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Survival After Transplantation in Patients With Mutations Other Than Val30Met: Extracts From the FAP World Transplant Registry

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Background. Liver transplantation (LTx) has been performed for hereditary transthyretin amyloidosis (ATTR) since 1990. Outcomes for a relatively large series of LTx ATTR patients with the Val30Met (mutation are available, but for non-Val30Met patients, only a few reports with a small number of patients exist. Here, we present outcomes for non-Val30Met ATTR patients after LTx, as reported to the Familial Amyloid Polyneuropathy World Transplant Registry (FAPWTR). **Methods.** Data regarding outcome were extracted for all non-Val30Met patients reported to the registry. Survival rates were analyzed by the Kaplan-Meier method and log-rank test. **Results.** The total number of patients with a non-Val30Met mutation in the registry was 264 (174 men and 90 women), representing 57 mutations. The 10-year survival varied markedly for the 9 most common mutations, ranging from 21% for Ser50Arg to 85% for Val71Ala. Poor survival was noted for all mutations with leptomeningeal complications except for those with the Tyr114Cys mutation. **Conclusions.** Large differences in survival were observed relative to different mutations and between mutations with similar phenotypes. Excellent survival was noted for mutations, such as Leu111Met, Val71Ala, and Leu58His. Patients with mutations other than Val30Met are not a homogeneous group, and the term non-Val30Met should be used with caution or avoided. Moreover, for several mutations, data are too limited to allow evaluation of the efficacy of LTx, and continuous international collaboration is important for obtaining treatment guidance.

(*Transplantation* 2016;100: 373–381)

Hereditary transthyretin (TTR)-mediated amyloidosis (ATTR) is a rare, autosomal dominantly inherited disease with a variable penetrance. The phenotype varies among and within the various mutations, where neuropathy and/or cardiomyopathy dominate the clinical presentation.[1-3] The expected survival is not available for most mutations, but patients with cardiomyopathy generally have a worse prognosis compared with that reported for the TTR Val30Met mutation, for which the expected survival is 10 to 15 years compared with less than 5 years for patients with cardiomyopathy.[4-10]

The exact amyloid formation process for ATTR has not been elucidated, but the prevailing hypothesis is that instability of the TTR tetramer because of mutation or aging leads to disassembly of the tetramer into monomers. After misfolding, these monomers re-assemble into amyloid fibrils.[11] Thus, ATTR can be derived not only from mutant TTR but also from wild-type TTR, as is the case with senile systemic amyloidosis.[12]

Liver transplantation (LTx) has been performed for hereditary ATTR since 1990, starting with the first transplantation done in Sweden on a patient with ATTR attributable to the TTR Val30Met mutation.[13] The basis for the procedure was to exchange the mutant TTR-producing liver with one that produces only the wild-type protein and thus halt disease progression. The initial positive report on the outcome of the procedure for this otherwise intractable disease facilitated rapid acceptance of LTx for hereditary ATTR; however, reports subsequently emerged, which revealed an unhalted disease progression and development of cardiomyopathy in the

Received 3 March 2015. Revision received 15 October 2015.

Accepted 15 October 2015.

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Funding and disclosures: O.S.'s work was supported by a central and local ALF grant from Västerbotten County and the Swedish Heart Foundation. O.S. is a member of the scientific board of the THAOS registry, founded by Pfizer Inc., and participates in clinical trials of medical treatment for transthyretin amyloidosis supported by Pfizer Inc. and Alnylam Pharmaceuticals. B.-G.E. is a member of the THAOS board and has received honoraria for lectures supported by Astellas, Novartis, and Pfizer. M.L. and H.W. have no conflicts of interest to disclose. The funding sources had no involvement in the collection, analysis, and interpretation of data, in the writing of the article, or in the decision to submit the article for publication.

Author contributions: O.S., B.-G.E., and H.E.W. initiated the working hypothesis and participated in the study design, performance of the study and data acquisition, the analysis and interpretation of data, and writing the article. M.L. maintained contact with reporting centers, assembled and validated the data for analysis, and participated in the writing of the article. All authors were active in reviewing and finalizing the article.

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ISSN: 0041-1337/16/10002-373

DOI: 10.1097/TP.0000000000001021

context of several non-Val30Met mutations[14-16] and later especially for elderly male ATTR Val30Met patients.[17,18] The rapid development of cardiomyopathy has led to combined LTx and heart transplantation (HTx) for mutations associated with cardiomyopathy.[4,19-22]

The outcomes of a relatively large series of LTx ATTR Val30Met patients have been reported from different centers.[23-27] However, for non-Val30Met ATTR, relatively few reports comprising only a small number of patients have been published.[19,28-31] Risk factors that have been noted to especially shorten survival are central nervous system manifestations and cardiomyopathy.[4,32,33] In addition, in the Familial Amyloid Polyneuropathy World Transplant Registry (FAPWTR), patients with non-Val30Met mutations have been recognized as having poorer outcomes than patients with the Val30Met mutation,[25] but an analysis of the survival associated with the various mutations in the registry has not been presented. Only a few reports have analyzed the outcome of simultaneous or sequential HTx and LTx.[19,20,22,34]

