ORIGINAL ARTICLE

Progression of transthyretin (TTR) amyloidosis in donors and recipients after domino liver transplantation—a prospective single-center cohort study

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SUMMARY

Liver transplantation (LT) is the first-line therapy in patients with transthyretin (TTR) amyloidosis and progressive familial amyloid polyneuropathy (FAP). Explanted organs from these patients can be used for domino liver transplantation (DLT). After DLT, *de novo* amyloidosis may develop in domino recipients (DR). Data were collected prospectively in a transplant database. Electroneurography by nerve conduction velocity (NCV), quantitative sensory testing, heart rate variability (HRV), sympathetic skin response, orthostatic reaction (tilt table test), transthoracic echocardiography, cardiac MRI and organ biopsy results were evaluated. The cohort included 24 FAP- (11 Val30 Met, 13 nonVal30Met) and 23 DR-patients. DR symptoms referred to post-DLT only, while those of FAP patients were both pre- and post-transplantation. Symptoms of TTR-amyloidosis in Val30Met and Non-Val30Met patients pre- and post-LT were similarly distributed. Biopsy-proven *de novo* amyloidosis occurred in 4/23 DR after a mean observation of 10 years. Analysis for manifestations of amyloidosis only included patients with available 5-year follow-up data (n = 13 FAP, n = 12 DR). Compared to Val30Met FAP patients pre-LT, Val30Met DR patients had better NCV (P = 0.04) and HRV (P = 0.015). In the Non-Val30Met group no differences were found between DR and FAP patients pre-LT. TTR-amyloidosis symptoms showed no differences in FAP patients pre- and 5 years post-LT, irrespective of Val30Met status. In DR patients, *de novo* amyloidosis occurred earlier than expected. Therefore, recipients for DLT need to be carefully selected and followed.

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Key words
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Background

Familial amyloid polyneuropathy (FAP) is an autosomal dominant hereditary disease which leads to neurologic, gastrointestinal and cardiac symptomsowing to the irreversible extracellular deposition of misfolded amyloid resulting from the mutation of a transthyretin (TTR) gene [1]. Over 100 different mutations, leading to various manifestations and time courses of the disease, are known [2,3]. The most common mutation is Val30Met, which causes mainly polyneuropathy (PNP) [3,4].

More than 90% of the TTR protein is synthesized in the liver [5]. Therefore, liver transplantation (LT) is the first-line therapy in patients with progressive FAP with disease control rates of >80% and a 5-year survival of 70% (non-Val30Met) to 80% (Val30Met) [6,7]. However, the disease may worsen after LT [8]. Because on average symptoms occur in FAP patients after 20 years [4], the explanted liver of FAP patients can be transplanted into patients with end-stage liver disease (domino liver transplantation, DLT) [7]. However, there are reports of accelerated transmission of disease in domino recipients (DR) with an earlier manifestation in older DR and DR of Val30Met organs [9–11].

Finding alternative therapies for FAP is a major target of ongoing research. To date, the most common strategy is to stabilize the physiologic tetramer structure of TTR and therefore, prevent protein misfolding; in Germany, the TTR-stabilizing drug Tafamidis was approved in 2011. Treatment with Tafamidis has been shown to delay PNP [12,13]. Diflunisal, which is not approved in Germany, reduces the onset of PNP and improves quality of life [6,14]. Enhancing the degradation of amyloid deposits by a combination of doxycycline and tauroursodeoxycholic acid (TUDCA) was investigated in a phase II trial, which indicated a stabilization of PNP and cardiac involvement [15]. Phase I and II trials on antisense oligonucleotide and siRNA therapies showed a 80–90% reduction of serum TTR [16–22]; phase III results are pending.

The aim of this prospective study was to evaluate the course and outcome of a single-center cohort of FAP and DR patients after DLT.

