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Review

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Amyloid diseases of the heart: current and future therapies

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Summary

Amyloid diseases in man are caused by as many as 23 different pre-cursor proteins already described. Cardiologists predominantly encounter three main types of amyloidosis that affect the heart: light chain (AL) amyloidosis, senile systemic amyloidosis (SSA) and hereditary amyloidosis, most commonly caused by a mutant form of transthyretin. In the third world, secondary amyloid (AA) is more prevalent, due to chronic infections and inadequately treated inflammatory conditions. Much less common, are the non-transthyretin variants, including mutations of fibrinogen, the apolipoproteins apoA1 and apoA2 and gelsolin. These rarer types do not usually cause significant cardiac compromise. Occurring worldwide, later in life and of less clinical significance, isolated atrial amyloid (IAA) also involves the heart. Heart involvement by amyloid often has devastating consequences. Clinical outcome depends on amyloid type, the extent of systemic involvement and the treatment options available. An exact determination of amyloid type is critical to appropriate therapy. In this review we describe the different approaches required to treat this spectrum of amyloid cardiomyopathies.

Introduction

Amyloid involvement of the heart is defined by demonstrating the presence of amyloidosis using endomyocardial biopsy combined with clinical and laboratory evidence of involvement.[1,2] Additionally, echocardiographic evidence for mean left ventricular wall thickness of >12 mm, in the absence of other causes, and a tissue biopsy demonstrating amyloid at an alternate site also suffice. A further clue to cardiac involvement by amyloid is a mean voltage of <0.5 mV in all limb leads, and/or an elevated (>332 ng/l) concentration of N-terminal pro B-type natriuretic peptide (NT-proBNP) in the absence of renal failure or atrial fibrillation.[2] In many clinical contexts brain natriuretic peptide (BNP), rather than NT-proBNP is used, largely on the grounds of cost.

Broadly, treatment aims are two-fold, supportive care for the patient with amyloid cardiovascular disease and therapy to abrogate the amyloid process, usually by reducing the abundance of the individual pre-cursor protein. The reduction of 'monomer' units reduces the supply of amyloid-forming proteins, diminishing the concentration of potentially toxic soluble oligomeric intermediates and impairing the further deposition of amyloid fibrils.[3,4] Many pre-cursor proteins actually circulate as dimeric units.[5]

The types of amyloidosis discussed in this review are listed in Table 1. In AL amyloidosis the fibrils are

Table 1 Amyloid type and degree of heart involvement

Amyloid type	Amyloid sub-units	Extent of heart involvement
AL	Immunoglobulin light chains	Frequent and severe
ATTR (familial)	Mutant transthyretin	Severe with particular mutations (Leu55Pro, Val30Met, Val122Ile, Tyr78Phe)
SSA (sporadic)	Wild-type (non-mutant) transthyretin	Severe heart involvement possible
AFib (familial)	Mutant fibrinogen	Severe heart involvement can occur
Apo A1 (familial)	Mutant apolipoprotein A1	Severe heart involvement can occur
AA	Amyloid protein A	Rare, but severe heart involvement can occur
IAA	Atrial natriuretic peptides	Severe heart involvement possible in the elderly

AFib, hereditary fibrinogen amyloidosis; Apo A1, hereditary apolipoprotein A1 amyloidosis.

