Val30Met areas; thus, from centers where Ltx for hTTR amyloidosis is relatively infrequently performed. However, the outcome for patients with non-TTR Val30Met mutations, such as Ser77Tyr, Thr60Ala, and Ser50Arg, is still disappointing, and can be explained neither by their generally higher age because the mortality was similar for late- and early-onset patients, nor by impaired nutritional status, because the mBMI was significantly higher in the non-TTR Val30Met group of patients. In addition, disease duration before transplantation was similar for both groups of patients. However, it should be noted that for several non-TTRVal30Met mutations, such as Val71Ala and Leu58His and especially Leu111Met, Ltx with or without simultaneous heart transplantation was successful. Considering that cardiomyopathy dominates the clinical presentation in patients with the Leu111Met mutation,[21] the outcome is surprisingly good.

Previous reports have identified various risk factors, and several were confirmed by our analysis.[6,22,23] Risk factors analyzed that had an independent negative impact on survival included: non-TTR Val30Met mutation, late onset, advanced disease reflected by long disease duration before transplantation, and malnutrition measured by the mBMI.

An important finding was the close to 20% annual increase in mortality risk noted for early-onset TTR Val30Met patients waiting for Ltx. This needs to be taken into consideration when pharmacotherapy is considered for early-onset patients, who have the best expected outcome after Ltx and who are also subject to substantially increased risk if pharmacotherapy proves to be inefficient.

The presence of h-TTR in the family history was not a risk factor, and neither was sex. However, in an analysis of survival in the subgroup of late-onset patients, female sex was associated with significantly better survival compared to male sex, for which survival was no different from that expected for nontransplanted patients. This sex difference for late-onset patients was previously reported from Sweden.[8] We do not know why there are such marked differences between genders and between early- and late-onset patients, or between TTR Val30Met and other mutations. However, differences in amyloid fibril composition have been found between early- and late-onset TTR Val30Met patients and also between early-onset TTR Val30Met patients and other mutations: late-onset TTR Val30Met patients and non-TTR Val30Met patients display a fibril composition similar to that noted in senile systemic amyloidosis (SSA).[24,25] The SSA is caused by amyloid fibril formation from wild-type TTR, and it is therefore not affected by Ltx. In addition, an increase in or development of amyloid cardiomyopathy after transplantation has lately been shown to occur predominantly in patients with an amyloid fibril composition similar to that of SSA.[26]

The importance of heart complications with regard to outcome after transplantation is reflected by the causes of death. Cardiac-related death was markedly more frequent for hTTR amyloid patients compared to that reported to the ELTR for Ltx in patients with nonamyloid diseases.

The FAPWTR registry does not report in detail on symptomatic changes after Ltx, but for TTR Val30Met patients,

especially early-onset patients, the disease progression appears to come to a halt.[5,27] However, Ltx does not affect variant TTR production in the eye or brain. Several reports have been published on the development of vitreous opacities and glaucoma after Ltx.[28,29] The development of CNS complications is still an open question, but patients carrying the rare occulomeningeal h-TTR mutations, such as Gly53Glu, are not helped by Ltx.[30] In addition, the development of conduction disturbances necessitating pacemaker treatment has been reported for early-onset h-TTR Val30Met patients after the procedure.[9] Consequently, prophylactic pacemaker insertion before transplantation is performed at several centers.

Data from the FAPWTR clearly show that using the livers of h-TTR patients for other patients in need of a liver transplant has no impact on the survival of the donors. Recently, the development of TTR amyloidosis in domino liver recipients was reported,[22,31] but TTR amyloid livers are still an important source of organs for selected patients, such as elderly patients, patients with liver cancer, and hepatitis-C cirrhosis patients, in whom graft loss or patient death is more likely to occur from the recipient's original disorder than from the transfer of TTR amyloidosis by a variant TTR liver.

In summary, long-term survival after Ltx for h-TTR amyloidosis is excellent in well-selected patients. Good nutritional status, short duration of disease at the time of Ltx, and early onset of the disease are significant independent factors for survival. The TTR Val30Met patients had a better outcome compared to non-TTR Val30Met patients. The risk of delaying Ltx by testing alternative treatments, especially in early-onset TTR Val30Met patients, requires further consideration.

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Effects of tafamidis treatment on transthyretin (TTR) stabilization, efficacy, and safety in Japanese patients with familial amyloid polyneuropathy (TTR-FAP) with Val30Met and non-Varl30Met: A phase III, open-label study

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ABSTRACT

Introduction: The efficacy and safety of tafamidis in transthyretin (TTR) familial amyloid polyneuropathy (TTR-FAP) were evaluated in this open-label study.
Methods: Japanese TTR-FAP patients ($n = 10$; mean age 60.1 years) received tafamidis meglumine (20 mg daily; median treatment duration 713.5 days). The primary endpoint was TTR stabilization at Week 8. Secondary endpoints included Neuropathy Impairment Score-Lower Limb (NIS-LL), Norfolk QOL-DN total quality of life (TQOL), and modified body mass index (mBMI).
Results: TTR stabilization was achieved in all patients at Weeks 8 and 26, 9 out of 10 patients at Week 52, and 8 out of 10 patients at Week 78. The percentage (95% CI) of NIS-LL responders (increase from baseline in NIS-LL < 2) was 80.0% (44.4, 97.5), 60.0% (26.2, 87.8), and 40.0% (12.2, 73.8) and mean(SD) NIS-LL change from baseline was 2.1 (5.6), 3.6 (4.4), and 3.3 (4.7), at Weeks 26, 52, and 78, respectively. Mean (SD) changes from baseline in TQOL and mBMI at Weeks 26, 52, and 78 were 11.8 (20.0), 9.1 (12.5), and 10.8 (13.7) for TQOL, and 26.6 (61.9), 64.9 (80.0), and 53.7 (81.4) for mBMI, respectively. Ambulation status was preserved in 4 out of 8 patients at Week 78. Most adverse events (AEs) were mild/moderate, with no discontinuations due to AEs.
Conclusions: Tafamidis stabilized TTR, was safe and well-tolerated, and was effective over 1.5 years in slowing neurologic progression and maintaining TQOL and nutrition status in TTR-FAP.

1. Introduction

Transthyretin (TTR) familial amyloid polyneuropathy (TTR-FAP) is a rare, inherited, life-threatening amyloidosis that presents as a progressive sensorimotor and autonomic polyneuropathy with death occurring approximately within 5–10 years from initial presentation of symptoms [1,2]. Val30Met is the most common mutation associated with TTR-FAP, accounting for approximately 85% of cases worldwide [3–6]. The age at onset of TTR-FAP varies between the second and ninth decade of life, and is dependent on phenotype, genotype, and environmental factors [4,7]. For Japanese patients with the Val30Met mutation, the mean age of onset is 35 years in endemic areas [8] and around 60 years in non-endemic areas [9].

The prevalence of FAP in Japan was estimated to be 0.87–1.1 per 1 000 000 individuals (case numbers: 110.8–135.4) in 2003–2005 [2], and to date, the number of patients with TTR-FAP in Japan have been gradually increasing with improvement of diagnostic processes and advances in disease awareness that have accompanied the availability of treatment, however the prevalence still seems to be lower than Europe.

Liver transplantation is the historic standard of care for mild or moderate TTR-FAP [3,4], but is associated with high procedural risks,

Abbreviations: TTR, transthyretin; TTR-FAP, TTR familial amyloid polyneuropathy; mBMI, modified body mass index; NIS, Neuropathy Impairment Score; NIS-LL, Neuropathy Impairment Score-Lower Limb; NIS-UL, Neuropathy Impairment Score-Upper Limb; TQOL, Norfolk QOL-DN total quality of life; NSAID, nonsteroidal anti-inflammatory drug.