Methods

Patient characteristics and diagnostic criteria

Between May 1998 and March 2016 23 DLT were performed at the University Medical Center Mainz. In addition, 40 FAP patients visited the outpatient clinic, 24 of whom received LT. All data were collected prospectively in our transplant database. All patients were followed up at least every 6 months in our outpatient clinic. GI symptoms (diarrhea, nausea, incontinence, indigestion, malabsorption and constipation) were assessed. Electroneurography (nerve conduction velocity, NCV), quantitative sensory testing (QST), heart rate variability (HRV), sympathetic skin response (SSR) and orthostatic reaction (tilt table test) were measured every 6 months in all 24 FAP- and 23 DR-patients after LT. Transthoracic echocardiography (TE) and cardiac MRI were performed annually post-transplantation, and organ biopsies (myocardium, salivary glands, stomach, sural nerve, rectum) with Congo red staining were initiated whenever clinical suspicion for *de novo* amyloidosis occurred. Diagnosis of *de novo* amyloidosis was defined as two or more abnormalities identified on neurologic evaluation, the ruling out of other etiologies, and biopsy-proven amyloid as published by Bolte *et al.* [10]. If biopsy was negative, fewer than two abnormalities were identified on neurologic evaluation, or conditions such as concurrent illnesses or immunosuppression best explained symptoms and signs of neuropathy, then *de novo* amyloidosis was unlikely as published previously [10]. In cases of clinical progression of symptoms, biopsies were repeated every 6 months until amyloid deposits were histologically proven. All patients underwent protocol liver biopsy 1 year and every 5 years post-LT/DLT.

Statistical analysis

For descriptive analysis, continuous normally distributed variables were expressed as means (±standard deviations (SD)) and continuous non-normally distributed variables were expressed as median and quartiles. For categorical variables absolute and relative frequencies were analyzed and expressed as pie charts and contingency tables. Survival was analyzed in a Kaplan–Meier curve. For explorative analysis, observations between groups were compared using Fisher's exact test for 2x2 contingency tables or the chi-square test for more than 2x2 contingency tables for categorical variables. Correlation was analyzed with the Pearson correlation test for linear dependencies. P-values less than 0.05 were considered significant. No adjustments for multiple testing were done. The statistical tests were performed for illustrative purposes only. P-values were given for descriptive reasons only and should be interpreted with caution.

All statistical analysis was performed using IBM SPSS statistics version 22 (SPSS Inc., Chicago, IL, USA).

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Patients signed informed consent for the recording and analyzing of data and they agreed to the forwarding or publishing of data in a pseudonymized or anonymized form. This research was approved by the local ethics committee of Rhineland-Palatinate and was conducted according to the ethical guidelines of the Declaration of Helsinki 1975 and Good Clinical Practice guidelines.

Results

Characteristics of FAP patients

The cohort included 24 FAP patients (11 Val30Met, 13 nonVal30Met). These patients were on average 41.5 ± 9.07 (range: 36–61) years old, 16 patients (66.7%) were male and eight patients (33.3%) were female. Mean duration of symptoms pre-LT was 3.81 ± 2.65 (range: 2.22–11.4) years. Only one patient (4.2%) received Tafamidis therapy before LT (Table 1A). Four FAP patients underwent additional heart transplantation [23].

Survival of FAP patients

The post-LT survival rates of 23 FAP patients were compared with those of 670 LT patients, who were transplanted for other reasons and who did not receive a FAP organ (Fig. 1a).

The 5-year survival of FAP patients was 70%, which was comparable to the 5-year survival of control patients (64%) ($P > 0.05$).

Causes of death in FAP patients

During a mean follow-up of 11.7 years, 12 out of 24 FAP patients died. The majority of FAP patients died post-LT for cardiac reasons (cardiac insufficiency or arrhythmia, probably related to amyloidosis; $n = 5$, 42%) or from sepsis ($n = 4$, 33%). Seventeen percent died because of noncardiac complications of amyloidosis, such as physical decay and cachexia related to amyloid deposits (Fig. 2a).

