Chapter 1

Cardiac and Multi-Organ Transplantation in Patients with Amyloidosis

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Background

Amyloidosis is a group of diseases characterized by the extracellular deposition of a proteinaceous material in various organs and tissues, leading to progressive multiple organ failure and death. The 2 most common subtypes of amyloid that infiltrate the heart are: (1) immunoglobulin AL amyloid which is derived from an indolent clone of plasma cells and (2) ATTR amyloid. ATTR amyloidosis has two subtypes within its classification: familial ATTR which is caused by misfolding of a mutated TTR genes and senile systemic amyloidosis (SSAI which is a non-genetic disease caused by misaggregation of wild-type transthyretin. The presence of cardiac involvement and it relative predominance varies with the type of amyloidosis, tends to progress rapidly and has a very poor prognosis.
AL Amyloidosis

AL-amyloidosis is the most common form of the disease. In AL amyloidosis, the heart is affected in close to 50% of cases and amyloid deposition can progress very rapidly if untreated and myocardial walls can thicken at rates of up to 1.45–2.16 mm/month [1]. Heart failure is the presenting clinical manifestation in about half of these patients [2]. Even among patients in whom another organ system dysfunction predominates, the presence of cardiac amyloidosis is frequently the worst prognostic factor [3]. Once heart failure occurs, the median survival is < 6 month in untreated patients [2].

The overall survival of AL amyloidosis patients can be improved by the use of high dose chemotherapy and autologous stem-cell transplantation (ASCT) [4]. A recent study showed that patients with BNP <300 pg/ml and/or normal levels of troponin-I should be considered ASCT candidates [5]. In a retrospective analysis of 47 patients with AL amyloidosis and cardiac involvement, treatment with high-dose melphalan and ASCT resulted in cardiac response achievement in 53% of the patients [6]. Predictors of poor outcome were marked heart failure with wall thickening and left ventricular ejection fraction < 40%, elevated brain natriuretic peptide and elevated troponin and resulted in a 30% risk of peri-treatment mortality [7]. These factors were considered to be absolute contraindication to high-dose chemotherapy and ASCT [8-10].

A staging system incorporating troponin-t (TnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP) and plasma cell related characteristics with free light chain difference (involved and uninvolved) has been described in pivotal studies from the Mayo Clinic group and is crucial for prognosticating AL-amyloidosis and considering HTx [10]. More recently, Wechalekar et al [11] further stratified stage III patients based on BNP and systolic blood pressure (Table 1). Median survival ranged from 6 to 94 months based on these criteria [12], and although not definitive, these biomarkers may guide referral for HTx strategies in AL patients.

Table 1: Amyloidosis: HTx for AL Amyloidosis followed by ASCT - Reports of the Largest Case-Series to Date.

<table>
<thead>
<tr>
<th>Center</th>
<th>Transplanted</th>
<th>Time from HTx to ASCT (months)</th>
<th>Median F/U (months)</th>
<th>Number Survived at F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK (2006)[19]</td>
<td>5</td>
<td>13</td>
<td>95</td>
<td>3/5</td>
</tr>
<tr>
<td>Columbia University (2007)[21]</td>
<td>10</td>
<td>6</td>
<td>15</td>
<td>7/10</td>
</tr>
<tr>
<td>Mayo Clinic (2008)[23]</td>
<td>26</td>
<td>8</td>
<td>24</td>
<td>6/11</td>
</tr>
<tr>
<td>Heidelberg University (2009)</td>
<td>13</td>
<td>7</td>
<td>14</td>
<td>9/12</td>
</tr>
</tbody>
</table>

HTx for AL Amyloidosis

HTx for AL amyloidosis was first described in 1994 [13]. Early experience came from individual case reports and small series, which demonstrated that short- and medium-term mortality did not differ from that in other disorders [14,15]. However, reports generated from a survey of HTx centers in the USA, Canada and Europe
showed outcome were significantly inferior to those seen in cardiac transplantation for primary cardiomyopathy [15,16]. Survival at 4 years was 39% and systemic progression was seen in the majority of patients. The Heart Transplant Centers in the European consortium reported a 5-year survival of 38% in recipients with AL amyloidosis compared with 67% in recipients with heart failure due to non-amyloid causes [14]. UNOS published the largest series of patients [17] which included 69 cardiac transplantations performed at 24 different centers in the USA and found a 5-year survival of 54%. Based on these discouraging outcomes amyloid heart disease has been considered a contraindication for isolated heart transplantation and the need for adjunctive chemotherapy to suppress production of monoclonal light chains became obvious.