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potential life-threatening post-procedural complications, and there is a shortage of donors, especially in Japan. Additionally, large numbers of patients are not suitable transplant candidates because of their age and/or advanced disease status [10]. Therefore, there is a substantial unmet medical need for other beneficial therapies.

Tafamidis, a specific stabilizer of TTR that inhibits tetramer dissociation [11], is an oral, non-NSAID medicine that has emerged as the new standard of care for TTR-FAP. Tafamidis is the only disease-modifying therapy approved in Europe, Japan, and several Latin American and other Asia-Pacific countries to delay neurologic impairment in adult patients with early stage TTR-FAP [12–14]. The efficacy and safety of tafamidis over 30 months has been demonstrated in clinical trials, including a pivotal, double-blind, placebo-controlled trial and its open-label extension in patients with Val30Met TTR-FAP; and an open-label study in patients with non-Val30Met TTR-FAP (in which eight different TTR mutations were evaluated) [15–17]. Tafamidis slowed neurological progression, was generally safe and well tolerated, and was associated with a high degree of TTR stabilization in these studies.

In the pivotal study, pre-specified analyses of five measures of clinical disease progression, including Neuropathy Impairment Score for Lower Limbs (NIS-LL), small and large fiber measures of neuropathy, modified body mass index (mBMI), and Norfolk Quality of Life-Diabetic Neuropathy total score were improved in tafamidis-treated patients versus placebo-treated patients. Significant positive treatment group differences were observed in NIS-LL total score, small fiber measures, and mBMI at month 18 [15]. A 12-month open-label extension of the registration trial showed reduced rates of neuropathic progression with tafamidis that were sustained for a total of 30 months [16]. In a 12-month evaluation of tafamidis safety and efficacy in TTR-FAP patients with non-Val30Met TTR mutations [17], the efficacy observed with tafamidis in the prevention of disease progression was similar to that seen in TTR-FAP patients with Val30Met mutations [15].

This study was a multicenter, single-arm, open-label Phase III study in Japan to assess TTR stabilization and evaluate the efficacy, safety, and tolerability of tafamidis treatment in TTR-FAP patients with Val30Met and non-Val30Met mutations.

2. Methods

2.1. Study design

This study (ClinicalTrials.gov: NCT01435655) was a single arm, open-label, multicenter study aiming to determine TTR stabilization in addition to tafamidis safety and tolerability, and efficacy in TTR-FAP patients with Val30Met and non-Val30Met mutations. The study was conducted at two centers in Japan between 2011 and 2014.

Eligible patients were men and women aged 20 to 75 years with documented amyloid deposition by biopsy and Val30Met or other TTR mutation (non-Val30Met) that was associated with peripheral neuropathy and the symptomatic neuropathy with Karnofsky Performance Status ≥ 50.

Key exclusion criteria included the presence of primary/secondary amyloidosis; other causes of sensorimotor neuropathy; impaired renal or hepatic function; prior liver transplantation; and New York Heart Association Functional classification ≥ 3. The study protocol was approved by the Institutional Review Board at each site, and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

2.2. Study procedures

After screening and baseline assessments, all patients self-administered a once-daily oral dose of tafamidis meglumine 20 mg. Study visits for assessments were scheduled at screening (Days −30 and −1), baseline (Day 0), Weeks 2, 4, 8, 12, 26, 39, 52, 78, and then 26-week interval visits and the end of study.

2.3. Outcome measures

The primary efficacy outcome was TTR stabilization at Week 8, as measured using a validated immunoturbidimetric assay [11], and TTR stabilization at each follow-up visit after Week 8 (Weeks 26, 52, 78, and study completion or withdrawal before Week 78) was evaluated as a secondary endpoint.

Secondary outcome measures included changes from baseline in NIS (total score), NIS-LL and NIS-Upper Limbs (NIS-UL) scores, Summated 3/7 Nerve Tests Normal Deviate Scores (Σ7 and Σ3 NTs NDS), Norfolk Quality of Life-Diabetic Neuropathy Questionnaire (Norfolk QOL-DN) TQOL, mBMI, and ambulatory status over time. Changes from baseline in all of these measures were summarized using descriptive statistics.

The NIS scale [18,19] provides a total body single score of neuropathic deficits and subset scores for cranial nerves, muscle weakness, reflexes, and sensation. NIS scores range from 0 to 244, with a higher score indicating a greater degree of impairment. NIS assessments were performed twice at least 24 h apart within a 7-day period at baseline, Weeks 26, 52, 78, and the end of study. The averages of the two assessments at each visit were used for analysis. A subset of the NIS, the NIS-LL, was used to provide a total neuropathic deficit score for the lower limbs. The NIS-LL was calculated as the sum of subset scores including muscle weakness, reflexes, and sensation in great toe. The range of the NIS-LL total score is 0 to 88, with a higher total score indicating greater degrees of impairment (i.e. a score of 0 indicates no impairment). A patient with change from baseline in NIS-LL < 2 was categorized as a responder; change from baseline in NIS-LL ≥ 2 was categorized as a non-responder. NIS-UL (range 0 to 156) was used to provide a total neuropathic deficit score for the upper limbs and was calculated as NIS-UL = NIS − NIS-LL.

Summated scores including Σ7 NTs NDS and Σ3 NTSF NDS, which are obtained by summing multiple objective measures of nerve fiber impairment, have been used to detect disease progression in other neuropathies [20,21]. Σ7 NTs NDS assessed with nerve conduction studies (NCS), vibration detection threshold (VDT), and Heart Rate Response to Deep Breathing (HRDB), primarily measures large-fiber function. A higher score indicates worse nerve function. Σ3 NTSF NDS, which measures small-fiber function, is assessed using cooling and heat pain thresholds by QTS with Computer Assisted Sensory Examination (CASE IV) and HRDB. The potential range of Σ3 NTSF NDS is approximately −11.2 to 11.2, with a higher score demonstrating worse nerve function.

The Norfolk QOL-DN [22] is a self-administered questionnaire containing 35 items across five domains to assess the impact of neuropathy with higher scores reflecting worse quality of life. The TQOL ranges from −4 to 136. TQOL was assessed at baseline, Weeks 26, 52, 78, and the end of the study.

mBMI, calculated as the product of body mass index (BMI; kg/m^2) and serum albumin level (g/L), provides a more accurate indicator of malnutrition and gastrointestinal dysfunction than BMI and is an important measure of wasting in patients with TTR-FAP [23]. Change in mBMI from baseline was calculated at Weeks 8, 26, 52, and the end of study.

Ambulatory status (according to walking ability scale in polyneuropathy disability score) was evaluated at baseline, Weeks 26, 52, 78, and the end of study.

An echocardiography was performed for all patients at baseline, Week 52, Week 104, and end of study. Echocardiographic parameters (intra-ventricular septum diastole thickness, stroke volume) actual values and change from baseline were summarized descriptively at each visit.

2.4. Evaluation of TTR stabilization

Blood samples for determination of TTR stabilization were collected at Weeks 8, 26, 52, 78 and study completion or withdrawal before Week 78. Each blood sample was collected into a potassium edetic acid tube

and 1.5 mL plasma was collected from each sample and analyzed for TTR stabilization using a validated immunoturbidimetric method [11] at LabCorp Clinical Trials (Los Angeles, CA).

2.5. Safety evaluations

Safety endpoints were evaluated as secondary endpoints and included adverse events (AEs), vital signs (temperature, blood pressure, pulse rate, respiratory rate), electrocardiograms (ECGs), echocardiography, clinical laboratory evaluations, and physical evaluation. Observed or volunteered AEs included adverse drug reactions, illnesses with onset during the study, and exacerbation of previous illnesses. The investigator recorded the severity (mild, moderate, or severe) of the events, and any clinically significant changes in physical examination findings and abnormal objective test findings as AEs.

A serious AE (SAE) was defined as any AE at any dose that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or resulted in congenital anomaly/birth defect.