Symptoms of FAP patients

The majority of patients suffered from multiple symptoms with a mean duration of 3.81 years before LT. For each patient individual symptoms were assessed and analyzed separately. In FAP patients with the Val30Met mutation ($n = 11$), symptoms pre-LT were 48% ($n = 11$) neurologic, 22% ($n = 5$) cardiac (sick sinus syndrome, atrioventricular block and ventricular extra systoles or cardiomyopathy), 22% ($n = 5$) gastrointestinal (GI) and 8% ($n = 2$) renal (Fig. 3a).

For non-Val30Met FAP patients ($n = 13$), manifestation of amyloidosis pre-LT affected 50% ($n = 12$) in the neural system, 21% ($n = 5$) in the GI tract, 21% ($n = 5$) in the heart and 4% ($n = 1$) in each kidney and lung (Fig. 3b).

Post-LT symptoms in FAP patients bearing the Val30Met mutation ($n = 11$) were 42% ($n = 8$) neurologic, 32% ($n = 6$) cardiac, 21% GI ($n = 4$) and 5% renal ($n = 1$; Fig. 3c).

Forty-seven percent ($n = 8$) of non-Val30Met FAP patients ($n = 13$) suffered from neurological symptoms post-LT. In 24% ($n = 4$) of these patients, symptoms were cardiac, 23% ($n = 4$) were GI and 6% ($n = 1$) were pulmonary (Fig. 3d).

Manifestation of amyloidosis in FAP patients before and after LT

Only patients with available 5-year follow-up data after LT were included in the analysis of the manifestation of amyloidosis ($n = 13$; Table 2).

Comparing FAP patients with the Val30Met ($n = 7$) and non-Val30Met mutations ($n = 6$) pre- or 5 years post-LT, no significant differences were found in symptoms of diarrhea, NCV, QST, HRV, SSR, orthostasis, TE and cardiac MRI (Table S1). In addition, no significant differences could be detected in FAP patients pre- versus post-LT irrespective of their Val30Met status.

Characteristics of DR patients

About 23 DR patients underwent LT with a mean age of 59 ± 5.97 (range: 46–69) years; 18 patients were male (78.3%), five female (21.7%) and the mean body mass index (BMI) was 25.06 ± 4.15 kg/m². Median follow-up was 11.7 years (25th percentile: 8.9, 75th percentile: 12.9, range: 5.5–16.1). The majority of DR patients were transplanted owing to hepatocellular carcinoma ($n = 19$, 82.6%). Only four DR patients (17.4%) had other indications for LT. The majority were Child–Pugh A ($n = 13$, 56%) with a mean labMELD score of 13.3 (±9) points (Table 1B).

Survival of DR patients

The post-LT survival rates of the 23 DR patients in comparison to 670 LT patients, who were transplanted for other reasons and who received no FAP organ, are presented in Fig. 1b.

Table 1. Patient characteristics of 24 FAP- (A) and 23 DR-patients (B).