Medical treatment of ATTR using small molecules has been tested in 2 controlled clinical trials.[35,36] The trials were based on the hypothesis that stabilization of the TTR tetramer should prevent it from disassembling into amyloidogenic monomers.[37] Two compounds were tested: tafamidis, and a nonpriority, nonsteroidal anti-inflammatory drug, diflunisal.[35,36] The tafamidis trial on patients in stage I of neuropathic ATTR (mobilization without need for support) failed to achieve statistical significance for its primary endpoints of neurological deterioration and quality of life. However, because all measured endpoints indicated that the drug decreased the rate of disease progression, tafamidis was approved by the European Medical Agency in 2011 for patients in stage I of neuropathic ATTR. An open-label extension study on patients completing the trial found a similar decrease in disease progression.[38] The diflunisal trial included patients in the early as well as later stages of neuropathic ATTR[35] and identified significance for its primary and secondary endpoints. As a nonpriority drug, it has not been registered for ATTR.

No study has been completed of the effect of small molecules on patients with ATTR cardiomyopathy. Recently, anti-TTR small-interfering RNA and antisense oligonucleotides have demonstrated a capacity to profoundly decrease wild-type and mutant TTR synthesis in the liver.[39,40] Because wild-type TTR plays a major role in the continued amyloid formation observed after LTx,[41,42] it seems likely that this approach holds the potential to stop disease progression. An open-label study with silencing RNA (patisiran (ALN-TTR02); Alnylam Pharmaceuticals, Cambridge, MA) identified a cessation of neurological disease progression after 12 months of treatment.[43]

Liver transplantation has now been used for the treatment of ATTR for more than 20 years. Although outcomes for non-Val30Met patients have been reported as poor compared with those for Val30Met patients, differences associated with various mutations have been described.[4,21,27,32] The aim of the present study was to assess the long-term survival of non-Val30Met patients after LTx and combined LTx/HTx based on the data in the FAPWTR.

MATERIALS AND METHODS

All non-Val30Met patients, from September 13, 1991 (first reported non-Val30Met patient to the FAPWTR), until December 31, 2012, with a minimum follow-up of 1 year, were included in the present study. Patients not reported as dead and with no follow-up after January 1, 2012, were regarded as lost to follow-up. We analyzed the pretransplant value of the modified body mass index (mBMI) as a measure of patient nutritional status at transplantation because this value has been reported to correlate with the prognosis after LTx in patients with familial amyloidotic polyneuropathy.[8,44,45] The index is calculated by multiplying the BMI of the patient by the level of serum albumin to compensate for the presence of edema in malnourished patients, which may yield a falsely high BMI. The phenotype of the various mutations is given according to reports to the FAPWTR, the literature, and web-based registries.[46-49]

Statistics

Nonparametric statistics were applied for characterization of the populations and the Mann-Whitney *U* test for comparison between and within groups. The Fisher exact probability test was used for analysis of categorical frequency data. Patient survival probabilities were analyzed by Kaplan-Meier estimation and comparison between groups made with the Log-rank test. A *P* value below 0.05 was considered statistically significant.

RESULTS

The total number of ATTR patients with a non-Val30Met mutation in the registry was 264, representing 57 different mutations. The demographic data for the patients are displayed in Table 1. The median age at LTx was 53 years, with a median disease duration of 3 years, indicating that a similar number of patients had early (≤50 years of age at onset) versus late onset (>50 years at onset). Patients who underwent LTx or combined LTx/HTx had a similar duration of disease before transplantation, even though significantly more patients who underwent combined LTx/HTx were older ($P < 0.01$). As expected, because of a higher incidence of cardiac amyloidosis in men, a significantly higher number of combined LTx/HTx was performed in men compared with women ($P < 0.02$). Women who underwent combined LTx/HTx had the following mutations and cardiomyopathy: Asp18Glu (n = 2), Gly47Glu (n = 1), Ser50Arg (n = 1), Glu89Lys (n = 2), Leu111Met (n = 3), and Ser77Tyr (n = 1).

Transplantation Procedures and Survival

A total of 211 patients were given a liver graft alone, of whom 22 received liver segments (21 from a living donor, 1 split liver from a deceased donor). One patient underwent a simultaneous liver/kidney transplantation (LTx/KTx). In the analysis, this patient was included in the group who received a liver graft alone. Death within 3 months after transplantation occurred in 19 (9%) of the 212 patients subjected to LTx without HTx. There were no significant differences in the 90-day mortality rate among the 9 most common mutations. The median survival time from transplantation for the 212 patients subjected to LTx alone was 7.1 years (SE, 0.7; 95% CI: lower bound, 5.8; upper bound, 8.5), indicating a median survival from onset of disease of approximately 10 years (Table 1). Among the 52 recipients undergoing combined LTx/HTx, the median survival time from transplantation

TABLE 1.