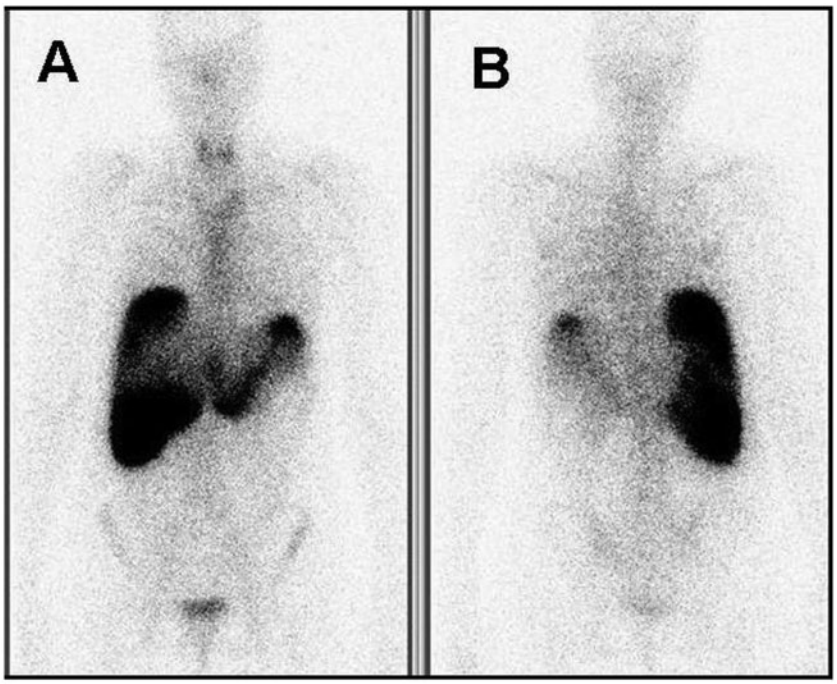

Figure 1. Iodine-123 labelled SAP scan showing tracer uptake in the liver and spleen. **A**, anterior view; **B** posterior view. [Reproduced with permission from *Am Soc of Haematology*[22]

derived from immunogloblulin free light chains (FLC) produced from a monoclonal B-cell process usually involving a clone of plasma cells but occasionally involving a mature B-cell lymphoma. Treatment has centred on reducing or eliminating the free light chains (FLC) by attacking the cells that produce them. The ability to measure light chain levels has now enabled therapies to be tailored to individual patients and response to therapy to be gauged.[6–8] Serum amyloid P (SAP) scintigraphy in more than 3000 patients has now shown that suppression of the underlying disease process often results in regression of amyloid deposits (Figure 1).[9] Amyloid deposits appear 'fluid' and amenable to 'dissolution' but in practice recovery of organ function is often slow and delayed, lagging behind control of the pre-cursor protein by months.[10]

General cardiovascular management for amyloid heart disease

Amyloid involvement of the heart causes a restrictive cardiomyopathy associated with reduced

cardiac output. In combination with autonomic dysfunction, hypoalbuminaemia and in rare cases adrenal failure, this can result in cardiovascular collapse. With respect to pharmacologic management of cardiac dysfunction, one must be cautious in the use of vasoactive medications in patients with amyloid heart disease due to complications associated with a 'stiff' under-filled heart. Diuretics are the mainstay of therapy but their use incurs the risk of exacerbating hypotension and further compromising cardiac output; frequent clinical monitoring and dose adjustments are required. Salt intake should be limited and fluid status monitored with daily weight measurements. Peripheral oedema can be helped with support stockings. Hypotension may require fludrocortisone, or the more potent alpha-agonist midodrine. Concomitant renal, liver and gastrointestinal amyloidosis will contribute to hypoproteinaemia and symptoms of light headedness, pre-syncope and fatigue with minimal exertion. Patients must be taught to change position carefully from lying to sitting, sitting to standing and standing to walking in order to allow their cardiovascular system to equilibrate.

Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are poorly tolerated and can result in profound hypotension. This may reflect vascular tone being disproportionately dependent on angiotensin receptors due to impaired sympathetic nervous system function.[11] Negative inotropes, such as calcium channel blockers have no standard role in the management of these patients,[12] although low doses of beta blockers may be used to stabilize filling and manage arrhythmic tendencies. Digoxin binds to amyloid fibrils and can result in accumulation and toxicity;[13] its use is contra-indicated, except in low dose for the control of atrial fibrillation. No studies have reported on bi-ventricular pacing in amyloid heart disease but this procedure should theoretically be of benefit.

Cardiac arrhythmias are common but anti-arrhythmic medications, pacemakers for atrio-ventricular (AV) block[14] and automatic implantable cardio-defibrillators (AICDS)[15] have proved less than successful in preventing dysrhythmias or death.[16] This is largely due to most cases of sudden death in cardiac amyloidosis being caused by electro-mechanical dissociation. The Mayo Clinic reported on 53 patients (33 AL, 10 senile, nine familial and one AA) with amyloid cardiomyopathy who underwent AICD implantation. Although a high rate of appropriate AICD shocks were delivered, almost exclusively to the AL group, this therapy did not appear to translate into an overall survival (OS) benefit.[17]