A. Patients with familial amyloidosis (n = 24)	
Age at the time of transplantation (years)	
Mean ± SD (range)	41.5 ± 9.07 (36–61)
Gender, *n* (%)	
Male	16 (66.7)
Female	8 (33.3)
TTR mutation, *n* (%)	
Val30Met	11 (45.8)
Non-Val30Met	13 (54.2)
Leu12Pro	2 (8.3)
Leu58His	1 (4.2)
Ala97Gly	1 (4.2)
Val107	1 (4.2)
Asp18Glu	1 (4.2)
Gly47Glu	1 (4.2)
Glu89Lys	1 (4.2)
Val20Ile	1 (4.2)
Thr49Ala	1 (4.2)
Duration of symptoms pretransplantation (years)	
Mean ± SD (range)	3.81 ± 2.65 (2.22–11.4)
Tafamidis therapy, *n* (%)	
Yes	1 (4.2)
No	23 (95.8)
Survival (overall), *n* (%)	
Alive	12 (50)
Dead	12 (50)
B. Domino recipients (n = 23)	
Age at the time of transplantation (years)	
Mean ± SD (range)	59 ± 5.97 (46–69)
Gender, *n* (%)	
Male	18 (78.3)
Female	5 (21.7)
Body mass index (kg/m²)	
Mean ± SD	25.06 ± 4.15
Survival (overall), *n* (%)	
Alive	11 (47.8)
Dead	12 (52.2)
Follow-up (years)	
Median (25.; 75. percentile)	11.7 (8.9; 12.9)
Range	5.5–16.1
Indications, *n* (%)	
HCC induced by autoimmune hepatitis, alpha-1 antitrypsin deficiency or hereditary hemochromatosis liver cirrhosis	3 (13)
HCC induced by viral hepatitis liver cirrhosis	7 (30.4)
HCC induced by alcoholic liver cirrhosis	7 (30.4)
HCC induced by viral hepatitis and alcoholic liver cirrhosis	2 (8.7)
Alcoholic cirrhosis	2 (8.7)
Autoimmune hepatitis liver cirrhosis	1 (4.3)
Retransplantation	1 (4.3)
Child–Pugh, *n* (%)	
A	13 (56)
B	3 (13)
C	7 (30.4)
labMELD	
Mean ± SD	13.3 (±9)
Comorbidities, *n* (%)	
Smoking	4 (17.4)
History of alcohol consumption	11 (47.8)
Diabetes	10 (43.5)
Arterial Hypertension	8 (34.8)
Retransplantations, *n* (%)	1 (4.3)
De novo amyloidosis, *n* (%)	4 (17.4)

SD, standard deviation; FAP, familial amyloid polyneuropathy; DR, domino recipients.

The 5-year survival of DR patients was 70%, which was comparable to the 5-year survival of control patients (64%) ($P > 0.05$).

Causes of death in DR patients

Twelve out of 23 DR patients died during a mean observation time of 11.66 years. The majority of DR patients died because of recurrence of the underlying disease for which transplantation was required (n = 5, 42%) or sepsis/multiorgan failure (n = 4, 34%). Only 8% died by complications of *de novo* amyloidosis, such as cardiac arrhythmias related to biopsy-proven cardiac amyloid deposits (Fig. 2b).

The relatively high proportion of multiorgan failure in DR patients in contrast to FAP patients occurred mainly early after transplantation. This could be accounted for the poor physical condition of DR patients pre-DLT in comparison to FAP patients pre-LT; DR patients pre-DLT were older and the majority suffered from malignancy (Table 1B).

Symptoms of DR patients

In contrast to FAP patients with clinical alterations both pre- and post-transplantation, DR symptoms refer to post-DLT only.

Biopsy-proven *de novo* amyloidosis occurred in 4/23 DR patients after a mean observation of 10 years. In two patients biopsies showed amyloid deposits in the rectal mucosa. In one patient cardiac amyloidosis was