**Combined Organ Transplant: Heart and Bone Marrow Transplant**

In 2004, Skinner et al reported a complete hematologic response, defined as no evidence of an underlying plasma cell dyscrasia 1 year after treatment, in 40% of patients with primary AL amyloidosis who received high-dose melphalan followed by autologous stem cell transplantation [4,18]. More recently, combined transplantation with HTx along with chemotherapy/ASCT has been performed for AL amyloidosis and results from several centers have been published [19-24]. This treatment is feasible and prevents recurrence of amyloid in the cardiac allograft and progression of extra-cardiac disease, thus long-term remission and apparent improvement in long term survival can be achieved.

Gillmore [19] reported 5 patients with AL amyloidosis and predominant cardiomyopathy undergoing sequential HT followed by ASCT: three patients survived for more than 9 years without evidence of recurrence and 2 patients died of progressive amyloidosis at 33 and 90 months after HTx. This study also showed that relapse of the plasma cell dyscrasia after ASCT was associated with characteristic echocardiographic evidence of cardiac amyloidosis and rise in serum NT-pro-BNP. Maurer reported on 10 patients who underwent HTx for AL amyloidosis [21]; among 8 patients who received subsequent ASCT, 2 died from sepsis and lymphoma. The median survival from cardiac transplantation of 9.7 years in this series is comparable to US all-cause cardiac transplant survival.

The largest case series initially came from Mayo clinic and Massachusetts General Hospital. In report of Dey et al, five of eight patients who underwent sequential heart transplantation/ASCT were alive with a good functional status at a median follow-up of 56 months (range, 7–101 months). None had evidence of recurrent amyloidosis, and four remain in complete hematologic remission. The survival of these patients was 60% at 7 years, which is not significantly different from the outcomes of 17,389 patients collected in the ISHLT database of patients who underwent HT for non-amyloid heart disease during the same time [4].
In 2013 Gilstrap had analyzed 31 AL amyloidosis patients with end stage heart failure listed for HTx at Massachusetts General Hospital [25]. The long-term survival of amyloid patients who underwent HTx was no different from the post-HTx survival for non-amyloid causes. However, survival of AL amyloidosis patients on the waiting list was poor. Low body mass index was the only predictor of survival to OHT in patients with end-stage heart failure caused by cardiac amyloidosis.

Estep et al described the experience of the Methodist DeBakey Heart Center [26]. Four of the 9 end-stage cardiac amyloidosis patients underwent ASCT with a median time of 14 months between HTx and ASCT. There was 100% survival at 23 and 39 months post-HTx follow-up and no evidence of amyloid recurrence in the cardiac allograft endomyocardial biopsies.

A recently published analysis of 19 patients undergoing HTx at Stanford University Medical Center for amyloid cardiomyopathy between 2008 and 2013 [27], found that free light chain levels in these patients decreased by a median of 85% from peak values and only one patient developed recurrent asymptomatic graft amyloidosis 3.5 years post-HTx. After a median follow-up of 380 days, 17 (89.5%) patients were alive.

Mayo clinic published a series of 11 selected patients who underwent sequential HTx /ASCT and reported a 1- and 5-year survival of 82% and 65%, respectively [23].

The survival was comparable to patients undergoing heart transplantation for non-amyloid disease. Overall at Mayo clinic over a 20-year period, greater than 3000 patients were evaluated for AL amyloid, 668 patients (21%) had an overt heart failure and a highly selected group of 23 patients ultimately underwent HTx. Overall median survival was 3.5 years, whereas median survival for patients able to complete ASCT was 6.3 years, and for those achieving a complete remission, median survival was 10.8 years [28]. The most common cause of death after HT/ASCT was the recurrence of light-chain production and end-organ disease and dysfunction, including cardiac recurrence [4, 19, 23].

Thus, these data indicate that reasonable outcomes are achievable in patients with severe cardiac AL amyloidosis after HTx if underlying plasma cell dyscrasia is successfully treated afterward (Table 1).
Table 2: Evaluation of Extracardiac Organ Amyloid Light-Chain Amyloid Involvement.