Systemic AL amyloidosis

Staging for AL cardiac involvement is a critical part of the initial evaluation. Criteria for the assessment of organ involvement at baseline and of organ response after treatment have been standardized (Table 2).[1] Prognosis in systemic AL amyloidosis remains a function of the extent of cardiac involvement, with median survival of 6 months for untreated or non-responding patients with symptomatic cardiac AL.[18,19] Patients with cardiac involvement can present with fatigue, progressive dyspnea on

Table 2 Organ response and progression criteria in AL amyloidosis

Organ	Response	Progression
Heart	**NT-proBNP response** (>30% and >300 ng/l decrease in patients with baseline NT-proBNP ⩾650 ng/l) or **NYHA class response** (⩾2 class decrease in subjects with baseline NYHA class 3 or 4)	**NT-proBNP progression**[a] (>30% and >300 ng/l increase)[a] or **cTn progression** (⩾33% increase) or **ejection fraction progression** (⩾10% decrease)
Kidney	**50% decrease (at least 0.5 g/day) of 24-h urine protein** (urine protein must be >0.5 g/day pre-treatment). Creatinine and creatinine clearance must not worsen by 25% over baseline	**50% increase (at least 1 g/day) of 24-h urine protein** to >1 g/day or 25% worsening of serum creatinine or creatinine clearance
Liver	**50% decrease** in abnormal alkaline phosphatase value. **Decrease in liver size** radiographically at least 2 cm	**50% increase** of alkaline phosphatase above the lowest value
Peripheral nervous system	Improvement in electromyogram nerve conduction velocity (rare)	Progressive neuropathy by electromyography or nerve conduction velocity

[a]Patients with progressively worsening renal function cannot be scored for NT-proBNP progression.

exertion, findings of diastolic dysfunction, an echocardiographic appearance of left ventricular 'hypertrophy' in the absence of hypertension, and low voltage on electrocardiogram.[16] Serum troponins (I or T) and B-type natriuretic peptides (either BNP or NT-proBNP) are highly sensitive markers of cardiac involvement, and normal values exclude clinically significant cardiac amyloid.[20] Cardiac MRI is emerging as a useful tool, particularly in patients with left ventricular hypertrophy and prior hypertension or valvular heart disease, although large studies defining its role are lacking at this time.[21]

The cardiac biomarkers NT-proBNP and troponin T (or I) are prognostic with respect to survival in AL patients.[18] A cardiac risk assessment or 'cardiac staging' system incorporating these biomarkers is currently in use, with patients assigned to stage I, II or III based on the presence of 0, 1 or 2 of the biomarkers exceeding threshold levels (NTpro-BNP > 332 ng/l; troponin T > 0.035 μg/l).[18,19] Patients in these three stages differ significantly with respect to survival (Figure 2).[18] At this time, biomarker criteria for clinical cardiac improvement and progression after therapy are being incorporated into the consensus criteria for organ response.[2] Post-therapy, in patients with cardiac involvement, a >30% reduction and a >300 ng/l decrease in the NT-proBNP level from baseline correlate with improved OS while increases of that magnitude correlate with progression and worse survival (Figure 3).[22]

Therapies for AL are aimed at eliminating the clonal plasma cells producing the toxic pre-cursor protein, resulting in the achievement of a haematologic response.[23] With current approaches kidney

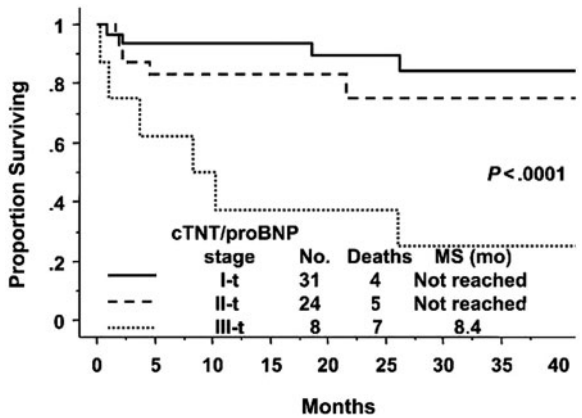

Figure 2. The survival of AL SCT patients by cardiac stage is shown. Staging is defined by NT-proBNP and troponin T thresholds of 332 pg/mL and 0.035 ng/mL: stage I both NT-proBNP and troponin T under, stage II either over, and stage III both equal to or over, threshold. [Reproduced with permission from *Blood* 2004; **104**:1881–7].[18]