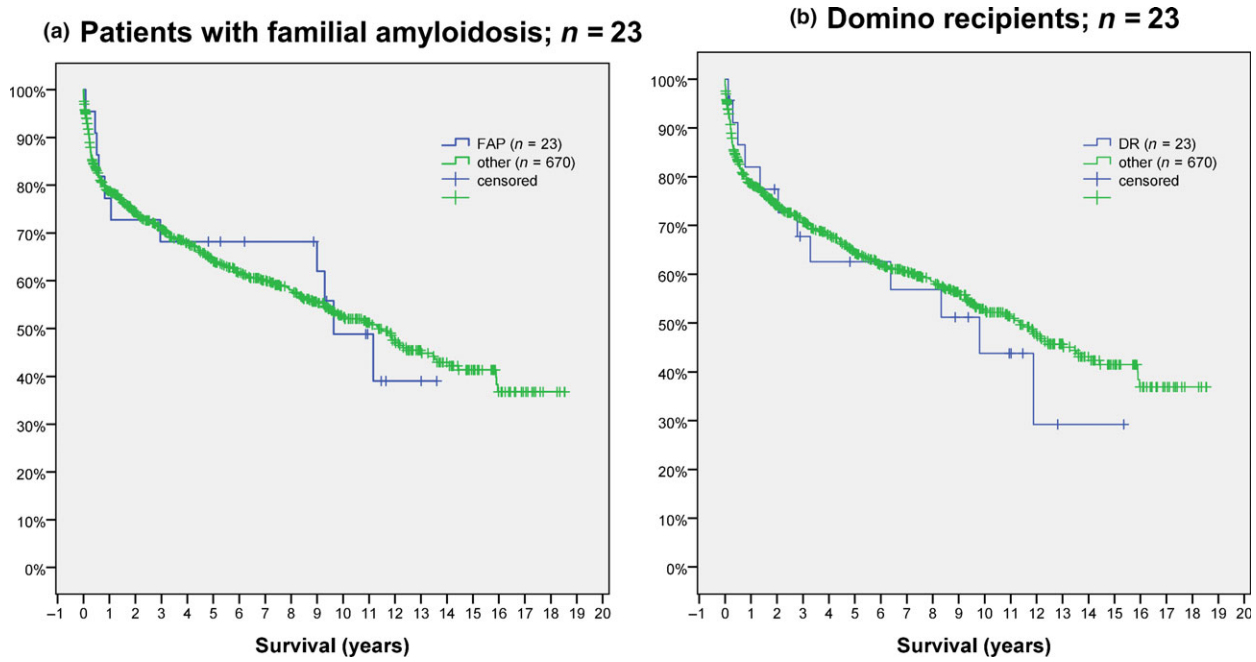

Figure 1 Survival. Post-LT survival rates of the 23 patients transplanted for FAP (a) and the corresponding 23 DR patients (b) in comparison to 670 LT patients, who were transplanted for other reasons than FAP and who were not domino recipients.

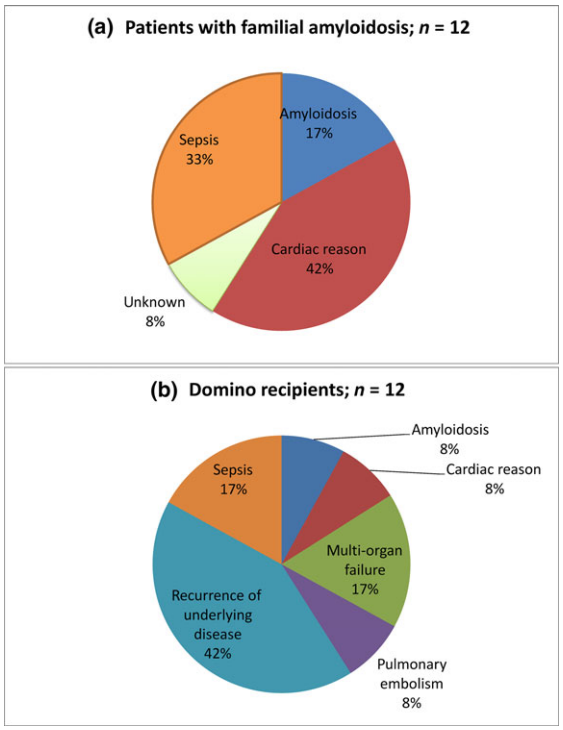

Figure 2 Causes of death. Causes of death in the 12 deceased FAP- (a) and the 12 deceased DR- patients (b).

verified by myocardial amyloid deposits and in one patient amyloid deposits were found in gastric and rectal mucosa.

The two patients who developed *de novo* amyloidosis following Val30Met DLT suffered from PNP starting 4 and 5 years post-LT and GI symptoms starting 4.5 and 8 years post-LT. In both patients rectal mucosa showed a slight stromal fibrosis and congophilic deposits in the fiber bundles of smooth muscle 8 and 11 years post-LT.