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Screening tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>• Pulmonary function testing, including arterial oximetry, diffusion capacity</td>
</tr>
<tr>
<td></td>
<td>• Chest X-ray imaging and computed tomography to assess for interstitial disease, effusions</td>
</tr>
<tr>
<td></td>
<td>• Thoracentesis may be necessary to differentiate manifestations of amyloidosis from heart failure</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>• Nutritional assessment, including plasma pre-albumin, albumin</td>
</tr>
<tr>
<td></td>
<td>• Assessment for bleeding by esophagogastroduodenoscopy, colonoscopy</td>
</tr>
<tr>
<td></td>
<td>• Assessment of amyloid deposition by random biopsy</td>
</tr>
<tr>
<td></td>
<td>• Assessment of intestinal motility with gastric-emptying studies</td>
</tr>
<tr>
<td>Hepatic</td>
<td>• Serum alkaline phosphatase, bilirubin</td>
</tr>
<tr>
<td></td>
<td>• An alkaline phosphatase &gt; 1.5× upper limit of normal in the absence of congestion should prompt liver biopsy to assess for portal and parenchymal amyloid deposition. The presence of solitary vascular deposition should not be considered a contraindication to HT/ASCT</td>
</tr>
<tr>
<td>Renal</td>
<td>• Measured creatinine clearance or eGFR</td>
</tr>
<tr>
<td></td>
<td>• 24-hour urinary protein excretion</td>
</tr>
<tr>
<td>Coagulation</td>
<td>• Factor X and thrombin time</td>
</tr>
</tbody>
</table>

A eGFR or measured creatinine clearance < 50 mL/min/1.73 m² in the absence of decompensated heart failure or urinary protein excretion > 0.5 g/24 hours should prompt renal biopsy to assess the renal amyloid burden.

Reproduced from Mehra MR et al. [31].

Selection Criteria

Retrospective analyses and small prospective series have demonstrated the prognostic influence of organ involvement in AL amyloid patients receiving ASCT [29,30]. The assessment of amyloid involvement in potential HT/ASCT recipients must include both an evaluation of the anatomic extent of light-chain infiltration and the functional effect of the light-chain protein on organ function. The 2016 International Society for Heart Lung Transplantation listing criteria for HTx presented recommendations for assessment of extra-cardiac organ involvement in AL amyloidosis in addition to the usual studies performed to evaluate cardiac transplant candidates (Table 2) [31].

The baseline evaluation of all patients being considered for transplantation includes bone marrow aspirate and biopsy, an echocardiogram, serum and 24-hour urine monoclonal protein studies, immunoglobulin-free light-chain assay, a chemistry panel including creatinine and liver function tests, renal clearance estimates and neurologic evaluation [32]. In the Mayo Clinic series, selection criteria for cardiac transplantation included advanced cardiomyopathy, age under 60 years, and absence of myeloma or extensive extracardiac amyloidosis [23]. In the MGH data, however, in addition to advanced cardiac disease, extracardiac solid organ involvement by amyloidosis was present in all patients at the time of evaluation: all but one of the patients had evidence of amyloid deposition in the gastrointestinal tract, significant proteinuria was pre-
sent in two patients and peripheral neuropathy was present in three HTx patients. Monoclonal plasma cells comprised 5% to 10% of marrow cellularity [24]. In Stanford University Medical Center [27] patients with severe peripheral neuropathy were excluded. GI mucosal amyloid deposition was a relative contraindication to HTx if significant signs or symptoms of GI amyloidosis were absent. Low GFR was an indication for combined heart–kidney transplantation and asymptomatic myeloma was not an absolute contraindication to HTx. Similarly, The Methodist DeBakey Heart Center exclusion criteria for HTx included significant GI involvement, multiple myeloma and severe lifestyle limiting peripheral neuropathy [26].

Waiting Period

Unfortunately, patients with AL amyloidosis and severe heart failure have an extraordinarily poor prognosis on completing their cardiac transplant evaluation. Prolonged time without treatment may allow progression of the amyloidosis and therefore impair the candidacy and increase mortality while awaiting transplantation. Of the 31 patients that were listed for cardiac transplantation in the MGH series [25], only 18 (58.1%) survived to HTx. The only predictor of survival to HTx was a low body mass index, which correlated with a shorter time on the waiting list. In the Mayo clinic experience, of 54 patients evaluated, 27 patients were selected and listed for HTx but 9 died while on the waiting list and 6 were removed from the list due to progressive disease. Only 11 patients (20%) underwent cardiac transplantation. In the study of Sattinayagam et al, less than 2% of all patients with systemic AL amyloidosis assessed at the UK National Amyloidosis Center underwent cardiac transplantation [33]. Overall it appears that the waiting list mortality for cardiac amyloidosis may be 3-fold higher than that noted for patients with an idiopathic DCM.