and liver organ responses occur even in those who achieve a partial haematologic response (a ⩾50% reduction in the involved immunoglobulin free light chain (iFLC) protein). In one series, achievement of a > 90% reduction in the iFLC or of a complete haematologic response (CR) was associated with organ improvement over 90% of the time.[24] Organ responses can lag 6–12 months behind haematologic response (reduction of the iFLC), necessitating aggressive supportive care and collaborative management with other subspecialists, particularly in patients with advanced cardiac or renal involvement. The organ response rate for patients with cardiac involvement, however, is the lowest of all organ systems, in part perhaps, because the criteria for cardiac response have included echocardiographic changes in wall thickness or ejection fraction (Table 2).[1]

Oral melphalan and dexamethasone (MDex) is a standard front-line therapy, inducing a haematologic response 67% of the time with 33% CR in a phase II study of 45 patients.[25] An update of this cohort with 5-year follow-up showed impressive median progression free and OS periods of 3.8 and 5.1 years, respectively.[26] Subsequent studies have confirmed the activity of this regimen,[27] although outcomes for symptomatic AL patients with advanced cardiac involvement remain relatively poor (median OS 10.5 and 17.5 months).[28] High-dose melphalan (HDM) with autologous stem cell transplant (SCT) is also a standard front-line therapy. High rates of haematologic and organ response have now been documented at multiple centres and median survivals of over a decade seen for SCT patients achieving complete response.[29,30] Enthusiasm for SCT has been tempered by the high treatment-related mortality (TRM).[31,32] Risk-adapted SCT, which tailors the dose of melphalan conditioning to the age and risk status of the patient, may improve early survival with a TRM of 4% in a phase II study.[31] To compensate for the loss of efficacy related to attenuated conditioning, adjuvant therapy post-SCT for patients not achieving a CR has been tested and shown to improve haematologic response. Both thalidomide and dexamethasone (TD) and bortezomib and dexamethasone (BD) have been studied as adjuvant therapy post-SCT. Complete response rates at 12 months post-SCT were achieved in 39 and 65% of evaluable patients, respectively, on these two studies with high rates of organ improvement.[31,32] An up-dated analysis of survival on the adjuvant TD trial showed 69% of patients alive with a median follow-up of 52 months (Figure 4).[33]

Despite such success, only a quarter of newly diagnosed AL patients are candidates for melphalan at dose levels of 140 or 200 mg/m^2. Indeed, the

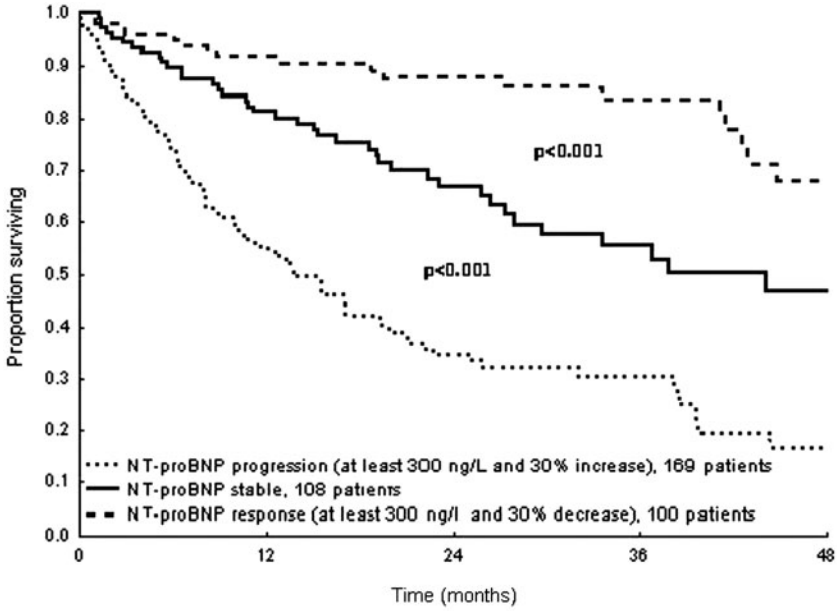

Figure 3. New cardiac biomarker criteria OS curves. Survival of 377 patients with AL amyloidosis and baseline NT-proBNP $\geqslant$650 ng/l according to NT-proBNP response and progression at 6 months. [Reproduced with permission].[22]

