Invited Review

Liver Transplantation and Transthyretin Amyloidosis

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Educational Objectives
Upon completion of this monograph, the reader will acquire skills to: (1) review use of liver transplantation as a treatment of transthyretin amyloidosis, (2) explain the genetics and pathophysiology of familial amyloidotic polyneuropathy, and (3) to improve the care of patients with transthyretin amyloidosis.

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Orthotopic liver transplantation as a specific treatment for transthyretin (TTR) amyloidosis was first performed 22 years ago (1990). 1,2 Although not based on any prospective study, it was hypothesized that removal of the liver, the sole source of mutant plasma TTR, would halt amyloid formation. Since then it has become an accepted treatment for this fatal disease, but has shown variable results. Some patients definitely have both prolonged survival and improved quality of life. Other patients, however, have lesser benefit, and some seem not to have any alteration in disease progression. It now seems an appropriate time to gather information gained in the last 20 years, analyze the pluses and minuses of the therapy, and formulate a basis for counseling patients and their physicians.

TRANSTHYRETIN AMYLOIDOSIS

TTR amyloidosis is an autosomal dominant hereditary disease. 3 A single gene on chromosome 18q codes for the 127-amino-acid single polypeptide, which is expressed by hepatocytes, epithelial cells of the choroid plexus in the brain, and retinal pigment epithelium of the eye. 4

Familial amyloidotic polyneuropathy (FAP) is the hereditary form of TTR amyloidosis. It is caused by mutations in the TTR protein, which are mostly single amino acid substitutions that presumably alter the secondary and tertiary structure to cause altered metabolism and amyloid fibril formation. 5 TTR is a structural protein that transports thyroxine and retinal binding protein (RBP)/vitamin A, and the product of only 1 mutant allele is necessary to initiate the pathway to amyloid fibril formation and deposition. Tissue pathology is the result of displacement of normal cellular structures with impairment of organ function. 6 Although leptomeningeal and ocular involvement may be prominent features of clinical disease associated with some of the TTR mutations, the peripheral nerves and heart are the most frequent targets of TTR amyloid deposition. 7,8 Although involvement of the kidney may be the first clinical manifestation of TTR amyloidosis, this is uncommon. Renal insufficiency often is a factor in late-stage disease and is mainly the result of end-stage cardiac failure.

Greater than 100 mutations in TTR associated with amyloidosis have been described (latest count 112). 9 A smaller number of TTR mutations (~10) have shown no propensity to cause amyloidosis. It has been well documented, however, that normal TTR (without mutation) can form amyloid in older individuals (>60 years of age) and result in fibril deposits in essentially all vascular organs. 9 These deposits may cause no clinical consequences; the name senile systemic amyloidosis (SSA) has been given to this condition. More important is that a significant number of elderly individuals will have massive deposition of TTR amyloid in the heart. In this case, the term senile cardiac amyloidosis (SCA) is perhaps more appropriate. For unknown reasons, SCA predominantly affects men >60 years of age, whereas FAP has a relatively equal male/female ratio.

FAP is an adult-onset disease that can clinically present as early as the second decade of life, but usually after 30 years of age. 6 The age of onset and pattern of disease varies with each TTR mutation, but considerable clinical variability is seen between families and even within families. In general, the disease phenotype is consistent within close family

Liver Transplantation for ATTR

INVITED REVIEW

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ABSTRACT: Liver transplantation as a specific treatment of transthyretin amyloidosis was first performed in 1990. The rationale for this treatment was that removal of the source (liver) of the amyloid precursor protein (mutated transthyretin) would stop progression of the disease. Indeed, after orthotopic liver transplantation (OLT), mutant transthyretin (TTR) is rapidly cleared from circulation. In the last 20 years, >2000 familial amyloidotic polyneuropathy (FAP) patients have received liver transplants. For these patients, prospective monitoring has shown prolongation of life compared with FAP patients who have not undergone liver transplantation. The most favorable results have been for FAP patients with the Val30Met TTR mutation. Less favorable results have been seen for patients with other TTR mutations where progression of amyloid tissue deposition has been documented as the result of amyloid fibril formation from normal (wild-type) TTR. Although it is obvious that OLT has benefited many FAP patients, there remains a need for further therapies.


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After liver transplantation the concentration of mutant TTR in the blood approaches 0 within a few days. There is no good evidence that TTR synthesized in the choroid plexus of the brain or retinal pigment epithelium in the eye contributes to the circulating TTR pool, and therefore after liver transplantation the peripheral nerves, heart, and gastrointestinal tract should be rid of the abnormal protein. However, circulating TTR is a tetramer with combinations of variant and normal TTR molecules, and fibril deposits are composed of both variant and normal TTR (Fig. 1). We know that normal TTR can, in certain circumstances (old age), participate in amyloid fibril deposition without the presence of variant TTR and, therefore, the disease process might continue despite absence of the variant—“Ay there’s the rub.”12 Is it better to proceed with liver transplantation with the uncertainty that it will arrest the disease and prolong life, or just face the adversities attendant to a progressive disease that usually spans at least 10–15 years?