Demographic data for 264 ATTR patients with non-Val30Met mutations treated with either liver transplantation or liver and heart transplantation

	All transplantations	LTx[a]	LTx/HTx[b]	P
Patient population	No.	No.	No.	
All subjects	264	212	52	0.0138
Male	174	132	42	
Female	90	80	10	
Age at LTx, y	Median (range)	Median (range)	Median (range)	
All subjects	53 (23-70)	53 (23-70)	55 (38-68)	0.008
Males	55 (23-70)	54 (23-70)	58 (38-68)	0.061
Females	51 (23-68)	50 (23-68)	53 (47-58)	0.230
Duration of disease at LTx[c], y	Median (range)	Median (range)	Median (range)	
All subjects	3 (0-20)	3 (0-20)	3 (1-15)	0.158
Males	3 (1-20)	3 (1-20)	3 (1-15)	0.423
Females	3 (0-17)	3 (0-17)	3 (1-15)	0.301

[a] Liver transplanted; one liver + kidney-transplanted patient is included in the group.
[b] Liver and heart transplanted.
[c] Duration of disease before transplantation is calculated until the date of liver transplantation, also for patients subjected to sequential heart and liver transplantation; information on disease duration is missing for 77 patients.

was 7.8 years (SE, 1.1; 95% CI: lower bound, 5.6; upper bound, 10.0).

Fifty-two patients (42 men and 10 women) also received a heart, and 11 of these patients received the heart before the liver. One patient underwent HTx 7 years after LTx (Ser77Tyr), and 2 patients underwent simultaneous LTx, HTx, and KTx. The remaining 38 patients underwent simultaneous LTx/HTx with organs from the same donor. Most of the simultaneously combined liver-heart transplantations were performed in the United States, whereas the largest experience with sequential transplantation is from Europe, where patients first underwent HTx and between 0.2 years and 6.5 years (median 0.5 years) later received a liver. Of the 52 combined LTx/HTx patients, 32 (62%) are alive with a follow-up time of 0.9 years to 16.5 years (median, 4.5 years). The numerically increased survival for patients undergoing simultaneous LTx/HTx compared with those who underwent a sequential procedure did not reach statistical difference. Death within 3 months of transplantation occurred in 4 (11%) of the 38 patients who underwent simultaneous LTx/HTx, representing 31% of all deaths in this group. In patients given the liver after the heart, 1 (9%) of 11 patients died within 3 months after LTx, representing 17% of all deaths in this group. Patients subjected to HTx only are not reported to the registry.

Of the 2 patients who received liver, heart, and kidney grafts, 1 man (Ser77Tyr) died 8 years after the procedure, and the other patient, a woman (Asp18Glu), is alive 7 years after the procedure. The patient who received a simultaneous liver and kidney graft (Val94Ala) died 3 years after the procedure.

Survival analysis, comparing patients carrying the same type of mutation but undergoing either LTx only or combined LTx/HTx, showed no statistically significant difference in outcome; however, the combined LTx/HTx patients did numerically better from 3 years after transplantation onward (Figure 1).

Survival According to Mutation and Phenotype

Clinical data and survival associated with the 9 most prevalent mutations, each with 10 or more patients, are displayed in Table 2. For mutations present in fewer than 10 patients, an outline of the outcome is presented in Table 3. The largest group consisted of the Ser77Tyr mutation, representing 39 patients, 6 of whom had received both heart and liver grafts. The 10-year survival was low at 33% for LTx-only patients and 44% for combined LTx/Htx recipients. The 10-year survival for patients with the Thr60Ala mutation who underwent combined LTx/HTx was 58% compared with 36% for those patients who underwent isolated LTx. An excellent 10-year survival (>70%) was noted for mutations, such as Leu111Met, Val71Ala, and Leu58His (Figure 2 and Table 2). The only patient with the Ser50Arg mutation who underwent sequential HTx/LTx died 1 month after LTx.

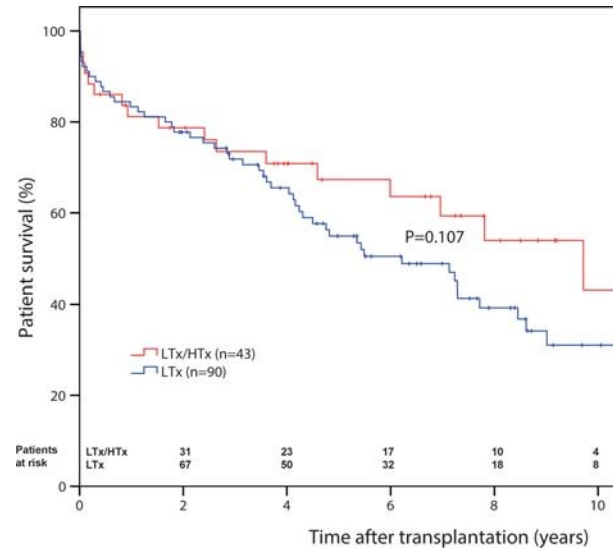

FIGURE 1. Kaplan-Meier survival plot for patients with mutations for whom both treatment modalities were used, but undergoing either LTx only or combined LTx/HTx. Demographically, the 2 groups were similar (LTx: n = 90, 64 men, 26 women; mean age at transplantation, 52 years; median, 53 years; LTx/HTx: n = 43, 33 men, 10 women; mean age at transplantation, 54 years; median, 53 years).