Symptoms of non-Val30Met DR patients were 50% ($n = 2$) PNP starting 7 and 11 years post-LT, 25% ($n = 1$) GI 10 years post-LT and 25% ($n = 1$) cardiac (cardiac insufficiency as a result of amyloid cardiomyopathy) 11 years post-LT. In one patient cardiomyocytes had a broadened sarcoplasm and hyperchromatic as well as unrounded nuclei. Muscle fiber bundles were dissociated and deposits of homogenous eosinophilic material, which was positive with Congo red staining, were found 11 years post-LT. One patient showed focal stromal deposits with polarization-optical apple-green double refraction in gastric and rectal mucosa 10 years post-LT.

Symptoms of *de novo* amyloidosis in DR patients correlated well with the symptoms of amyloidosis in donors pre-LT (Pearson: $r = 1.0$; $P < 0.001$). One patient died after 12 years because of *de novo* amyloidosis.

One patient was retransplanted because of progression of *de novo* amyloidosis. Another patient with Glu89Lys developed cardiomyopathy and underwent

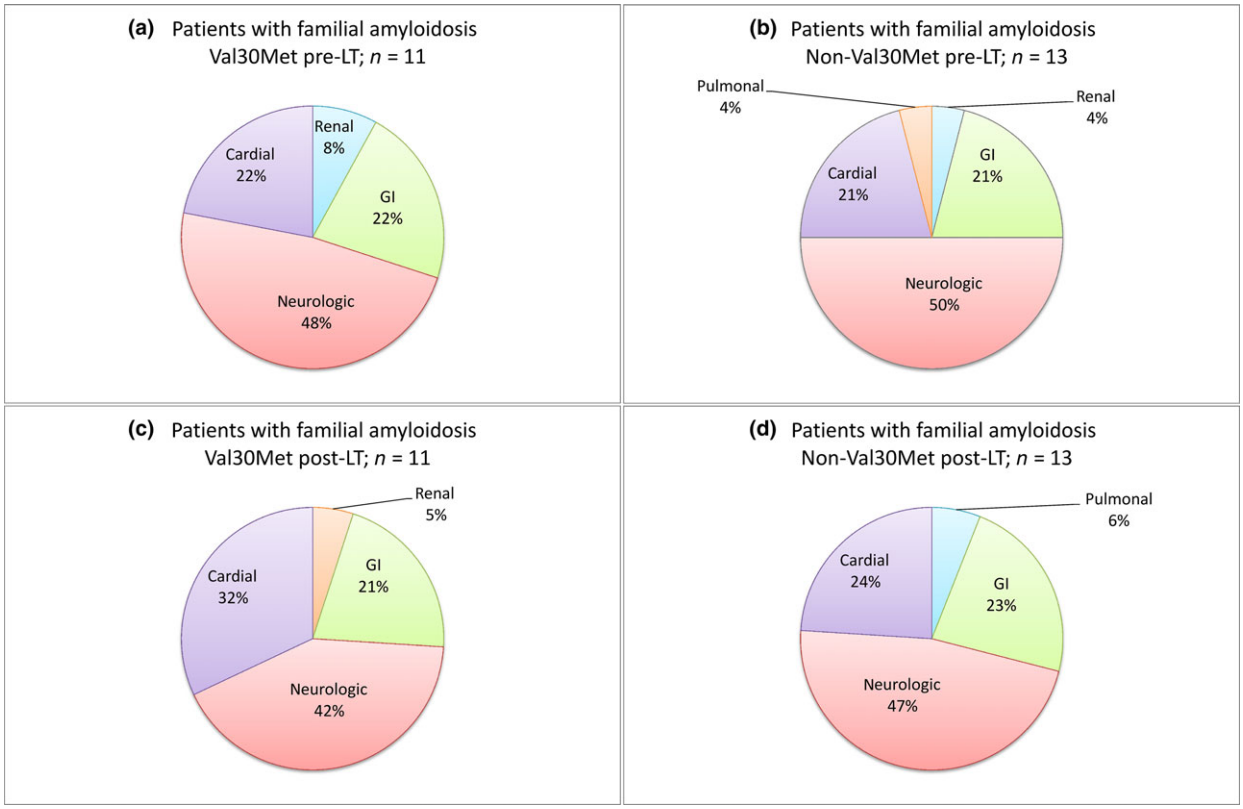

Figure 3 Symptoms. Symptoms of FAP-patients pre-LT (a, b) and post-LT (c, d) depending on the Val30Met status (n = 11 Val30Met and n = 13 Non-Val30Met). The majority of patients had multiple symptoms with a mean duration of 3.81 years pre-LT. For each patient individual symptoms were assessed and analyzed separately. GI: gastrointestinal, PNP: polyneuropathy.