So, what has been the track record of liver transplantation in this setting? After all, organ transplantation is a relatively invasive form of therapy with a significant, although small, risk related to the surgery and additional risk commensurate with the systemic nature of the disease, such as cardiac arrhythmias and cardiomyopathy. The need for anti-rejection medications and close medical observation posttransplantation is a given. Liver transplantation for TTR amyloidosis is not to be approached without thorough analysis by the patient and his/her physicians.

Over the past 20 years, liver transplantations have been reported to the FAP World Transplant Registry (http://www.fapwtr.org). The FAP Registry was formed to provide just the data we analyze in this review. We know that a fair number of transplants have been done without being reported to the Registry, and we cannot include them in our analysis. Even so, we can make some useful observations. Approximately 2000 liver transplants have been reported to the Registry. Portugal, France, and Sweden have reported the largest numbers (see Registry website for more details). The largest number of transplants have been done on patients with the Val30Met mutation, which is most prevalent in Portugal, Sweden, France, and Japan.13–16 In Portugal and Japan the Val30Met disease presents at a younger age (mean 32–33 years) than in Sweden (∼56–58 years of age). Age is a significant factor in prognosis, and the early-onset patients have better 1- and 5-year survival after transplantation than later-onset patients. Overall, the Val30Met patients have an 85% 5-year survival (Fig. 2). Perhaps the best results are from a recent report from Japan in which there was 100% 10-year survival for this group of patients as compared with estimated probability of survival at 10 years of 56.1% for patients with similar disease who did not receive a transplant.17 Val30Met patients with later-onset disease have not fared quite as well as younger patients, but they still have better results from transplant than patients with other TTR variants.18,19

In some cases, gastrointestinal (GI) symptoms of TTR amyloidosis have improved after liver transplantation but not on a consistent basis.20,21 Nerve regeneration was reported in a study of a patient who had sural nerve biopsy before and 1 year after transplantation.22 In general, however, recovery of nerve function has not been the rule.

From the patient’s point of view, liver transplantation in general has met with favorable reports. Improvement in autonomic and peripheral nerve symptoms has been reported mainly for transplant recipients with the Val30Met mutation.14–24

In a significant number of patients negative results have included progression of disease after transplantation. This was first noted in patients with the Glu42Gly and Ala36Pro mutations, among whom significant progression of left ventricular (LV) wall thickness was noted within 1 year after transplant.25 The same report indicated no significant progression of LV wall thickness in Val30Met transplant patients followed for up to 4 years. A later report, however, noted progression of LV wall thickening in Val30Met transplant recipients.26 Subsequent studies have indicated that progression of cardiac amyloid deposition is of more significance in non-Val30Met transplant recipients.
and largely explains the less favorable long-term survival rates in this group of patients when compared with Val30Met patient survival (Fig. 2).27 Another aspect of disease progression is the change in cardiac autonomic denervation and development of life-threatening arrhythmias in some patients.28,29

Vitreous opacities have also been observed after liver transplantation, and this supports the hypothesis that amyloid fibrils in the vitreous are a result of retinal pigment epithelium TTR synthesis and not of hepatic origin.30 Accordingly, it is obvious that leptomeningeal amyloid deposition in patients with TTR mutations that are associated with this phenotype is not altered by removing the hepatic source of variant TTR.31

The continued deposition of amyloid after liver transplantation is mostly noted by progression of restrictive cardiomyopathy. This is best illustrated by echocardiographic demonstration of advancing LV wall thickening.25 Biochemical data from fibril analysis supports the hypothesis that cardiac amyloid deposition may continue with fibril synthesis from wild-type TTR.32 In the majority of cases in which TTR amyloid fibrils have been analyzed, variant TTR comprises 60–70% of the total protein.33 In patients who have died from cardiomyopathy 3–5 years after liver transplant, the amyloid contains more normal (wild-type) TTR than variant, indicating that the ratio of variant/normal is changed by continued fibril formation from only the normal protein. If, however, heart transplantation is done at the same time as liver transplantation, amyloid deposition in the transplanted heart is not seen. This suggests that amyloid derived from normal (wild-type) TTR produced by the transplanted liver will continue to add to existing deposits but will not form new deposits in the absence of the variant TTR. This can be seen in hearts at postmortem, where there is no amyloid in myocardium distal to the atrial suture line of the graft, yet there is abundant amyloid in the native atrial tissue above the anastomosis (Fig. 3).