TABLE 2.
Clinical data and survival rates of the 9 most common non-Val30Met mutations in the FAPWTR (each mutation present in a minimum of 10 patients)

TTR mutation	No. patients (male/female)	Sex: male, %	Age at transplantation, y	Duration of disease, y	mBMI at transplantation (LTx All) median (range)	Phenotypic organ involvement	LTx/LTx + HTx (n)	LTx/LTx + HTx 10-y survival, %
Ser50Arg	11 (5/6)	45	42 (32-50)	3.5 (0.5-6)	824 (687-933)	N, heart	10/1	23/0
Leu58His	12 (8/4)	67	60 (54-66)	3 (1-20)	1126 (717-1531)	N, heart	12/—	76/—
Thr60Ala	23 (22/1)	96	61 (49-66)	2.75 (1-8)	900 (612-1212)	N, heart	14/9	36/58
Val71Ala	13 (8/5)	62	38 (23-56)	3 (1.5-12)	841 (756-1070)	N	13/—	85/—
Ser77Phe	10 (8/2)	80	60 (57-67)	Information missing	837 (717-1126)	N, heart	10/—	24[a]/—
Ser77Tyr[b]	39 (30/9)	77	57 (40-67)	3 (2-15)[c]	975 (658-1366)	N, heart	33/6	33/44
Glu89Gln	10 (9/1)	90	47 (39-61)	2.5 (1-8)	895 (862-977)	N, heart	5/5	30/60[d]
Leu111Met	12 (7/5)	58	48 (40-54)	4 (0-18)	928 (690-1278)	heart	5/7	100[e]/71
Tyr114Cys	15 (7/8)	47	50 (34-55)	4 (0.8-9)	950 (677-1371)	LM	15/—	47/—

N indicates neuropathy (includes autonomic and somatic neuropathy); LM, leptomeningeal complications.
[a] 9-year survival.
[b] Includes 1 liver-, heart-, and kidney-transplanted patient.
[c] Information missing on 30 patients.
[d] 7-y survival.
[e] 8-y survival.

Several mutations with leptomeningeal complications, such as the Leu12Pro, Ala36Pro, Thr49Pro, Phe64Ser, and Tyr114Cys mutations, have been reported to the registry. In almost all patients with these mutations, the outcome was poor. The exception was those who had the Tyr114Cys mutation, who had a 10-year survival close to 50% (Figure 2 and Table 2). For other mutations with leptomeningeal complications (4 mutations, 6 patients), no patient survived beyond 3 years after transplantation. The causes of death were septicemia (n = 4), subarachnoid bleeding (n = 1), and not stated (n = 1).

The 10-year survival varied markedly for the 9 most common mutations, ranging from 21% for Ser50Arg to 85% for Val71Ala (Figure 2). Three of these mutations were associated with a 10-year patient survival rate exceeding 50% and exhibited a markedly variable phenotype: neuropathy/heart (Leu58His), neuropathy (Val71Ala), and heart (Leu111Met). For the Thr60Ala mutation (neuropathy/heart), the survival rate exceeded 50% only in those patients who underwent LTx and HTx.

Survival in Relation to Nutritional Status as Reflected by the mBMI

In the present patient cohort, significantly better 10-year patient survival was observed in transplant recipients with a pretransplant mBMI of 900 or greater compared with patients having a mBMI less than 900 (52.6% vs 22.0%, respectively; $P < 0.001$; Figure 3).

Outcome in Patients Receiving a Living Donor Liver

Analyzing the outcome in recipients who received a living-donor liver graft and those who received a liver graft from a deceased donor showed a numerically, but not statistically significant, better 10-year survival in the former group (living-donor liver graft group 72.3% and deceased-donor liver graft group 33.8%, respectively; $P = 0.092$) (Figure 4).

Clinical Status Posttransplant Compared With Status Before Transplantation

The FAPWTR collects information on each patient's subjective clinical symptoms before and after transplantation. Thus, the registry receives reports if the patient has experienced deterioration in symptoms, status is unchanged, or status has improved symptomatically. Figure 5 illustrates the subjective long-term neurological outcome after LTx in Val30Met patients and patients with mutations other than Val30Met. Among patients with mutations other than Val30Met, significantly fewer were reported as being unchanged/improved compared with Val30Met patients.

Cardiac-Related Death

Of the 212 patients who underwent LTx alone, 119 (56%) patients died. Of these 119 patients, 45 (38%) died of heart-related complications. Of the 52 combined LTx/HTx recipients, 20 (38%) patients died, and 3 (15%) of these patients died of heart-related complications. All 3 patients had undergone a simultaneous combined LTx/HTx.

DISCUSSION

By the end of 2012, the FAPWTR had received data from 78 centers in 19 countries on patients subjected to LTx for TTR amyloidosis. Participating centers are requested to provide annual follow-up data on patients who were previously

TABLE 3.