retransplantation recently. An 81-year-old man suffered from severe PNP with limited therapeutic options. All patients with *de novo* amyloidosis were placed under treatment with Tafamidis. In general, DR patients who developed *de novo* amyloidosis were older than DR patients without amyloidosis symptoms.

Manifestation of amyloidosis in DR patients after LT

Only patients with available 5-year follow up data after LT were included in the analysis (n = 12; Table 2).

DR patients of Val30Met- (n = 6) and Non-Val30-Met- (n = 6) organs did not show significant differences in evaluated parameters pre- and 5 years post-DLT (Table S1). However, compared to FAP patients pre-LT, DR patients as a group had significantly better HRV (P = 0.002) and SSR (P = 0.019). Val30Met-DR patients had significantly better NCV (P = 0.04) and HRV (P = 0.015) than their Val30Met-FAP donors pre-LT. In the Non-Val30Met-group no differences were found between DR and FAP patients pre-LT.

Discussion

LT is the standard of care for progressive transthyretin FAP [6,7]. However, the disease may progress after LT [8]. Comparing seven Val30Met- and six Non-Val30Met-FAP patients pre- and 5 years post-LT we did not find significant differences in symptoms for the parameters tested (diarrhea, NCV, QST, HRV, SSR, orthostasis, TE and cardiac MRI), suggesting stable disease after LT. These findings are in line with the previously described good disease-control rates [6,7] after LT and confirm LT as an effective treatment of FAP. Further studies are needed to evaluate if alternative pharmacologic treatments can achieve comparable results. Recent studies give hope that new treatment options achieve a relevant delay in disease progression [24] and therefore the need for LT.

Because no adjustments for multiple testing have been done in our study p-values are given for descriptive reasons only and should be interpreted with caution.

However, assessment of patients beyond 5 years post-LT revealed cases with progressive PNP and cardiac amyloidosis. Progression of PNP post-LT might be

Table 2. Manifestations of amyloidosis in FAP patients before and after LT and in DR patients post-LT depending on Val30Met-genotype (Contingency Table)

	Diarrhea		NCV			QST		HRV		SSR		Orthostasis		TE		Cardiac MRI	
Frequency	Yes, %	No, %	Normal, %	Sens, %	Senso-mot, %	Normal, %	Path, %	Normal, %	Path, %	Normal, %	Path, %	Normal, %	Path, %	Neg, %	Pos, %	Neg, %	Pos, %
FAP pre-LT Val30Met (n = 7)	20	80	0	28.6	71.4	25	75	33.3	66.7	0	100	66.7	33.3	57.1	42.9	100	0
FAP pre-LT Non-Val30Met (n = 6)	0	100	0	50	50	33.3	66.7	50	50	0	100	66.7	33.3	16.7	83.3	0	100
FAP post-LT Val30Met (n = 7)	57.1	42.9	14.3	0	85.7	0	100	0	100	14.3	85.7	80	20	50	50	50	50
FAP post-LT Non-Val30Met (n = 6)	75	25	33.3	16.7	50	0	100	33.3	66.7	50	50	80	20	66.7	33.3	60	40
DR Val30Met (n = 6)	33.3	66.7	16.7	50	33.3	16.7	83.3	80	20	83.3	16.7	66.7	33.3	100	0	100	0
DR Non-Val30Met (n = 6)	66.7	33.3	50	33.3	16.7	0	100	100	0	80	20	100	0	83.3	16.7	100	0

GI-symptoms, electroneurography (NCV), QST, HRV, SSR, orthostatic reaction (tilt table test), TE and cardiac MRI were assessed in 13 FAP- (7 Val30Met and 6 non-Val30-Met) and 12 DR- (6 Val30Met and 6 non-Val30Met) patients pre- and 5-years post-LT/DLT. Detailed comparisons between groups are given as supplementary data (Table S1).