2.6. Statistical analysis

The full analysis set (FAS) included all randomized patients who received at least one dose of tafamidis as did the efficacy analysis and safety analysis sets.

The number and percentage (95% confidence interval [CI]) of responders in TTR stabilization (percent stabilization ≥ 32%), were summarized using descriptive statistics. Changes from baseline in NIS, NIS-LL, NIS-UL, TQOL, Σ7 NTs NDS, Σ3 NTSF NDS, mBMI, and echocardiography were summarized using descriptive statistics. The number and percentage (95% CI) of responders in NIS-LL (increase from baseline in the NIS-LL < 2) were also summarized using descriptive statistics.

3. Results

3.1. Patient characteristics

A total of 10 patients were enrolled and assigned to treatment. Of these, seven patients completed study treatment and three discontinued from the study; two patients died (sudden death and suicide), and one patient discontinued because of other reasons (unable to visit site because of disease progression). Data from all 10 patients were analyzed for efficacy and safety. The median duration of treatment was 713.5 days (range 380–796 days).

Demographic and baseline characteristics for all patients are shown in Table 1. The majority were male (70%) with a mean age of 60.1 years (range: 35 to 73 years) and a mean BMI of 20.9 kg/m^2 (18.2 to 26.3 kg/m^2). The TTR genotypes were Val30Met in nine patients and non-Val30Met (Ser77Tyr) in one patient. Of the 10 subjects treated in the present study, 7 subjects were 'late-onset', who were diagnosed at ≥50 years (mean onset age: 65.6 yrs., mean duration from diagnosis: 1.8 years), and 3 subjects were 'early-onset' who were diagnosed at <50 years old (mean onset age: 41.0 years, mean duration from diagnosis: 2.0 years).

3.2. Efficacy

3.2.1. TTR stabilization

Fig. 1 shows mean (SD) patient TTR percent stabilization data plotted over time (Weeks 8, 26, 52, and 78). All 10 patients (95% CI 69.2 to 100.0) achieved TTR stabilization (percent stabilization ≥ 32%) at Week 8 (primary endpoint) and at Week 26 (95% CI 69.2 to 100.0). At Weeks 52 and 78, TTR stabilization was maintained in 9 out of 10 patients (95% CI 55.5 to 99.7) and 8 out of 10 patients (95% CI 44.4 to 97.5), respectively, although at Week 78, two patients (20%) had missing data.

Table 1
Baseline demographics and characteristics.

	Tafamidis 20 mg $N = 10$
Sex	
Male	7
Female	3
Age (years)	
20–44	1
45–64	5
≥65	4
Mean (SD)	60.1 (13.0)
Range	35–73
Weight (kg)	
Mean (SD)	55.6 (10.8)
Range	42.2–73.3
Height (cm)	
Mean (SD)	162.5 (6.3)
Range	152.4–170.0
BMI (kg/m^2)	
Mean (SD)	20.9 (3.1)
Range	18.2–26.3
TTR genotype, *n* (%)	
Val30Met	9 (90.0)
Ser77Tyr	1 (10.0)

BMI, body mass index; SD, standard deviation; TTR, transthyretin.

3.2.2. NIS

The mean (SD) NIS, NIS-LL, and NIS-UL scores at baseline were 31.03 (26.26), 16.99 (13.14), and 14.03 (13.72), respectively. Increases in NIS, NIS-LL, and NIS-UL scores over the study duration of 1.5 years were relatively small but gradual (Fig. 2a–c). The percentage (95% CI) of responders in NIS-LL score was 80.0% (44.4, 97.5) at Week 26, 60.0% (26.2, 87.8) at Week 52, and 40.0% (12.2, 73.8) at Week 78.

NIS total, NIS-LL, and NIS-UL at baseline were 39, 20, and 19, respectively, in the late-onset patients (≥50 years), and 12, 10, and 3, respectively, in the early-onset patients (<50 years). The mean (SD) change in NIS-UL from baseline over time was higher in the late-onset group (Week 26: 3.2 (4.6), Week 52: 7.0 (4.3), Week 78: 8.7 (9.3)) than in the early-onset group (Week 26: 0.3 (1.4), Week 52: −0.7 (1.0), Week 78: 0.4 (0.5)).

3.2.3. TQOL

The mean TQOL (SD) score at baseline was 52.9 (32.8). Mean (SD) change from baseline in TQOL over time is shown in Fig. 3, and change from baseline in each domain is summarized in Table 2.

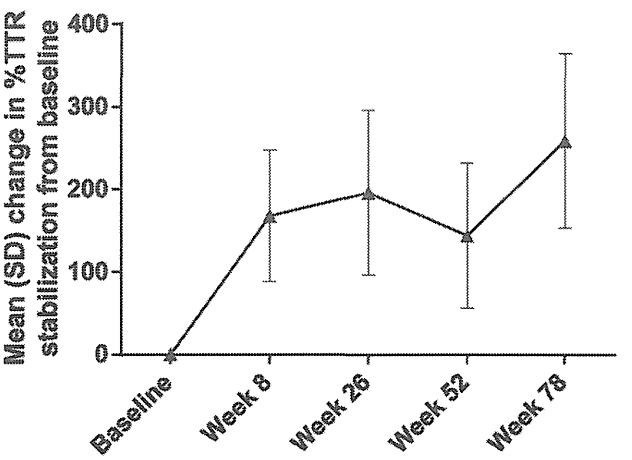

Fig. 1. Mean (SD) TTR percent stabilization at Weeks 8, 26, 52, and 78. TTR, transthyretin. Two patients had missing data at Week 78.