Outcome with non-Val30Met mutations present in fewer than 10 patients reported to the registry

Mutation	Organ tx	Patients transplanted (n)	Alive (n)	Lost to follow-up (n)	Deceased patients (time after transplantation)	Organ involvement according to genotype
Cys10Arg	LTx	1	0	0	1 (10 mo)	N, heart
Leu12Pro	LTx	2	0	0	2 (6 mo, 2 y)	LM, N
Asp18Glu	LTx	2	1 (8 y)	0	1 (3 y)	N, heart
	LTx/HTx	2	1 (7 y)	0	1 (9 y)	N, heart
Val20Ile	LTx/HTx	1	0	0	1 (9 y)	heart
Pro24Ser	LTx/HTx	2	1 (1 y)	0	1 (7 y)	N, heart,
Ala25Ser	LTx	2	0	1 (8 y)	1 (1 mo)	N, heart
Val28Met	LTx	3	2 (3 y, 5 y)	0	1 (3 y)	N
Val30Ala	LTx	4	2 (6 y, 7 y)	0	2 (2 mo, 11 y)	N, heart
Val30Leu	LTx	2	0	0	2 (1 y, 1 y)	N, heart, kidney
Val32Ala	LTx	1	1 (3 y)	0		N
Val32Gly	LTx	1	0	0	1 (7 y)	N
Phe33Cys	LTx	1	1 (10 y)	0		heart, kidney
Phe33Leu	LTx	2	1 (2 y)	0	1 (7 y)	N, heart
	LTx/HTx	2	0	0	2 (1 mo, 9 mo)	N, heart
Phe33Val	LTx	3	0	2 (3 y, 4 y)	1 (4 y)	N
Arg34Thr	LTx	1	0	0	1 (1 wk)	N, heart
	LTx/HTx	1	0	1 (10 mo)		
Lys35Asn	LTx	1	0	0	1 (3 y)	N, heart
Ala36Pro	LTx	2	0	0	2 (2 y, 3 y)	LM
Glu42Asp	LTx	1	0	0	1 (5 y)	heart
Glu42Gly	LTx	6	0	0	6 (3 mo, 3 y, 3 y, 7 y, 7 y, 16 y)	N, heart
Ala45Asp	LTx	1	0	0	1 (5 y)	N, heart
Ala45Ser	LTx	2	1 (9 mo)	0	1 (4 y)	heart
Gly47Arg	LTx	2	0	0	2 (0 d, 4 y)	N
Gly47Glu	LTx	5	2 (3 y, 7 y)	0	3 (5 mo, 7 mo, 7 y)	N, heart
	LTx/HTx	1	0	0	1 (3 d)	N, heart
Gly47Ala	LTx	5	0	0	5 (3 mo, 4 y, 7 y, 8 y, 14 y)	N, heart
	LTx/HTx	1	1 (2 y)	0		N, heart
Gly47Val	LTx	1	1 (2 mo)	0		N, heart
Thr49Ala	LTx	6	1 (8 y)	1 (3 y)	4 (1 mo, 1 y, 2 y, 4 y)	N, heart
	LTx/HTx	1	0	1 (3 y)		N, heart
Thr49Ile	LTx	1	1 (2 y)	0		N, heart
Thr49Pro	LTx	1	0	0	1 (1 y)	N, heart, LM
Ser50Ile	LTx	2	1 (8 y)	0	1 (3 y)	N, heart,
Ser52Pro	LTx	7	1 (4 y)	0	6 (2 mo, 4 mo, 1 y, 3 y, 7 y, 10 y)	N, heart, kidney
Glu54Gly	LTx	4	2 (2 wk, 4 mo)	0	2 (3 y, 5 y)	N
Glu54Lys	LTx	1	0	0	1 (3 y)	N, heart
Leu55Gln	LTx	1	0	0	1 (2 y)	N
Thr59Lys	LTx	1	1 (2 y)	0		N, heart
	LTx/HTx	1	1 (3 y)	0		N, heart
Phe64Leu	LTx	1	0	1 (5 y)		N, heart
Phe64Ser	LTx	1	0	0	1 (1 y)	LM, N
Gly67Glu	LTx	1	1 (4 y)	0		N, heart
Ile68Leu	LTx/HTx	1	0	1 (2 y)		heart
Ile84Thr	LTx	1	0	1 (5 y)		N, heart
Glu89Lys	LTx	1	1 (5 y)	0		N, heart
	LTx/HTx	6	3 (8 mo, 3 y, 8 y)	1 (1 y)	2 (11 mo, 6 y)	N, heart
Val94Ala	LTx/KTx	1	0	0	1 (1 y)	N, heart, kidney
Ala97Gly	LTx	1	1 (7 y)	0		N, heart
Ala97Ser	LTx	1	1 (1 y)	0		N, heart
Ile107Val	LTx	9	4 (2 y, 2 y, 5 y, 6 y)	0	5 (2 wk, 1 y, 2 y, 6 y, 11 y)	N, heart
Tyr116Ser	LTx	2	2 (3 y, 6 y)	0		N
Val122Del	LTx/HTx	2	2 (1 mo, 6 mo)	0		N, heart
Val122Ile	LTx/HTx	3	2 (3 mo, 2 y)	0	1 (8 mo)	heart

Tx, transplanted.