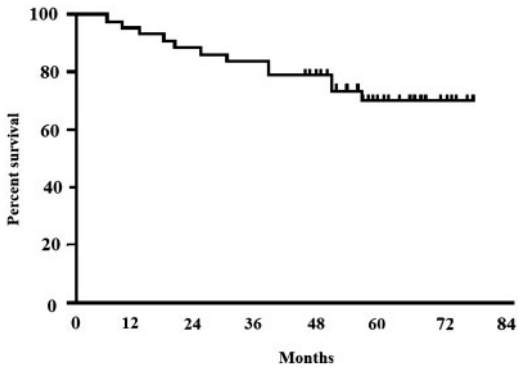

Figure 4. Up-date survival is shown for AL patients undergoing stem cell transplantation and then receiving adjuvant TD therapy if clonal plasma cell disease persists. With median follow-up of 52 months, 69% of patients survive. [Reproduced with permission from *Blood* 2009; **114**:3147–57][33]

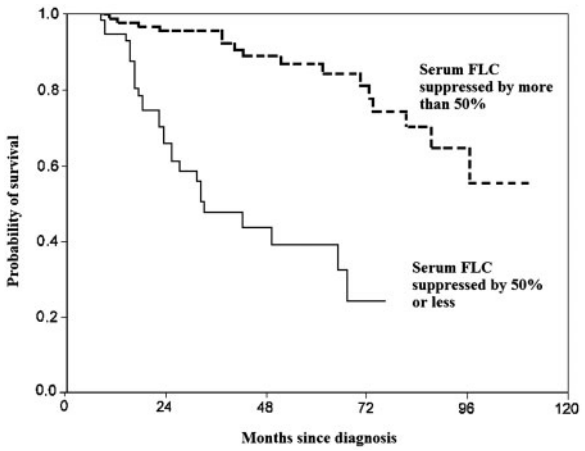

Figure 5. OS, in patients with systemic AL amyloidosis, with a 50% reduction in free immunoglobulin light chains [Reproduced with permission *Br J Haematology* 2003; **122**(1):78-84].[7]

outcomes reported above with SCT reflect selection bias. The two front-line therapies, MDex and SCT, were compared by the French Myélome Autogreffe Groupe (MAG) in a multi-centre randomized phase III trial in newly diagnosed AL patients. There were no significant differences in haematologic or organ responses but median OS was significantly better in the MDex arm (56.9 vs. 22.2 months, $p=0.04$).[27] However, 22 of the 50 patients assigned to SCT (44%) were not evaluable for response or long-term survival, including 13 who never received SCT due to death or progression and nine who died peri-SCT. A reduction in amyloidogenic FLC by more than 50% results in a substantial survival benefit, regardless of chemotherapy used (Figure 5).[7]

Recently, Sanchorawala *et al.* reported on 201 patients ineligible to receive HDM due to significant organ dysfunction and an age over 65 years. Patients who received modified melphalan doses (140 mg/m^2) and STC had a median survival of 42 months compared with 27 months in patients receiving a lower dose of melphalan (100 mg/m^2)

and SCT. For 49 patients achieving a complete haematologic response the median survival was 112 months (9.3 years), a truly durable remission with prolonged survival from a modified melphalan regime.[34]

In terms of demonstrating regression of cardiac involvement, the Boston University amyloid research group reported a reduction in left ventricular wall thickness of 1.07 ± 1.98 mm in patients ($n = 21$) with a complete haematologic response to HDM and peripheral blood stem cell transplantation. Patients without a complete haematologic response ($n = 34$) showed an increase in wall thickness of $0.37 + 2.21$ mm ($p = 0.0018$).[35] The Mayo Clinic reported a conventional cardiac response in 30% (overall haematological response rate of 69%) in 187 patients undergoing treatment with HDM and SCT.[36]

The first novel agent to be investigated in relapsed AL was thalidomide. It was not tolerated at high doses but when used in combination with dexamethasone as adjuvant therapy after risk-adapted melphalan and SCT it showed efficacy at a median dose of 150 mg daily with improved haematologic responses in almost 50% of patients.[31,37–39] The combination of oral cyclophosphamide, thalidomide and dexamethsone (CTD) showed promise in the relapsed setting. In a single-centre retrospective series of 122 newly diagnosed patients (48% with heart involvement) CTD had high haematologic response rates with a median time to response of 2 months and 74% survival at 3 years.[40] Unlike MDex, CTD can be used as a prelude to SCT because it is not toxic to bone marrow stem cells but the side effects of thalidomide, particularly neuropathy, bradycardia and congestive heart failure, remain considerable.