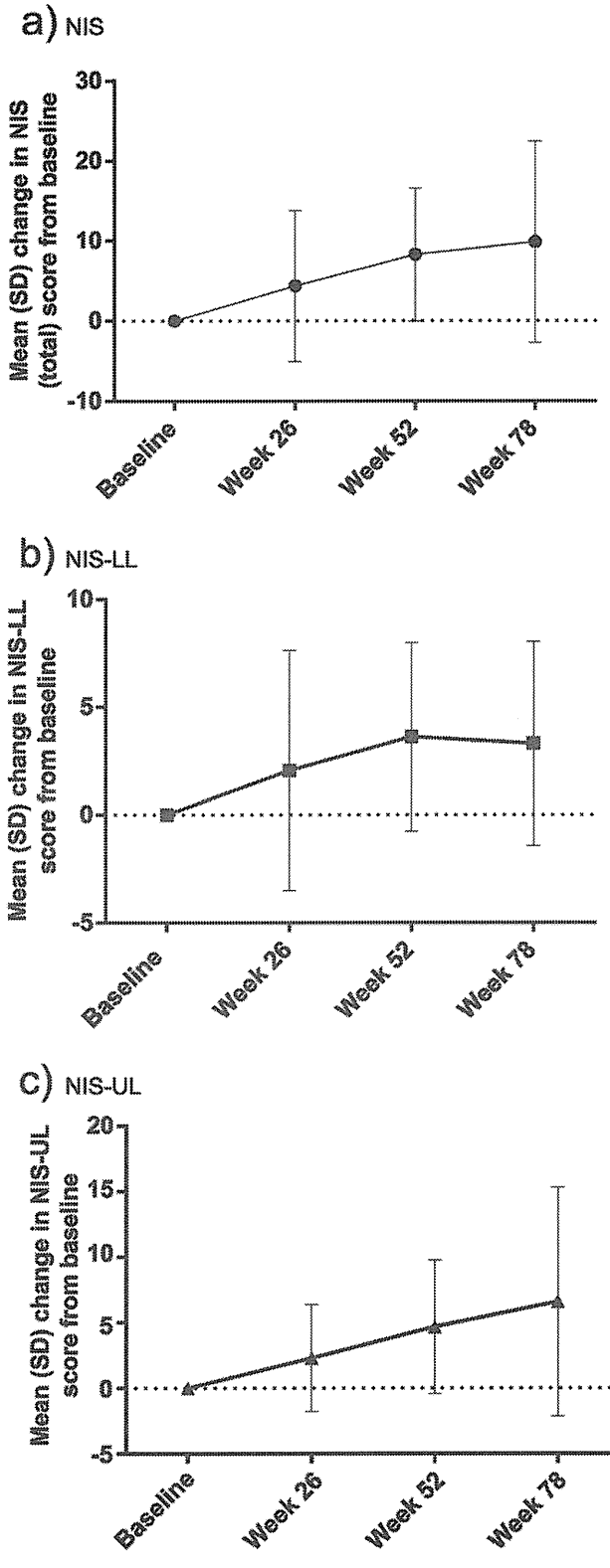

Fig. 2. Mean (SD) change from baseline in NIS scores (NIS total, NIS-LL, NIS-UL) at Weeks 26, 52, and 78. NIS, Neuropathy Impairment Score; NIS-LL, Neuropathy Impairment Score-Lower Limb; NIS-UL, Neuropathy Impairment Score-Upper Limb; SD, standard deviation. Two patients had missing data at Week 78.

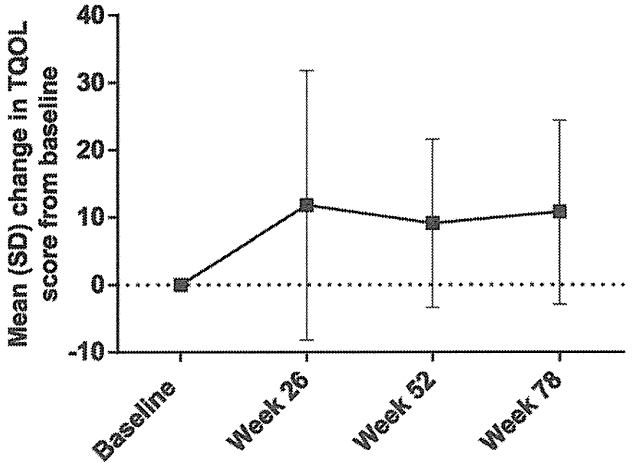

Fig. 3. Mean (SD) change from baseline in TQOL by Norfolk QOL-DN at Weeks 26, 52, and 78. Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy Questionnaire; SD, standard deviation; TQOL, total quality of life.

3.2.4. Echocardiography

At baseline, the mean (SD) intra-ventricular septum diastole thickness was 18.8 (5.1) mm, and mean (SD) change in septum diastole thickness from baseline was −1.3 (2.7) mm at Week 52 and −3.7 (3.7) mm at the end of study. Mean (SD) stroke volume at baseline was 54.8 (9.7) mL, and change of stroke volume from baseline was 1.1 (5.0) mL at Week 52 and 6.0 (13.0) mL at the end of study.

3.2.5. mBMI

At baseline, the mean (SD) mBMI was 805.7 (193.4). By Week 8, there was a mean (SD) increase from baseline mBMI of 74.9 (88.7) and an increase in mBMI from baseline was maintained over the study period. Mean (SD) changes from baseline in mBMI at Weeks 8, 26, 52, and end of study are summarized in Fig. 4.

3.2.6. Large and small fiber functions (Σ7 NTs NDS and Σ3 NTSF NDS)

The mean (SD) Σ7 NTs NDS at baseline was 8.33 (5.57) and the mean (SD) changes from baseline at Weeks 26, 52, and 78 were 0.55 (2.66), 1.04 (2.99), and 1.92 (5.13), respectively, indicating a small degree of worsening in large fiber function over time. The mean (SD) Σ3 NTSF NDS at baseline was 6.39 (3.16) and the mean (SD) change from baseline at Weeks 26, 52, and 78 was 0.16 (1.62), −0.13 (1.33), and 0.40 (1.99), respectively, reflecting some worsening in small fiber function at Week 78.

The mean (SD) sural sensory nerve amplitude NDS at baseline was −1.74 (1.16). The mean (SD) sural sensory nerve amplitude NDS change from baseline at Weeks 26, 52, and 78 were −0.261 (0.462), −0.173 (0.415), and −0.131 (0.273), respectively, suggesting no significant change from baseline.

3.2.7. Ambulatory status

At Week 26, ambulatory status was unchanged in seven patients, had worsened in two patients, and improved in one patient. By Week 78, ambulatory status had improved from baseline in one patient, worsened in four patients, and was unchanged in three patients (Table 3). These results indicate that walking is preserved in half of the patients over the 1.5-year treatment duration with tafamidis.

3.3. Safety

A total of 85 all causality AEs were reported in ten patients and two AEs (gingival swelling and sudden death) in two patients were assessed by the investigator as related to treatment. Severe AEs occurred in three

Table 2
Change from baseline in TQOL and each domain by Norfolk QOL-DN.

	TQOL	Tafamidis 20 mg $N = 10$				
		Physical functioning/large fiber	Activities of daily living	Symptoms	Small fiber	Autonomic
Baseline, *n*	10	10	10	10	10	10
Mean (SD)	52.9 (32.8)	25.6 (15.3)	8.5 (7.6)	8.5 (5.3)	6.3 (5.3)	4.0 (3.1)
Median	54.5	24.5	7.5	8.5	5.5	4.0
Range	4, 105	3, 48	0, 20	0, 18	0, 13	0, 9
Change from baseline						
Week 26, *n*	10	10	10	10	10	10
Mean (SD)	11.8 (20.0)	4.8 (10.0)	1.2 (3.6)	2.6 (3.5)	1.9 (4.3)	1.3 (1.4)
Median	5.5	0.0	0.5	3.0	0.5	1.0
Range	−6, 54	−5, 27	−5, 8	−2, 7	−2, 11	0, 4
Week 52, *n*	10	10	10	10	10	10
Mean (SD)	9.1 (12.5)	2.2 (8.9)	0.8 (3.5)	4.0 (5.7)	1.6 (2.3)	0.5 (1.4)
Median	10.0	3.5	1.0	4.0	0.5	0.0
Range	−14, 26	−12, 16	−7, 5	−3, 16	−1, 6	−1, 3
Week 78, *n*	8	8	8	8	8	8
Mean (SD)	10.8 (13.7)	4.1 (7.8)	0.6 (2.3)	3.1 (3.9)	2.1 (3.8)	0.8 (1.9)
Median	12.5	4.0	0.5	3.0	0.5	0.5
Range	−7, 34	−6, 18	−4, 4	−2, 10	−3, 8	−2, 4

Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy Questionnaire; SD, standard deviation; TQOL, total quality of life.

patients and included ileus, sudden death, and suicide. No patients discontinued due to AEs. The most common AEs (all causalities, reported in two patients or more) were nasopharyngitis and muscular weakness (five patients each), bacterial pneumonia and thermal burn (three patients each), and atrioventricular block second degree, cataract, vitreous opacities, nausea, vomiting, muscle spasms, myalgia, and insomnia (two patients each). In total, there were 13 SAEs reported in seven patients; one of which (sudden death) was assessed by the investigator to be related to the study drug.

4. Discussion

Tafamidis treatment was generally safe and well tolerated in this Japanese patient population with primarily Val30Met TTR-FAP, with most AEs mild or moderate in severity, consistent with previous trials [15–17]. There was a rapid onset of TTR stabilization (at Week 8) in 100% of patients following initiation of tafamidis treatment that was generally maintained over the long-term (Week 78), also consistent with earlier reports [15–17].