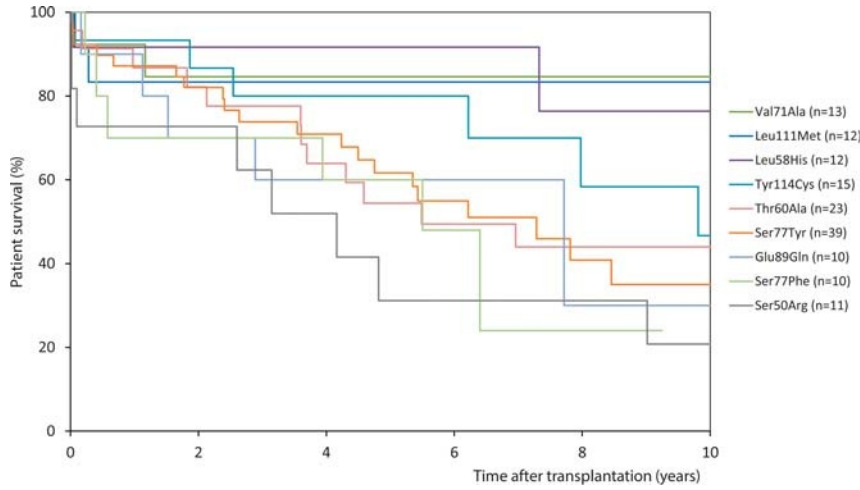

FIGURE 2. Kaplan-Meier survival plot for liver transplanted patients carrying mutations represented by more than 10 patients in the registry. Patients undergoing heart transplantation are included in this survival analysis. See also Table 2.

reported to the register. Information regarding demographics, heredity, type of TTR mutation, clinical manifestations, and peripheral and autonomic neuropathy are recorded. The registry covers a wide range of mutations and a large number of patients, of whom 13% constitute mutations other than Val30Met. For 9 such mutations, each with more than 10 individuals, the registry data provide a basis for recommendations concerning transplantation. Even though the number of patients reported with rare non-Val30Met mutations is relatively small, our findings are of interest concerning the relationship between mutation/phenotype and outcome after LTx alone or combined LTx/HTx.

Males dominate among transplanted patients with non-Val30Met mutations, especially among patients who receive both liver and heart grafts. This result is expected because cardiomyopathy is more commonly observed in male patients.[50,51] In addition, men are also almost exclusively affected in senile systemic amyloidosis, in which wild-type TTR assembles into amyloid fibrils predominantly in the heart.[52] Of interest, the only combined LTx/HTx patient with the Ser50Arg mutation was a woman. This mutation is prevalent in patients with an early disease onset,[53] similar to the Leu111Met mutation that 3 women who underwent LTx/HTx carried. For Leu111Met, the high survival in isolated LTx patients is especially interesting because the associated phenotype is characterized by a rapidly progressing cardiomyopathy, and pronounced neuropathy has rarely been noted.[19,54] With this mutation, early LTx seems to prevent the development of cardiomyopathy.[55] Also, in Leu111Met patients subjected to combined LTx/HTx, an encouraging outcome was noted, a finding that accords with previous observations for mutations in which the phenotype is characterized by cardiomyopathy.[20,22,34]

Survival in patients with mutations that led to combined LTx/HTx was for the first years similar to patients undergoing LTx alone, but long-term survival seems to be better for those undergoing combined transplantation and is maybe the preferred treatment for these mutations. This possibility is also reflected in the outcome for Thr60Ala, in which isolated LTx seems not to be an option because rapid development of cardiomyopathy after the procedure has been reported,[4] which is in agreement with the outcome noted in our study.

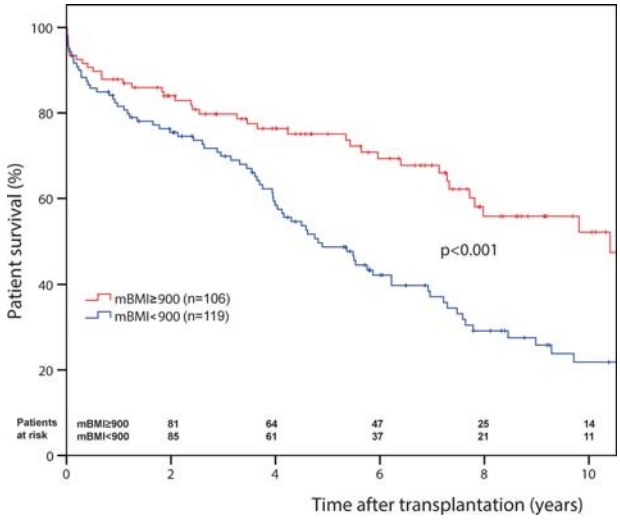

FIGURE 3. Survival in patients with mutations other than Val30Met with regard to nutritional status reflected as mBMI < 900 and mBMI ≥ 900 at the time of transplantation.