Poor waiting list prognosis has led to strategies involving the earlier application of plasma-cell-targeted treatment in an attempt to produce a remission in the disease. This improvement may result from the abolition of the production of freshly produced light chains, which have been shown to be toxic to myocardial cells, suggesting that AL amyloidosis is not simply an infiltrative cardiomyopathy but rather a toxic infiltrative disorder [9,34,35].

In selected patients treated with chemotherapy before HTx, a clinical improvement in heart failure despite an unchanged echocardiographic appearance has been reported [22]. In Stanford University Medical Center, 8 of 9 patients with AL amyloidosis began chemotherapy prior to HTx [27]. At the UK National Amyloidosis Center five patients received chemotherapy and achieved a partial hematologic response before HTx [33]. Similarly, selected patients at Mayo clinic and at MGH received systemic therapy consisting of melphalan and prednisone before HTx.

The use of vigorous chemotherapy in patients with AL cardiac amyloidosis, however, is associated with significant risk of death. Newer agents, such as bortezomib and
lenalidomide, beginning at the time of the evaluation process are effective and better tolerated than conventional chemotherapeutic agents, and improve patients’ chances for receiving a HTx [33,36]. A similar approach may also be considered for patients who are not ready for ASCT after HTx.

**Timing of ASCT After the Heart Transplantation**

The optimal timing of ASCT after the heart transplantation is debatable. Pursuing ASCT too soon may be problematic and increase the risk of infections if the patient continues to require intensive immunosuppression to prevent organ rejection. This suggests that a patient’s background immunosuppression be relatively low before ASCT to minimize the risk of infection. Waiting too long, on the other hand, may result in the amyloidosis progressing in other organs. Therefore, at the present time, it is recommended that ASCT be pursued approximately 6-7 months after HTx [4,23,24]. A positive experience with deferring ASCT to 1 year post HTx has been described [26]. Novel treatment algorithms, including the combination of cytotoxic drugs with proteosome inhibitors and immunomodulatory agents, may come to represent definitive therapy for AL amyloidosis in selected patients and is less toxic than ASCT [37]. Treatment with the newer agents may also be considered for patients who are not ready for ASCT after HTx.

**Recurrence of Cardiac Amyloidosis**

Although in the UK study the patients were followed for 2-6 years with serial endomyocardial biopsies with no evidence of recurrent amyloid deposition during this time [37], five of the 11 patients reported by Lacy et al. demonstrated biopsy-proven recurrence in the cardiac allograft. Interestingly, none of these patients had symptoms, echocardiographic evidence, or biochemical evidence of cardiac amyloidosis [23]. A similar observation was reported by Dey et al [4], demonstrating that amyloid deposition in their heart transplant patients has had little clinical consequence, with no echocardiographic evidence of amyloid cardiomyopathy. At the Stanford University Medical Center [27], only one AL patient developed asymptomatic recurrent graft amyloidosis, diagnosed by biopsy at 3.5 years post-HT.

By contrast, Gilmore showed that relapse of the plasma cell dyscrasia after ASCT was associated with characteristic echocardiographic evidence of cardiac amyloidosis and rise in serum NT-pro-BNP [19]. The varying results may be secondary to multiple factors, including the type of chemotherapy used, the timing of ASCT following heart transplant, the type of underlying plasma cell dyscrasia as well as individual patient factors [38]. Nevertheless, recurrent disease despite aggressive multimodality therapy is a reminder that it may be difficult to prevent recurrent protein deposition in patients with AL amyloidosis.
Although conclusions are limited by the small sample size, it is likely that ASCT following cardiac transplantation results in a lack of clinically significant recurrent amyloidosis and prolongs the interval of disease recurrence in the cardiac allograft. However, it is possible that future survival of patients with disease recurrence in the cardiac allograft beyond the time described may be limited [4].

**Combined Heart and Kidney Transplantation in Patients with AL Amyloidosis**

AL amyloidosis is a multi-organ disease and the proportion of patients with cardiac AL amyloidosis and minimal systemic disease at the time of diagnosis is less than 5% [2]. Cardiac amyloidosis frequently coexists with renal involvement which is characterized by nephrotic proteinuria and progressive worsening of renal function. There are few published cases of combined organ transplantation in patients with AL amyloidosis with good outcomes and no evidence of recurrence [4,39].