Overall, tafamidis delayed neuropathic progression and improved nutritional status (mBMI) over the 1.5-year study. Although there were slight decreases in neurologic function (NIS, NIS-LL, and NIS-UL scores) over time, it is noteworthy that the mean sural sensory nerve amplitude NDS did not change throughout the study, suggesting that treatment with tafamidis did suppress neuropathy progression in TTR-FAP patients. TTR stabilization, a favorable safety profile, slowing in decline of neurophysiologic functioning, and improvement in mBMI were similarly observed in tafamidis-treated patients with Val30Met TTR-FAP in a previous 18-month phase 3 randomized, placebo-controlled study of tafamidis [15].

The relationship between the age of onset of TTR-FAP in subjects and the efficacy of tafamidis in the present study was also explored. In this study, all indices of NIS at baseline were higher in the late-onset group than the early-onset group. In a retrospective study in patients with late-onset Val30Met TTR-FAP in a non-endemic area of Japan, Koike et al. [24] reported that the prognosis in these patients was relatively poor, and once neuropathic symptoms were noted, sensory and motor symptoms in both the upper and lower extremities appeared within a short time period. In this study, the differences observed in baseline values and in the time-course of NIS indices between late- and early-

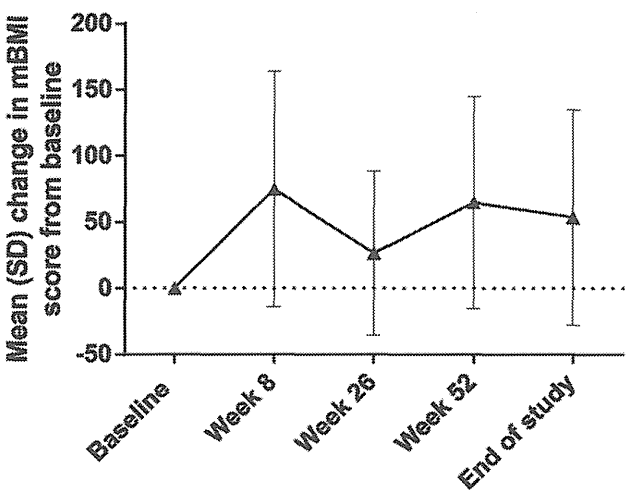

Fig. 4. Mean (SD) change from baseline in mBMI at Weeks 8, 26, 52, and end of study. mBMI, modified body mass index; SD, standard deviation.

Table 3
Mean change from baseline in ambulatory status.

Visit	Tafamidis 20 mg ($N = 10$)							
	n	Baseline status	Ambulatory status at each visit					
			0	1	2	3a	3b	4
Week 26	10	0						
		1	**1**	**2**				
		2			**3**	1		
		3a				**1**	1	
		3b					**1**	
		4						
Week 52	10	0						
		1	**1**	**1**	1			
		2			**3**	1		
		3a				**1**	1	
		3b					**1**	
		4						
Week 78	8	0						
		1	**1**	**1**		1		
		2			**2**	1		
		3a					2	
		3b						
		4						

Bolded data indicate improvement or no change in ambulatory status from baseline.
0: Good.
1: Sensory disturbances in the feet but able to walk without difficulty.
2: Some difficulties with walking but can walk without aid.
3a: Able to walk with 1 stick or crutch.
3b: Able to walk with 2 sticks or crutches.
4: Not ambulatory, confined to a wheelchair, or bedridden.

onset patients are thought to be more likely to be due to late-onset of disease than related to tafamidis treatment. However, the conclusions that can be drawn from this exploratory analysis are limited due to the lack of controls and the small sample evaluated.

Most patients with Val30Met mutation develop both neuropathy and cardiomyopathy during the course of the disease [25]. Myocardial infiltration of amyloid results in a progressive increase in the thickness of intra-ventricular septum and stroke volume is often reduced [7]. In late-onset FAP patients, serial values of intra-ventricular septum thickness obtained from 20 patients also indicated an increase from a mean (SD) of 14.4 (4.2) mm at the first assessment to 17.1 (5.6) mm at the last assessment performed 3.2 (1.5) (mean (SD)) years later [24]. The echocardiographic exploratory assessments in the current study showed an overall reduction in intra-ventricular septum diastole thickness and increase in stroke volume from baseline, which suggests an improvement in the status of cardiomyopathy with tafamidis treatment.

There were limitations of this study that are relevant to the majority of studies involving rare diseases. The recruitment of patients with TTR-FAP can be difficult as the overall prevalence is very low; this accounts for the small patient number, the single-arm design, and lack of placebo comparator that limit the generalizability of these findings. Nevertheless, our findings are in agreement with previous studies and show that in Japanese patients with primarily Val30Met TTR-FAP, tafamidis was generally safe and well-tolerated, demonstrated long-term TTR stabilization, and was beneficial in slowing peripheral neuropathy progression and weight loss over 1.5 years.

Disclosure of interest

All authors participated in study design, data collection, analysis, and in the decision to submit the article. M.O. and A.T. are employees of Pfizer Japan Inc. and participated as authors in this manuscript. K.M. was a previous employee of Pfizer Japan Inc. and has no other disclosures. Y.A. has received honoraria from Pfizer related to session chairman and speaker duties. Y.S. has received royalties from Pfizer related to tafamidis patents and has received speaker honoraria from Pfizer. S.I., H.M., Y.M., K.O., M.U., and T.Y. were investigators in the study funded by Pfizer and have no other disclosures.

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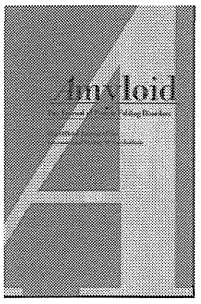

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ORIGINAL ARTICLE

Long-term outcome of patients with hereditary transthyretin V30M amyloidosis with polyneuropathy after liver transplantation

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Abstract

Background: Liver transplantation halts production of mutated transthyretin (TTR), and thus it is an accepted treatment, with improved survival, in patients with hereditary (familial) amyloidosis with polyneuropathy (FAP). However, the effects of transplantation on the clinical manifestations of FAP have not yet been adequately clarified. This study aimed to investigate whether liver transplantation would improve the long-term clinical manifestations in FAP patients who had undergone transplantations.

Patients and methods: We assessed 29 non-transplant and 36 transplant FAP V30M patients using an FAP clinical scoring system.

Results: The total clinical score of the non-transplant group increased and was significantly correlated with FAP duration; that of the transplant group increased slowly after transplantation. In patients 5 years or more after FAP onset, the total clinical scores of the transplant group were significantly lower than those of the non-transplant group. In the same patients, scores for sensory, motor, autonomic and organ impairments of the transplant group were significantly lower than those of the non-transplant group.

Conclusions: Liver transplantation had beneficial effects on FAP clinical manifestations in patients with FAP TTR V30M. Liver transplantation should therefore be considered as an effective treatment in the clinical management of patients with FAP TTR V30M.

Abbreviations: FAP: familial amyloid polyneuropathy; TTR: transthyretin

Keywords

Autonomic, sensory and motor impairments, clinical score, disease-modifying therapy, hereditary transthyretin amyloidosis, polyneuropathy

History

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Introduction

Hereditary (familial) amyloidosis with polyneuropathy (FAP), which is a life-threatening disease that is transmitted as an autosomal dominant disorder, is characterized by the accumulation of polymerized transthyretin (TTR) in peripheral nerves and systemic organs [1–7]. Controlled studies to assess the effects of liver transplantation have been published; the surgery seems to benefit FAP patients because it stops the primary production of mutated TTR, and normal TTR produced by the new liver replaces TTR [8–11]. Improved survival of FAP TTRV30M patients after liver transplantation was reported in studies, with a low selection bias, that compared the survival of non-transplant patients with that of transplant patients [12].

However, the effects of liver transplantation on the clinical manifestations of FAP, including polyneuropathy, have not been satisfactorily investigated. Early uncontrolled case reports documented a favorable short-term course of disease in FAP patients who had liver transplantations [13–15]. Some patients, however, have progressive amyloidosis even after liver transplantation, given that amyloid fibril formation continues because preexisting amyloid deposits in tissues trap circulating wild-type TTR [16,17].