FAP, familial amyloid polyneuropathy; DR, domino recipients; n, number of patients; LT, liver transplantation; NCV, nerve conduction velocity; QST, quantitative sensory testing; HRV, heart rate variability; SSR, sympathetic skin response; TE, transthoracic echocardiography.

accelerated owing to the neurotoxicity of immunosuppression, especially in combination with calcineurin inhibitors. Furthermore, LT remains a complex treatment. Therefore, the optimal timing of LT in FAP patients needs discussion, especially considering the availability of new therapeutic drugs. LT might be delayed with a view to optimizing results post-LT. Data on the use of TTR tetramer stabilizers post-LT are pending.

DLT is a reliable option for patients with end-stage liver disease, without other therapeutic possibilities, who are unlikely to receive an organ in the labMELD-based allocation system. Little is known about incidence and onset of *de novo* amyloidosis after DLT. There are only a few studies on DLT, indicating a rare transmission of the disease 10 years post-LT; however, an accelerated time course with an earlier manifestation is seen in older DR patients and recipients of Val30Met organs [9–11]. In our cohort of 23 DR patients we found a relatively frequent transmission of FAP with 4/23 (17%) in comparison to 2/61 (3%) in another German retrospective multicenter study [10]. An 8–11 year time to manifestation of *de novo* amyloidosis is comparable with previous findings [10,11]; however, it is much earlier than the symptoms of FAP in genetically affected families, which usually occur after 20 years [4]. Therefore, candidates for DLT need to be carefully selected. For example, while elderly patients could be suitable DR, Misumi *et al.* [11] demonstrated that recipient aging is associated with an early onset of *de novo* amyloidosis and therefore, this needs discussion.

Interestingly, we found significant better HRV ($P = 0.002$) and SSR ($P = 0.019$) in DR patients of Val30Met organs in comparison to FAP donors. In contrast, no differences were found between non-Val30Met DR patients and FAP patients pre-LT. This counters the findings of Misumi *et al.* [11] of an earlier onset of *de novo* amyloidosis in Val30Met DR patients. It remains unclear whether organ selection for DLT should be based on the mutation. Val30Met organs seem to be unsuitable for patients suffering from PNP other than those with FAP and the Ala60 mutation, associated with cardiac manifestations, and so should be critically evaluated for cardiac disorders [25]. More data are urgently needed, especially for non-Val30Met- mutations.

Conclusion

Considering the availability of new therapeutic drugs, the optimal timing of LT in FAP patients needs discussion. *De novo* amyloidosis occurs in a number of DR. Recipients for DLT need to be carefully selected.

Limitations

As the mean time to *de novo* amyloidosis is after 10 years, data are limited. 10- and 15-year data are pending.

Allocation of domino organs in Germany has recently changed. Therefore, future studies and analysis will be complicated owing to the rareness and complexity of FAP. In our study FAP donors and corresponding DR were closely monitored because of center-based allocation.

Authorship

JV, JChS and TZ: wrote the manuscript. JV and TZ: designed the study. JV, JChS, ML, TE, MA, CG, AS, APB, GO, JM and TZ: collected and analyzed data. VW: checked the statistical analysis. HL, FB and PRG: critically reviewed and edited the manuscript. All authors contributed toward data analysis, drafting and critically revising the paper, and agreed to be accountable for all aspects of the work by approving the final paper.

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Conflicts of interest

The authors have declared no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Comparisons between groups displayed in Table 2 with Fisher’s exact test or chi-square test for more than 2x2 contingency tables.

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