In conclusion, transthyretin amyloid deposits in the the ligamentum flavum may be related to the pathogenesis of lumbar spinal canal stenosis in elderly patients.

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Disclosure/conflict of interest

The authors declare no conflict of interest.

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Liver Transplantation for Hereditary Transthyretin Amyloidosis: After 20 Years Still the Best Therapeutic Alternative?

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Background. Until recently, liver transplantation (Ltx) was the only available treatment for hereditary transthyretin (TTR) amyloidosis; today, however, several pharmacotherapies are tested. Herein, we present survival data from the largest available database on transplanted hereditary TTR patients to serve as a base for comparison. **Methods.** Liver transplantation was evaluated in a 20-year retrospective analysis of the Familial Amyloidosis Polyneuropathy World Transplant Registry. **Results.** From April 1990 until December 2010, data were accumulated from 77 liver transplant centers. The Registry contains 1940 patients, and 1379 are alive. Eighty-eight Ltx were performed in combination with a heart and/or kidney transplantation. Overall, 20-year survival after Ltx was 55.3%. Multivariate analysis revealed modified body mass index, early onset of disease (<50 years of age), disease duration before Ltx, and TTR) Val30Met versus non-TTR Val30Met mutations as independent significant survival factors. Early-onset patients had an expected mortality rate of 38% that of the late-onset group ($P < 0.001$). Furthermore, Val30Met patients had an expected mortality rate of 61% that of non-TTR Val30Met patients ($P < 0.001$). With each year of duration of disease before Ltx, expected mortality increased by 11% ($P < 0.001$). With each 100-unit increase in modified body mass index at Ltx, the expected mortality decreased to 89% of the expected mortality ($P < 0.001$). Cardiovascular death was markedly more common than that observed in patients undergoing Ltx for end-stage liver disease. **Conclusions.** Long-term survival after Ltx, especially for early-onset TTR Val30Met patients, is excellent. The risk of delaying Ltx by testing alternative treatments, especially in early-onset TTR Val30Met patients, requires consideration.

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The first report of the outcome of liver transplantation (Ltx) for hereditary transthyretin (h-TTR) amyloidosis, previously designated familial amyloid polyneuropathy (FAP), was published in 1993 in the Lancet,[1] and it described the outcome for 4 patients with the TTR Val30Met mutation who had been followed up for 1 to 2 years after the procedure. The impression was that the procedure was successful,

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with symptomatic improvement for some patients, and that a regression of the amyloid load, measured by serum amyloid protein scintigraphy, could be observed. This was a major achievement against this previously intractable fatal systemic amyloid disease. However, subsequent analysis over the following years disclosed less favorable outcomes for those carrying non-TTR Val30Met mutations[2-4] and also for malnourished patients and those with longstanding and advanced disease.[5-7] Differences between patients with early onset compared to those with late onset of the disease were observed.[8] Heart complications after transplantation were the dominant problem.[2-4,9,10] It is obvious that careful selection of patients is necessary to achieve acceptable outcomes.

The Familial Amyloidotic Polyneuropathy World Transplant Registry (FAPWTR) was established in 1995 by a group of investigators taking part in the First International Workshop on Liver Transplantation for Familial Amyloidotic Polyneuropathy, held at Karolinska Institutet in Stockholm, Sweden in 1993. The purpose was to monitor international experience with Ltx for this indication and to promote collaboration and ultimately improve patient selection and results. The registry now contains accumulated survival data from more than 20 years of follow-up of transplanted h-TTR amyloidosis patients from 1990 onward. These data are now of vital importance, with the arrival of medical therapy for the disease. The first compound, tafamidis, is a stabilizing agent that helps to prevent the tetrameric TTRs from dissociating into monomers and assembling into amyloid fibrils.[11] However, several other treatment modalities, including silencing RNA,[12] and diflunisal,[13] are going into clinical trials. Tafamidis demonstrated efficacy in slowing down the progression rate of the disease in a controlled trial,[14] and it is now approved by the European Medical Agency for treatment of h-TTR amyloidosis at early stages of the disease. However, its efficacy for long-term treatment has not been assessed, and the cost appears to be substantially higher than that of Ltx. Recently, it was suggested that patients with early-stage h-TTR amyloidosis should initially be treated by tafamidis, and if their disease progressed, they should be considered for Ltx.[15] However, this strategy is questionable because the patient would be in a less favorable position for transplantation with more-advanced disease.

The efficacy of new treatments should principally be compared with currently available treatment modalities. It appears to be impossible to carry out a comparative study between Ltx, which is the currently accepted treatment for h-TTR, and the new medical treatment, tafamidis. However, Ltx remains the gold standard against which new treatments should be measured, and the long-term outcome for Ltx patients can be assessed from the data in FAPWTR. The aim of the present study was to evaluate the mortality of h-TTR amyloidosis patients who underwent Ltx, based on data in the FAPWTR collected over the course of 20 years.

MATERIALS AND METHODS

Seventy-seven centers in 19 countries report data related to Ltx for TTR amyloidosis to the FAPWTR. An initial report is given at the time of Ltx. In addition, retransplantation, patient death, or loss to follow-up, as well as if an additional organ transplantation is performed, such as heart or kidney combinations with a Ltx, are also reported. Participating centers are requested to provide annual follow-up data on patients who were previously reported to the register. Information regarding demographics, heredity, type of TTR mutation, clinical manifestations, and peripheral and autonomic neuropathy are recorded. Patient weight, height, and serum albumin are recorded for calculation of the modified body mass index (mBMI). The pretransplant value of this index has been reported to correlate with the prognosis after transplantation.[18] The index is calculated by multiplying the BMI of the patient by the level of serum albumin; thus, there is compensation for the presence of oedema in malnourished patients, which may yield a falsely high BMI.