This study was undertaken to determine whether liver transplantation would have beneficial effects on the long-term clinical manifestations of FAP TTRV30M. We accomplished this assessment by comparing FAP patients who had had transplantations with FAP patients who had not had transplantations as concurrent controls.

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Patients and methods

Patients

Patients with FAP TTRV30M who visited Kumamoto University Hospital between January 1990 and December 2010 included 43 patients who had not had transplantations and 37 patients who had had transplantations. We assessed 29 of the 43 non-transplant patients (17 male, 12 female) and 36 of the 37 transplant patients (15 male, 21 female) using a clinical scoring system. Patients received a diagnosis of FAP if they had clinical manifestations of FAP such as autonomic dysfunction, sensorimotor polyneuropathy, vitreous opacity and amyloid deposits in the abdominal fat, gastric mucosa, duodenum or sural nerve, as well as TTR gene mutations (c.148G>A, p.V50M) [18]. Patients enrolled in this study had FAP TTRV30M, the most common type of FAP in the world. Because different TTR mutations cause a varied phenotypic expression of FAP, the study did not include patients with certain other types of TTR mutations [19–21]. All patients were Japanese.

As Japan has few liver donors, 16 patients who could afford to have a liver transplantation underwent cadaveric transplantation abroad. Twenty patients in Japan who located a donor underwent living donor liver transplantation by means of a partial hepatic graft. Two patients underwent liver transplantation 5 years after FAP onset. Other patients who did not meet the qualification conditions or who did not have liver transplantations comprised the non-transplant group and continued to receive their medications and all regular FAP treatments. One patient received diflunisal for 2 years and 7 months during this study. Tafamidis was not administered to patients because clinical trials and the medical use of tafamidis had not yet started in Japan. Disease-modifying therapy (a TTR stabilizer) had little effect in this study. The non-transplant control group of patients represented Japanese patients with the natural course of FAP TTRV30M.

Assessment

We performed a general assessment of patients using an FAP clinical scoring system that would allow analysis of various clinical manifestations of the disease (Supplementary Material). Points were assigned to the categories sensory disturbance, muscle weakness, autonomic dysfunction, and visceral organ impairment (0–24 points for each category) [22]. Clinical scores 5 years or more after FAP onset in non-transplant patients and transplant patients were compared to assess the effects of liver transplantation. The scores below 5 years in the both group were also compared as baseline. The scores below 5 years and those 5 or more years were compared in the both groups to assess the progression of FAP. Of all patients, 17 non-transplant patients with an FAP onset of less than 5 years and 15 non-transplant patients with an FAP onset of 5 years or more were examined; the corresponding numbers for transplant patients were 35 and 24. Of patients with an FAP onset before the age of 50 years, four non-transplant patients with an FAP onset of less than 5 years and 10 non-transplant patients with an FAP onset of 5 years or more were examined; the corresponding numbers for transplant patients were 34 and 23. The time periods between transplantation and examination with this scoring system were, given as the mean ± standard deviation, median (range), 7.8 ± 4.3, 8.6 (0.3–15.9) years in all patients and 7.7 ± 4.4, 8.3 (0.3–15.9) years in patients with an FAP onset before the age of 50 years.

We calculated the duration of disease from the onset of FAP in both transplant and non-transplant patients. Liver transplantation is recommended in Japan for patients younger than 60 years, and the natural history of FAP in patients with disease onset after the age of 50 years is different from that with disease onset before the age of 50 years [12,23,24]. Therefore, transplant and non-transplant patients younger than 50 years at the onset of FAP were analyzed as separate subgroups. FAP had developed before the age of 50 years in 35 of 36 transplant patients and in 12 of 29 non-transplant patients.

Statistical analysis

We analyzed the difference in scores by means of the two-sided Wilcoxon rank sum test. We performed correlation analysis to calculate the correlation coefficient and contribution ratio to evaluate the impacts of the duration of disease and the clinical score. Differences with p values of less than 0.05 were considered statistically significant. Data were presented as the mean ± standard deviation, median (range). Twenty-seven patients in the non-transplant group and 12 patients in the transplant group were examined once either at less than 5 years from FAP onset or at 5 years or more after FAP onset. Although some scores were obtained from the same patients more than once (at most twice), those data were included in the regression analysis and two-sided Wilcoxon rank sum test.

Standard protocol approval

This study was approved by the institutional review board of Graduate School of Medical Sciences, Kumamoto University (No. 1172).

Results

Tables 1 and 2 provide demographic data and clinical characteristics of all study patients and of patients with FAP TTRV30M onset before the age of 50 years, respectively. The non-transplant group had a significantly higher mean age at FAP onset than did the transplant group ($p<0.01$).

The total clinical score in the non-transplant group was significantly and strongly correlated with the duration of FAP (Figure 1). However, the total clinical score in the transplant group increased slowly after transplantation. The scores for sensory impairment, motor impairment, autonomic impairment and visceral organ impairment in the non-transplant group were significantly and moderately correlated with FAP duration (Figure 2). In contrast, correlation of FAP duration with scores for sensory impairment and motor impairment in the transplant group was weak and not significant.

The total clinical score for non-transplant patients and that for transplant patients below 5 years of onset showed significant differences. The total clinical score for non-transplant patients 5 years or more after FAP onset was

Table 1. Demographic data and clinical scores of study patients with FAP V30M.

Characteristics and scores	Non-transplant group	Transplant group	*p*
Total number of patients (male/female)	29 (17/12)	36 (15/21)	
Age at FAP onset (years)	50.9 ± 14.3, 52.5 (22.8–76.7)	33.9 ± 7.4, 32.1 (23.4–56.6)	<0.01
Time between FAP onset and transplantation (years) FAP clinical score below 5 years of onset		2.2 ± 1.6, 1.6 (0.5–7.2)	
Duration of FAP (years)	3.0 ± 1.0, 2.8 (1.4–4.9)	1.9 ± 1.4, 1.3 (0.3–5.0)	<0.01
Total clinical score	23.0 ± 14.3, 18 (9–59)	12.1 ± 7.9, 10 (1–33)	<0.01
Sensory impairment score	8.6 ± 5.2, 7 (0–20)	4.2 ± 3.5, 4 (0–15)	<0.01
Motor impairment score	4.9 ± 4.5, 4 (0–15)	0.1 ± 0.5, 0 (0–2)	<0.01
Autonomic impairment score	5.2 ± 3.5, 4 (0–14)	6.1 ± 4.0, 6 (0–14)	NS
Organ impairment score	4.2 ± 5.0, 4 (0–12)	1.7 ± 4.0, 0 (0–16)	NS
FAP clinical score 5 or more years of onset			
Duration of FAP (years)	7.1 ± 2.0, 6.5 (5.2–11.8)	9.1 ± 2.9, 8.0 (5.7–16.5)	NS
Total clinical score	39.1 ± 15.3, 46 (17–57)*	17.1 ± 13.4, 11.5 (5–55)	<0.01
Sensory impairment score	10.9 ± 4.8, 10.5 (1–17)	3.9 ± 3.2, 3.5 (0–13)	<0.01
Motor impairment score	7.9 ± 5.6, 9 (0–15)	1.2 ± 2.6, 0 (0–10)	<0.01
Autonomic impairment score	10.9 ± 4.6, 9.5 (5–18)*	8.8 ± 5.3, 6 (2–22)	NS
Organ impairment score	9.3 ± 7.2, 8 (0–24)	3.3 ± 5.6, 0 (0–16)	<0.01

Data are presented as the mean ± standard deviation, median (range). NS: Not significant.
*Significant increase in clinical scores for non-transplant patients 5 years or more after onset compared with those below 5 years of onset.