**Conclusions**

In selected patients for whom heart failure is the major manifestation of the AL amyloid, HTx combined with chemotherapy/ ASCT offers a good prognosis with long-term (5-year) survival of approximately 60%. A multidisciplinary approach dedicated to early diagnosis, appropriate and timely screening for heart transplantation and a multimodality plasma cell dyscrasia - specific strategy is essential. Clinical trials are required to clarify which patients are most likely to achieve durable remissions after HTx and which chemotherapy strategy and its timing is most effective to eradicate the plasma cell clone.

**Transthyretin (TTR) Amyloid**

**Introduction**

TTR, formerly known as prealbumin, is a 127-amino acid, 56-kDa transport protein. Under normal conditions, TTR circulates as a homotetramer, but because of genetic mutation or aging, tetramers can dissociate to monomers that misassemble into amyloid fibrils and deposit in several organs causing systemic disease [40]. Transthyretin related amyloidosis encompass 2 forms of disease: 1) familial disease, a fatal autosomal-dominant multisystem disorder induced by deposition of abnormal serum TTR which is synthesized mainly by the liver and 2) wild-type (non-genetic) disease, caused by misaggregation of TTR (senile systemic amyloidosis, SSA), which affects mainly the hearts of elderly men.

**Liver and Heart Transplantation in ATTR Amyloidosis**

Amongst the over 100 mutations described in familial amyloidosis, the Portuguese variant (ATTR Met30) is the most frequent and rarely associated with cardiomy-
Amyloidosis

opathy. Liver transplantation (LTx) is established as the treatment of choice for ATTR Met30 with stabilization and remission of symptoms after replacement the major organ synthesizing variant TTR. LTx was first undertaken by Sweden’s Karolinska Institute in 1990 and by Deaconess Hospital, Boston, MA, in 1991 [41]. Over the ensuing 20 years, transplant centers have voluntarily posted 1844 LTx on the FAP World Transplant Registry (http://www.fapwtr.org), with 911 (49%) reported by Portugal, 235 (12.7%) by France, 137 (7.4%) by Sweden, 97 (5.3%) by Brazil, 83 (4.5%) by the United States, and 80 (4.3%) by the United Kingdom. The vast majority of LTx have been performed in V30M ATTR patients (94.3%), with non-V30M ATTR limited to 5.7% of the transplanted population. The Karolinska Institute subsequently reported a single-center experience of 141 transplantations with 10- and 15-year survival rates of 83% and 60%, respectively, significantly better than a medically treated control cohort (62% and 19%, respectively) [42]. In 2004, Herlenius et al [43] published data on survival after LTx in 449 V30M ATTR patients and 62 non-V30M ATTR patients, reporting 85% 5-year survival in V30M and 60% 5-year survival in non-V30M patients. Cumulative data on 579 LTx performed over the first 10 years of FAP World Transplant Registry listing indicated a 5-year survival rate of 77% with a high percentage of cardiac deaths (39%) [43].

Reports of progressive cardiac infiltration after LTx began circulating 6 years after the first transplant in the United States, initially identifying those with non-V30M ATTR as the at-risk population [44]. Later, however, V30M ATTR patients were also noted to experience similar progression [45]. Heart biopsy from patients with progressive cardiomyopathy after LTx revealed increased deposition of wild-type TTR fibrils suggesting wild-type ATTR constitutes amyloid in the heart similar to the phenomenon observed in senile systemic amyloidosis [46-48].

Progression of pre-existing amyloid cardiomyopathy following LTx prompted consideration of combined heart and liver transplantation (CHLTx). The first case of CHLTx in familial amyloidosis patients was reported in 1995 by Rela et al, however, the world-wide experience is still small. To date, the FAP World Transplant Registry lists 26 patients who underwent CHLTx, including 16 simultaneous and 9 sequential heart and liver transplantations. CHLTx experience has been analyzed for ATTR disease in the United Kingdom and the 5-year survival has been shown to be comparable with survival after transplantation for other diseases suggesting that this procedure should be indicated for several non-ATTR Met30 variants with recognized risk for progressive amyloid cardiomyopathy [44]. A relatively large series from Mayo Clinic [49] demonstrates the feasibility and excellent short and long term success that can be achieved with CHLTx for selected high-risk patients with familial amyloidosis. Indeed, patient survival after combined heart and liver transplantation was shown to be equivalent to those with isolated heart and isolated liver transplantation (Figure 1).
In the Mayo Clinic study, among 11 patients with ATTR amyloidosis, the most frequent mutations were ALA 60 (4), and TYR 77 (3), followed by PRO 24 (1), SER (1) and ASP 18 GLU (1). The specific ATTR mutations did not affect the therapeutic success of CHLTx. Interestingly, ALA 60 ATTR has been reported as a mutation of particularly poor prognosis and five of eight patients with ALA60 mutation described in the literature have died after isolated LTx [50,51]. Moreover, the Tyr 77 ATTR (German variant) mutation is also typically associated with prominent and progressive cardiac involvement after isolated LTx [52]. In the Mayo Clinic report 3 of the 4 patients with ALA 60 ATTR mutation remain alive and one died of progressive renal failure; three patients with the TYR 77 ATTR variant remain alive and had no amyloid deposition on endomyocardial biopsies [49].