Combined liver and heart transplantation for FAP has been reported from a number of centers and has shown favorable results.34–36 The progression of neuropathy and GI pathology in some patients has added another variable to decision-making with regard to transplantation. Reversal of the variant/normal TTR ratio has also seen in peripheral nerve tissue harvested from patients who have had combined liver and heart transplantation and have had extension of life complicated by progressive disability from advanced peripheral and autonomic neuropathy (Fig. 4).37

**DOMINO TRANSPLANTATION**

Another aspect of liver transplantation for treatment of FAP that deserves discussion is the use of “domino” transplantation. The liver of a patient with FAP is usually fully functional. Although it produces mutant TTR, it does not suffer from amyloid deposition, except to a minor degree in blood

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**FIGURE 2.** Patient survival after liver transplantation for TTR amyloidosis comparing data for Val30Met subjects with composite data for subjects with all other TTR mutations reported to the FAP World Transplant Registry. Used with permission.
vessel walls. With a normally functioning liver, the FAP patient does not meet the criteria for liver transplantation that were formulated for the usual causes of hepatic failure. This problem can be circumvented by giving the FAP patient a cadaveric organ and then giving the explanted FAP liver to a patient with liver failure. This “domino” procedure was first performed in 1995 when the liver of a Val30Met FAP patient was given to a patient with liver cancer.38 With advances in surgical techniques this has become standard procedure in the last 10 years. The risk to the FAP patient is not increased, and graft survival in the recipient of an FAP liver is as good as for a graft of cadaveric origin. Explanted livers from FAP patients who receive a graft from related living donors can also be used for domino transplants.

The use of partial liver grafts from related living donors has been in practice since 1995. This has occurred mainly in Japan, where there was no brain-dead donor legislation before 1997, and Japanese FAP patients had to go abroad to receive an orthotopic liver transplant.39 Although this procedure presents surgical challenges, FAP patients have fared as well as recipients of cadaveric organs.40 This has been of significant benefit to FAP patients awaiting liver transplantation.41 There is, however, the possibility of amyloidosis occurring in the recipient of a liver from an FAP patient. This was first reported in 2005, when systemic amyloidosis was reported in the recipient of an FAP liver 8 years after transplantation.42 The disease was typical of FAP neuropathy. Nerve and rectal biopsies revealed amyloid deposition. The patient underwent retransplantation with a cadaveric liver. It is now known that amyloid deposits can be detected by tissue biopsy in many FAP liver recipients.43,44 However, it is still unknown how frequently significant clinical disease will result and require a second transplant to reverse the amyloidosis. It has generally been speculated that FAP livers should be given to older recipients, as there

FIGURE 3. Low-power histologic section of cardiac left atrium showing the atrial wall of a transplanted heart (N) and the opposing atrial wall of the native heart (O) with fibrotic scar of the suture line in between (S). This patient, who was heterozygous for the Thr60Ala TTR mutation, died 12 years after combined heart and liver transplantation. No amyloid is present in the graft, whereas the native atrial tissue shows extensive amyloid deposition. (A) Congo red–stained section viewed under bright light. (B) Congo red section viewed with polarization demonstrating green birefringence of amyloid.

FIGURE 4. Histologic section of sciatic nerve from a patient who had progressive neuropathy after combined heart and liver transplantation. (A) Nerve stained with Congo red viewed under bright light. (B) Same section viewed with polarization showing green birefringence of amyloid.
would be a shorter lifespan for amyloid deposition. However, if the delayed adult-onset of FAP normally seen is the result of metabolic “aging factors,” then this speculation may have less substance than one would wish.

In conclusion, there is no easy answer for the FAP patient who seeks prolongation of life from liver transplantation. The best we can do is to present the facts that we have accumulated over the past 20 years, because transplantation remains the only specific therapy for FAP.

SUMMARY
1. Many FAP patients have benefited from orthotopic liver transplantation.
2. Benefit (life expectancy) is better for FAP patients with the Val30Met mutation.
3. Benefit is less obvious for FAP patients with non-Val30Met mutations.
4. Survival statistics are better for patients transplanted earlier in their disease course and for those <50 years of age.
5. Low modified body mass index (<600) is a negative predictor for benefit.
6. In patients with combined liver and heart transplantation, survival may be lengthened, but they should expect progression, although perhaps slower, of neuropathy.
7. Liver transplantation for FAP related to predominantly leptomeningeal amyloidosis should not be approached with high expectations.

New Therapies. At present, a number of studies are underway aimed at developing specific medical therapies for FAP. These include the use of small organic compounds to stabilize the TTR tetramer and inhibit amyloid fibril formation.46 One drug, tafamidis, has received approval in Europe for treatment of Stage I neuropathy.47 Another drug, diflunisal, is presently under investigation. siRNA and ASO (antisense oligonucleotide) drugs have been shown to inhibit hepatic amyloid fibrillogenesis. Transplantation 1998;66:229–233.

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