Table 2. Demographic data and clinical scores of study patients with FAP V30M onset before the age of 50 years.

Characteristics and scores	Non-transplant group	Transplant group	*p*
Number of patients (male/female)	12 (6/6)	35 (14/21)	
Age at FAP onset (years)	36.8 ± 9.3, 36.7 (22.8–49.5)	33.2 ± 6.3, 31.7 (23.4–47.8)	NS
Time between FAP onset and transplantation (years)		2.4 ± 1.7, 1.9 (0.6–7.2)	
FAP clinical score below 5 years of onset			
Duration of FAP (years)	2.3 ± 0.6, 2.5 (1.4–2.9)	1.9 ± 1.4, 1.5 (0.3–5.0)	NS
Total clinical score	19.0 ± 7.6, 16.5 (13–30)	12.0 ± 8.0, 10 (1–33)	NS
Sensory impairment score	8.0 ± 2.7, 7 (6–12)	4.2 ± 3.5, 4 (0–15)	<0.05
Motor impairment score	2.5 ± 3.8, 1 (0–8)	0.1 ± 0.3, 0 (0–2)	<0.01
Autonomic impairment score	5.5 ± 1.9, 5 (4–8)	6.0 ± 4.1, 6 (0–14)	NS
Organ impairment score	3.0 ± 3.9, 2 (0–8)	1.8 ± 4.1, 0 (0–16)	NS
FAP clinical score 5 or more years of onset			
Duration of FAP (years)	7.8 ± 2.1, 7.8 (5.4–11.8)	9.2 ± 3.0, 8.0 (5.7–16.5)	NS
Total clinical score	43.4 ± 13.5, 49 (22–57)*	17.0 ± 13.7, 11 (5–55)	<0.01
Sensory impairment score	12.1 ± 4.0, 12 (5–17)	4.0 ± 3.2, 4 (0–13)	<0.01
Motor impairment score	9.2 ± 5.8, 10 (0–15)	1.1 ± 2.6, 0 (0–10)	<0.01
Autonomic impairment score	11.9 ± 4.9, 14 (6–18)*	8.4 ± 5.3, 6 (2–22)	<0.05
Organ impairment score	10.0 ± 5.7, 10 (0–20)	3.5 ± 5.7, 0 (0–16)	<0.01

Data are presented as the mean ± standard deviation, median (range). NS: Not significant.
*Significant increase in clinical scores for non-transplant patients 5 years or more after onset compared with those below 5 years of onset.

significantly increased compared with that for non-transplant patients below 5 years of onset (Table 1). However, for transplant patients, the total score 5 years or more after onset did not significantly increase compared with that below 5 years of onset. For patients 5 years or more after FAP onset, the total score for transplant patients was significantly lower than that of non-transplant patients. The sensory, motor and visceral organ impairment scores 5 years or more after onset for the non-transplant group differed significantly from these scores for the transplant group (Table 1).

For patients with an FAP onset before the age of 50 years, no significant difference occurred for the age at FAP onset of non-transplant patients and transplant patients (Table 2). Although no significant difference was observed in total clinical scores in non-transplant and transplant patients below 5 years of onset, the total clinical score 5 years or more after FAP onset in transplant patients was significantly lower than that in non-transplant patients (Table 2). Similarly, although no significant difference occurred in autonomic and visceral organ impairment scores for non-transplant and transplant patients below 5 years of onset, the sensory, motor, autonomic and visceral organ impairment scores for transplant patients 5 or more years after onset were significantly lower than those for non-transplant patients (Table 2).

Discussion

In this study, we demonstrated, via FAP clinical scores, that liver transplantation had beneficial effects on the clinical manifestations of FAP TTRV30M. Our analysis of data for patients with the onset of FAP TTRV30M before the age of 50 years also indicated that transplantation reduced the worsening of clinical manifestations of FAP TTRV30M. To the best of our knowledge, this study is the first to report class III

evidence of the benefit of liver transplantation on clinical manifestations for patients with FAP TTRV30M compared with concurrent controls. Liver transplantation should thus be considered as an effective clinical management tool for patients with FAP TTRV30M.

The total clinical scores for non-transplant patients increased rapidly after the onset of FAP. The total clinical scores for transplant FAP patients, in contrast, were maintained after liver transplantation, and their scores at 5 years or more after FAP onset were significantly lower than those of non-transplant patients, which indicated that liver transplantation reduced the progression of FAP. The total clinical scores for transplant FAP patients increased slowly but gradually even after liver transplantation. During this study, three patients died after liver transplantation. Because data for these patients before death were included in this study, the data for transplant patients did not include only patients with a good prognosis.

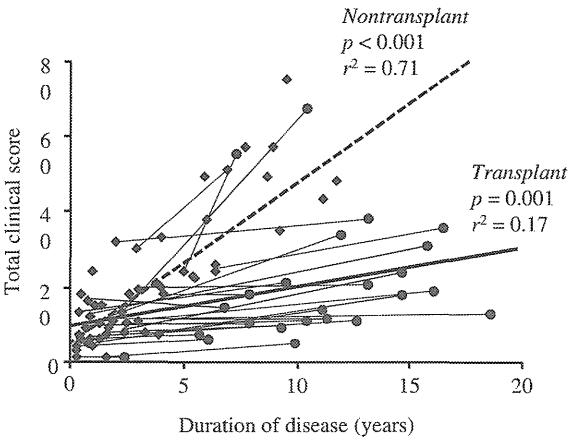

Figure 1. Changes in total clinical scores of patients with a FAP onset before the age of 50 years. Diamonds and circles indicate scores for non-transplant and transplant patients, respectively. Points representing scores for the same patient are connected by lines. Regression lines, p values and coefficients of determination (r^2) are shown.

All patients studied evidenced extremely severe autonomic disturbances from the early stage of FAP. Sensory and motor disturbances progressed during the late stage of disease, and some patients had scores of 0 for motor and organ manifestations at the examination less than 5 years after FAP onset. Some patients demonstrated improved clinical manifestations after liver transplantation, but motor, autonomic and organ scores tended to increase even after this transplantation. The sensory impairment score did not increase after liver transplantation, which suggests that this treatment is quite effective for sensory neuropathy. Liver transplantation should therefore be performed as early as possible after the onset of FAP, because the clinical manifestations that persist after transplantation limit the daily life of patients.

In addition to being effective for peripheral and autonomic neuropathies in FAP, liver transplantation has benefits for