Results from the FAPWTR are reported back to collaborating members on a yearly basis. The FAPWTR data are also to some extent shown on its homepage (www.fapwtr.org). It is also possible to download report forms from the homepage.

In the present analysis, patients who were reported to FAPWTR until December 2010, with a minimum follow-up of 1 year, were included. Patients not reported as dead and with no follow-up after January 1, 2010 were regarded as lost to follow-up.

Statistical Analysis

To test for differences between means of normally distributed data from different patient categories, Student *t* test was used. Patient survival probabilities were calculated by Kaplan-Meier estimation. The log-rank test (Mantel Cox) was used to test the equality of survival patterns among different categories of patients. All statistical tests were 2-sided and conducted at the 0.05 significance level. Unless stated otherwise, statistics are presented as mean ± standard deviation. Univariable analysis was performed using the logistic regression model and significant variables were put into the Cox multivariate proportional hazards model to determine the risk factors associated with survival. The assumptions of proportional hazards were checked by analyzing plots of the log cumulative hazard stratified by factors used in the model and by analyzing plots of Schoenfeld residuals versus survival time. Variables were added stepwise to the model, selecting the most statistically significant variable first. Then an analysis was done to find the following variable that, together with the first variable, best prognosticated survival. Variables were added until no improvement in prediction was seen as assessed by an increase in the log-likelihood value. Finally, findings based on stepwise addition were confirmed by a stepwise deletion. This was done by forcing all variables into the model after which variables were successively eliminated, based on which of the remaining variables delivered the smallest reduction in the log-likelihood value. Odds ratios and hazard ratios with their *P* values were estimated between different groups and reported in Table 2. Covariates were tested for independence, and no significant multicolinearity was identified for the covariates.

RESULTS

Approximately 125 liver transplants were performed and reported yearly worldwide for h-TTR amyloidosis, with a potential reduction in transplantation activity over the last 2 years (Figure 1). A total of 1940 patients underwent 2127 Ltxs, and 561 patient deaths were reported to the registry. One hundred and eighty-eight retransplantations were

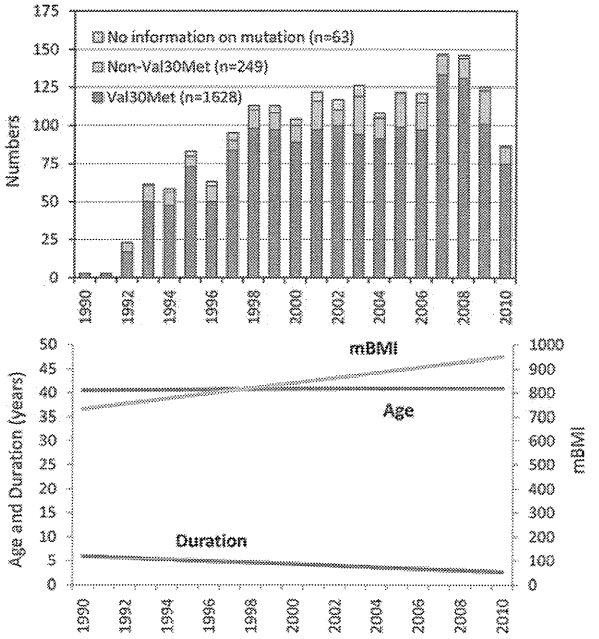

Figure 1. Number of patients with hereditary transthyretin amyloid disease transplanted annually between 1990 and 2010 and trends in age, duration, and mBMI.

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

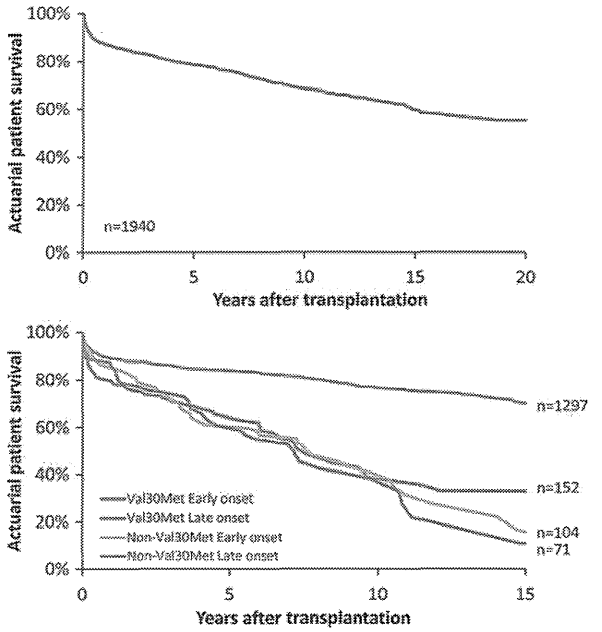

Figure 2. Overall actuarial patient survival between 1990 and 2010. For all patients (above), and according to TTR Val30Met/non-TTR Val30Met mutations and early or late onset of disease (below).

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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