Important factors to consider in the preoperative evaluation include autonomic disturbances, modified body mass index, duration of symptoms, polyneuropathy, disability score, orthostatic hypotension, gastrointestinal and urinary tract dysfunction [51,53,54]. Additionally, optimizing the timing for CHLTx appears to be crucial.

There are five isolated HTx described in literature for SSA of which the oldest recipient was a 77-year-old Korean man, who survived up to 4 years without biopsy evidence of amyloid recurrence in the transplanted heart [55,56].

**Acute Cellular Rejection**

Acute cellular rejection of the liver is infrequent in combined heart and liver transplantation [49]. The more aggressive immunosuppression regimen employed for combined heart and liver transplantation compared with that used for isolated liver transplantation may make rejection of liver allografts a relatively infrequent event. Inter-

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**Figure 1:** Survival for FA patients after CHLTx. Survival rates for FA patients at 1 month, 1 year, 5 years and 10 years were 100%, 100%, 75%, and 60% and did not differ from IHTx (97%, 93%, 83% and 65%, p=0.39, Log-Rank test). IHTx – isolated heart transplantation. CHLTx – combined heart and liver transplantation. Reproduced from Raichlin E et al. [49].
estingly, heart rejection was less frequent in CHLTx than in those receiving isolated HTx. One proposed mechanism to explain the favorable low rejection rate is an induction of partial tolerance due to the liver transplant. The liver has been demonstrated to permit acceptance of other simultaneously transplanted organs due to shedding soluble HLA antigens [57,58]. It has been hypothesized that maintaining a concentration of soluble HLA in the circulation would lead to tolerance to the allotype of the soluble HLA. This concept may help explain the protection of a simultaneous heart transplant by a successful human liver transplant [59]. Therefore, less intensive immunosuppression therapy for these patients after combined heart and liver transplantation than for IHTx may be justified.

Use of Amyloidotic Livers for Domino Liver Transplantation

Livers explanted from patients with familial amyloidosis (FA) contain only microscopic amyloid deposits and are otherwise essentially normal. It typically takes approximately 50 years for TTR deposition to progress to clinically apparent disease, therefore, the FA liver can be used as a domino donor liver for selected older patients awaiting liver transplantation. Combined heart and liver transplantation does not preclude domino donation of FA recipients’ liver. In contrast to caval sparing hepatectomy with an anastomosis between the donor suprahepatic cava and the recipient left/middle hepatic vein trunk, caval excision with veno-venous and portal-venous bypass has been employed for FA patients serving as domino liver donors. None of the domino donors have experienced any technical problems related to donation or veno-venous and porto-venous bypass [49,60].

Pharmacological Treatment for ATTR

Whereas liver and heart transplantation remain the established treatment for variant TTR–related amyloid neuropathy and cardiomyopathy, the availability of a pharmacological treatment for ATTR is a milestone in the field. Several small-molecule drugs including doxycycline, diflunisal, tafamidis, antisense and si RNA are under clinical evaluation and may prove effective alternatives to surgery. The role of new and developing medical treatments for ATTR gene carriers remains to be established.

Conclusion

Combined heart and liver transplantation for ATTR familial amyloidosis is a successful therapy for this disease and can be performed safely, with a acceptable level of morbidity. Given the 10-year survival of 60% with an associated freedom of rejection of 83%, the procedure is consistently curative in patients with ATTR familial amyloidosis and cardiac involvement. Specific ATTR mutations do not affect outcome. Gene-based therapy are a promising future strategy for TTR amyloidosis and may prove effective alternatives to surgery for both TTR-FAP and SSA.
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