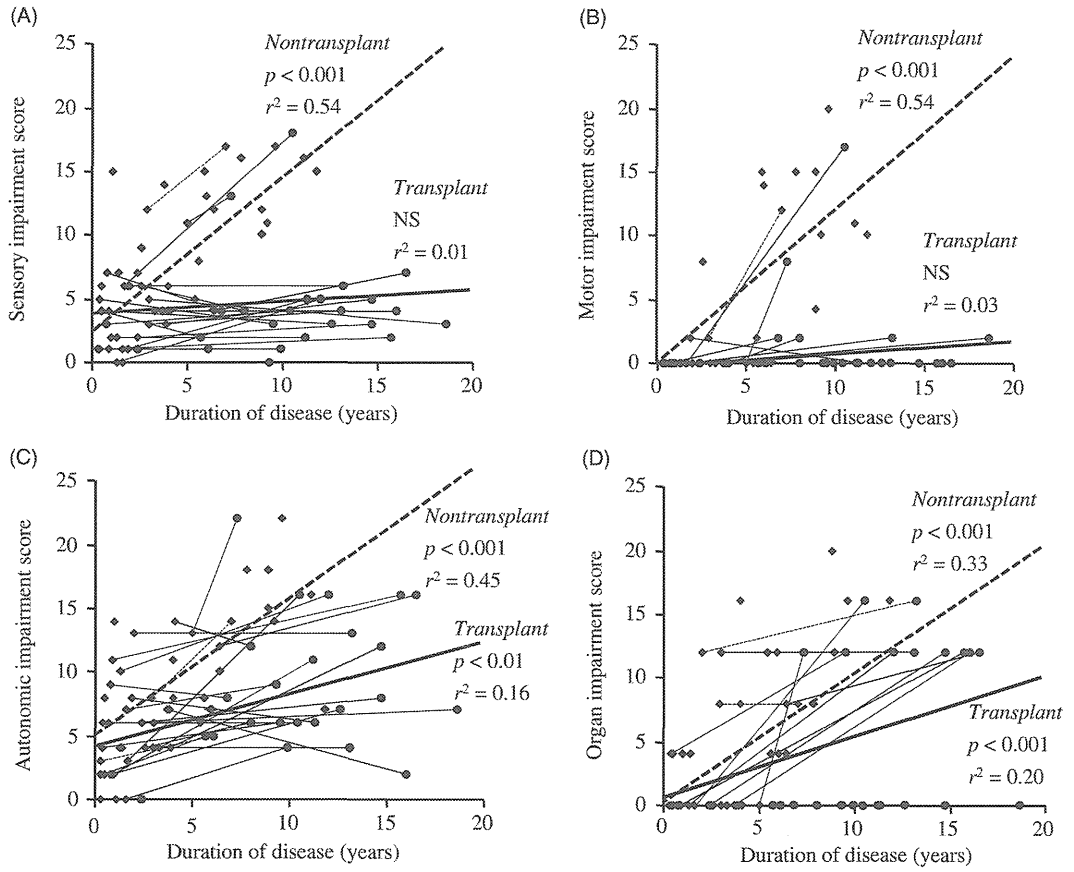

Figure 2. Changes in specific FAP clinical scores of patients with a FAP onset before the age of 50 years. Diamonds and circles indicate scores for non-transplant and transplant patients, respectively. Points representing scores for the same patient are connected by lines. Regression lines, p values and coefficients of determination (r^2) are shown.

organ impairment. Because FAP is a progressive disorder and FAP patients sometimes experience sudden death, early pacemaker implantation has been recommended for FAP patients [25]. Indeed, after liver transplantation some FAP patients underwent pacemaker implantation, which was performed later than implantation for non-transplant patients. Amyloid cardiopathy progression after liver transplantation was reported mainly for non-V30M FAP patients, but progression of amyloid cardiopathy was also reported, with sonographic image data, for TTRV30M FAP patients [26,27]. The relationship of amyloid TTR fragmentation to the development of heart complications after liver transplantation and to amyloid fibril formation has been reported [28].

For clinical studies, treated and untreated groups should have backgrounds that are as similar as possible. However, non-transplant patients in this study had a significantly higher age at FAP onset than did transplant patients, because liver transplantation in Japan is recommended for patients younger than 60 years [12,23]. Moreover, the natural history of patients with an FAP onset after the age of 50 years is different from that for patients with an FAP onset before the age of 50 years [24]. Therefore, we evaluated transplant and non-transplant patients who were younger than 50 years at FAP onset as separate subgroups. The two groups whose age at FAP onset was not significantly different evidenced a beneficial effect of liver transplantation on the clinical manifestations of FAP. These two groups with an FAP onset before 5 years had significant differences in sensory impairment and motor impairment scores. One reason for these differences may be that non-transplant patients had a longer time period between FAP onset and visits to the hospital than did transplant patients, rather than that the non-transplant group consisted of patients with rapidly progressive disease.

Here, we demonstrated the effects of liver transplantation via objective, quantitative clinical scores for certain patients with longer observation periods compared with concurrent controls. However, long-term clinical manifestations, which represent functional prognosis, have not been sufficiently analyzed statistically. Tashima et al. [22] previously examined the effect of liver transplantation on FAP patients, developed the FAP scoring system that we utilized here, and conducted a short-term evaluation of patients. They suggested that the clinical scores for transplant patients several years after liver transplantation tended to be lower than the clinical scores for non-transplant patients [22]. Because the FAP clinical score, which is correlated with the severity of FAP, is useful for quantitative evaluation of the clinical manifestations of FAP, it was used in clinical trials of diflunisal, which stabilized TTR and prevented the progression of FAP [29].

We found that the FAP clinical score correlated significantly with the duration of disease, so this score is also associated with the severity of FAP. Because the clinical score consists of discrete variables, and an ordered categorical scale does not necessarily reflect the severity of disease, using the score to compare treated and control groups with regard to the effect of therapy may be difficult. However, that increased FAP clinical scores correlated with the duration of disease indicates the usefulness of these scores for evaluating the benefit of liver transplantation for clinical manifestations of FAP.

In the future, a new clinical score should be developed to include the evaluation of nausea and vomiting, which lead to malnutrition and a poor prognosis after liver transplantation [9,30–32]. A new evaluation for central nervous system manifestations should also be included to account for cerebral amyloid angiopathy, which occurs in FAP TTRY114C, and for leptomeningeal amyloidosis, which may develop in TTRV30M FAP patients with prolonged survival because TTR production continues in the choroid plexus even after liver transplantation [33].

This study also addressed the natural history of FAP patients. The non-transplant group comprised patients with FAP TTRV30M who represented the natural history of the disease. The ongoing longitudinal observational Transthyretin Amyloidosis Outcomes Survey attempts to aid understanding of and characterize the natural history of TTR amyloidosis by investigating a large, heterogeneous population of patients. However, new disease-modifying drug treatments have made investigations of the natural history of FAP almost impossible, and having FAP patients as controls for transplant FAP patients is becoming impractical [29].

Patients should undergo liver transplantation during the early stage of the disease because transplantation reduces disease progression [34]. Certain patients in the late stage of disease, however, show FAP progression even after transplantation [35]. Information in the FAP World Transplant Registry (http://www.fapwtr.org) shows that disease lasting more than 7 years is correlated with reduced survival [36]. Transplantation early in the course of disease may prevent additional deposition of amyloid, aid remedial mechanisms and prevent decompensation that may occur and cannot be corrected by later transplantation, as in Parkinson disease treatment [37]. Changes in clinical manifestations in patients with more than 7 years between the disease onset and transplantation should also be studied.

Treatment strategies for hereditary TTR amyloidosis may include conversion of the TTR mutation to the normal TTR gene using single-stranded oligonucleotides; suppression of the mutant TTR gene using antisense oligonucleotides or small interfering RNAs; stabilization of the tetrameric TTR structure by means of diflunisal or tafamidis; prevention of amyloid formation using 4′-iodo-4′-deoxydoxorubicin, doxycycline or tauroursodeoxycholic acid; and dissolution of amyloid fibrils by means of immunotherapy [38–40]. Although liver transplantation has become a well-established treatment for reducing progression of hereditary ATTR amyloidosis, several problems have developed with its use, such as difficulties with surgical procedures, the need for lifelong immunosuppressant administration and the persistence or progression of clinical manifestations after transplantation. We must therefore develop new methods of treatment of FAP.

Conclusions

Our study determined that liver transplantation had beneficial effects on the clinical manifestations of FAP TTRV30M. These results may aid advances in treatment guidelines and recommendations. Additional studies are needed to elucidate the effects of liver transplantation on the clinical signs of

FAP, including electrophysiological, and the outcome of transplant patients with non-TTRV30M FAP. Longer term studies are also needed to assess the long-term clinical efficacy of liver transplantation in FAP.

Declaration of interest

The authors report no conflicts of interest. This study was supported by grants from the Amyloidosis Research Committee, the Pathogenesis, Therapy of Hereditary Neuropathy Research Committee and the Surveys and Research on Specific Diseases from the Ministry of Health and Welfare of Japan; and by Grants-in-Aid for Scientific Research (C) 23500430 from the Ministry of Education, Science, Sports and Culture of Japan.

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