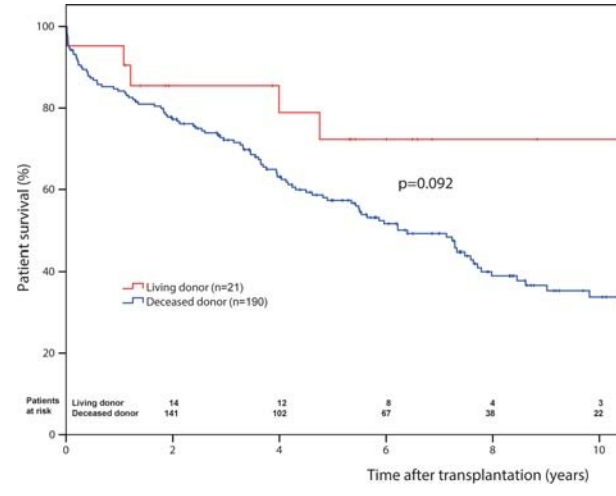

FIGURE 4. Liver transplantation using organs from deceased donors and living donors in patients with mutations other than Val30Met.

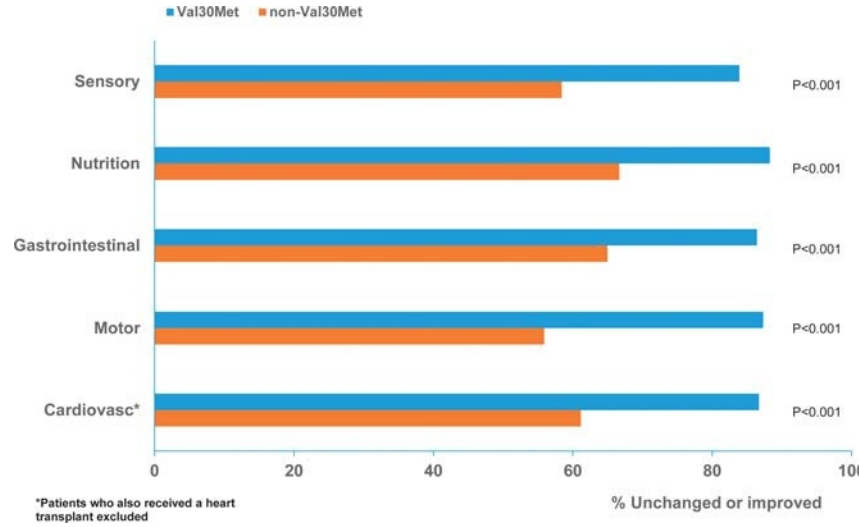

FIGURE 5. Clinical status compared to pre-transplant status (reported as unchanged or improved) in patients with the Val30Met mutation and in patients with other mutations.

It is still an open question whether LTx may prevent the development of cardiomyopathy if performed before a heart complication has developed. This potential may be relevant in patients with mutations, such as Leu58His, Ala25Ser, and Phe33Cys, for which a heart complication is part of the phenotype but with which patients have survived for more than 8 years after isolated LTx.

One of the interesting findings emerging from our registry data was the lack of a convincing relationship between phenotype and outcome after transplantation. As mentioned above, LTx may prevent the development of cardiomyopathy for Leu111Met and some additional mutations, but for others, such as Thr60Ala, this is not the case. In patients with mutations other than Val30Met, the expected survival is poorly defined. However, the 10-year survival of 58% after combined LTx and HTx compares favorably with the expected survival of 6.6 years after symptom onset and 3.4 years after diagnosis for nontransplanted Thr60Ala patients.[4] Similarly, the 47% 10-year survival for the Tyr114Cys mutation with a phenotype known for leptomeningeal complications, from which most patients die within 10 years after onset of disease, may be considered acceptable,[56] but patients in the registry with other mutations characterized by central nervous system manifestations all died within 3 years of LTx.

Why the outcome after LTx is so variable for different mutations remains obscure. Recently, differences in amyloid fibril composition have been reported in which 1 type consists of both full-length and truncated TTR (type A) and the other of full-length TTR only (type B). In ATTR Val30Met patients, the amyloid fibril composition is related to the phenotype of the disease where type B is noted in patients with cardiomyopathy and in those who developed cardiomyopathy after LTx.[57,58] In an investigation of fibril composition in 29 ATTR mutations, type A fibrils were observed only in 2 non-Val30Met patients, both carrying the Tyr114Cys mutation,[59] the only mutation in the present series associated with meningeal complications and showing an acceptable outcome after LTx.

Reports on the use of living-donor liver grafts in patients with hereditary ATTR are rare. Some studies in the Japanese population have involved living-donor livers for transplantation into FAP patients and reported good survival rates equal to those presented by LTx centers outside Japan that use grafts from deceased donors.[60] In our analysis of patients who received living-donor livers, we found that the 10-year survival in recipients of living-donor liver grafts was numerically better than that seen in recipients of liver grafts from deceased donors, but did not reach statistical significance. However, this finding has to be interpreted with caution because the small numbers at risk in the living-donor liver recipient group make interpretation uncertain.

A high incidence of early posttransplant thrombotic complications, in particular hepatic artery thrombosis, has been reported in ATTR patients.[61] The FAPWTR receives reports on hepatic artery thrombosis only if it has led to retransplantation of the patient or to the patient's death. In the cohort of non-Val30Met patients, no patient was reported to have been retransplanted because of hepatic artery thrombosis, and no patient death caused by hepatic artery thrombosis was reported.

An important question is whether LTx can improve long-term neurological outcome. The FAPWTR receives reports if a patient has experienced deterioration in symptoms or the status is unchanged or has improved symptomatically. This approach is, of course, a simple and crude way to assess the effect of LTx on patient symptoms, but it is nevertheless important if patients subjectively feel better after LTx. We could see that LTx in patients with mutations other than Val30Met resulted in significantly fewer patients being reported as having neurological symptoms as unchanged/improved.

With the introduction of medical therapy, the era of LTx for patients with the Val30Met mutation and mutations other than Val30Met may be nearing its end. However, all new treatment modalities need to be compared with previous treatments. The long-term survival after TTR stabilizer treatment has not been settled, and the variable response to TTR stabilizer treatment poses a problem because delayed transplantation for a patient in whom an acceptable outcome is to be expected significantly decreases survival.[27] Gene silencing that decreases levels of circulating TTR is a promising option, but its efficacy is not proven even though preliminary data are encouraging.[43] Medical therapy as adjuvant treatment to

LTx has not been evaluated, though a positive outcome for diflunisal treatment including regression of amyloid in biopsy specimens was reported in 2 liver transplanted Japanese patients carrying the Glu42Gly and Ser50Arg mutations, respectively.[62] Adjuvant medical therapy and LTx may be appropriate, especially for patients who deteriorate after LTx. An evaluation of the outcome within the frame of the FAPWTR registry is desirable.

In conclusion, the present analysis clearly reflects the large phenotypic variation among patients with mutations other than Val30Met in ATTR and points to the necessity of having large databases for drawing reliable conclusions. The FAPWTR is the largest available database on patients with amyloid mutations who have undergone transplantation, but the number of individuals carrying the same non-Val30Met mutation is limited in this global registry, as well. Our study does not resolve the question of whether one should perform LTx alone or combined LTx/HTx with regard to all presently known non-Val30Met mutations. However, based on our findings, we believe that for some mutations, guidelines are still possible. Liver transplantation alone seems to be a treatment option in patients carrying mutations, such as Val71Ala, Leu111Met, and Leu58His, but not for those carrying the Ser50Arg, Ser77Phe, or Ser77Tyr mutations. Combined LTx/HTx is a valid option for certain mutations, for example, Leu111Met with cardiomyopathy and to some extent Thr60Ala and Glu89Gln. Leptomeningeal manifestations make LTx alone a doubtful treatment option, with the exception of patients carrying the Tyr114Cys mutation for whom it may be considered. Finally, it is obvious from the presented data that each mutation needs to be evaluated separately with regard to the individual patient's phenotypic expression and disease manifestation. Preferably, the term "non-Val30Met" should be avoided. Because of the scarcity in numbers of transplanted patients with mutations other than Val30Met in individual centers and their phenotypic diversity, the importance of a centralized collection of data into a single database like the FAPWTR is emphasized.

ACKNOWLEDGMENT

The authors thank the physicians from all participating centers for providing information to the FAPWTR.

Participating Centers

USA: Mayo Clinic, Rochester. Lahey Clinic Medical Center, Burlington. UCSF Medical Center, San Francisco. NEDH/Harvard Medical School*, Boston. Mayo Clinic, Phoenix. Thomas E Starzl Transplant Institute, Pittsburgh. University of Maryland Medical Center, Baltimore. Medical University of South Carolina, Charleston. Cleveland Clinic Foundation, Cleveland. Jackson Memorial Hospital, Miami. University of North Carolina Hospitals, Chapel Hill. The Penn Transplant Center, Philadelphia. Northwestern Memorial Hospital*, Chicago. France: Hospital Paul Brousse/Kremlin Bicêtre, Villejuif. Hospital Edouard Herriot, Lyon. Pellegrin Hospital, Bordeaux. Germany: Der Johannes Gutenberg Universität, Mainz. Klinikum der Universität, Heidelberg. Medizinische Hochschule, Hannover. UK: King's College Hospital, London. Royal Post Graduate Medical School, London. Italy: Hospital Bellaria, Bologna. Netherlands: University Medical Center, Groningen. Denmark: Copenhagen University Hospital, Copenhagen. Spain: Hospital de Bellvitge, Barcelona. Hospital Virgen de la Arrixaca, Murcia. Hospital Vall D'Hebron, Barcelona. Hospital Ramón y Cajal, Madrid. La Fe Hospital, Valencia. Japan: Kumamoto University Hospital, Kumamoto. Shinshu University Hospital, Matsumoto. Tokyo University Hospital, Tokyo. Kyushu University Hospital, Fukuoka. Hokkaido University Hospital, Sapporo. Australia: Queensland LTS, Brisbane. South Australia Liver Transplant Unit, Bedford Park. Canada: London Health Science Center, London. China: Queen Mary Hospital, Hong Kong. Portugal: Hospital Curry Cabral, Lisbon. Hospital de Santo António, Porto. Coimbra University Hospital, Coimbra. Sweden: Karolinska University Hospital Huddinge, Stockholm. Sahlgrenska University Hospital, Gothenburg. Belgium: UCL St Luc, Brussels. University Hospital, Gent. University of Liège, Liège. Switzerland: Hospital Cantonal, Geneva. Singapore: Singapore General Hospital.

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