Similarly, full-dose lenalidomide had significant toxicity in phase II clinical trials. Dose reductions or discontinuation were required and the drug was better tolerated at 15 mg/day in combination with weekly dexamethasone (LenDex), with haematologic response rates of 40–50%.[41] In recent reports on over 100 patients with relapsed AL receiving LenDex, a 52% haematologic response rate with 16% CR, median OS of ~2 years and, in those achieving CR, progression free survival of over 3 years was observed.[42,43] Phase I/II studies combining LenDex with oral melphalan or cyclophosphamide have been conducted; dose modifications of the myelosuppressive agents were required and response rates were not substantially different from those seen with MDex.[44] The combination of LenDex has also been successfully used as salvage therapy for AL patients who have relapsed to $\geqslant 2$ prior therapies, with a haematologic response rate of 41%.[45]

In a phase II study of pomalidomide with weekly dexamethasone (PomDex), a haematologic response was observed by 6 months of PomDex in a third of heavily pre-treated relapsed AL patients, highlighting the promise of pomalidomide.[46] A notable aspect of immunomodulatory (IMiD) therapy in AL, however, is the rise seen in cardiac biomarkers that appears to correlate with worsening cardiac status, particularly in patients with high cardiac biomarkers at baseline.[47,48] Moreover, most patients receiving IMiDs experience increases in cardiac biomarkers irrespective of their haematologic responses.[48] This likely represents direct or indirect drug-related cardiotoxicity and should lead to discontinuation of the IMiD.

Heart transplantation

Cardiac transplantation does not affect the underlying systemic disorder. Several studies describe progressive amyloid deposition both systemically and in the graft, which will continue unless the underlying plasma cell dyscrasia is addressed.[49,50] The UK experience of 17 patients with AL amyloid showed that regardless of the use of adjunctive chemotherapy, the 5-year survival after heart transplantation for cardiac AL amyloidosis was generally poorer than following heart transplantation for other indications.[49] Progression of the systemic disease contributed to the increased mortality. Initial experience from the United States was disappointing in AL patients undergoing heart transplantation, but few, if any of these early patients had subsequent treatment of their plasma cell dyscrasia.[51] In 2005, the US experience was summarized for a total of 69 patients transplanted between 1987 and 2001. The 1- and 5-year survival values were 74.6 and 54%, respectively, although it is unclear as to what chemotherapy was used and the constituent amyloid types.[52] In the light of heart transplantation not achieving 'a cure' and a shortage of donor organs, a need emerged for more 'curative' therapies to be combined with cardiac transplantation.

Heart transplantation with chemotherapy and autologous stem cell transplantation

A study from the UK describes five patients undergoing combined sequential transplants, three of which were well at censor without evidence of intracardiac or extracardiac amyloid deposition. Two patients died of progressive amyloidosis at 33 and 90 months post heart transplantation after relapse of their plasma cell dyscrasia.[53] Kristen *et al*. describe 12 AL patients who, after heart transplantation, received HDM and stem cell transplantation

(if not in remission) or melphalan and prednisolone (for partial remission). The 1- and 3-year survival rates were both 83%. The survival rates in those with complete or partial haematological response were 100% at 1 and 3 years. There were no survivors in those with progressive disease.[54] The poor prognosis in AL heart disease is illustrated by the fact that seven of their original 19 patients died while waiting for heart transplantation. A French study reported on eight patients who received chemotherapy, including HDM and ASCT either before or after heart transplantation. Six were alive at 26 months with four exhibiting a sustained haematological remission.[55] A German study of seven patients with AL (and five patients with amyloid transthretin (ATTR) amyloidosis) who were successfully transplanted demonstrated an actual survival rate of 91.6%. Disease modifying chemotherapy and SCT was given to five of the seven AL patients (and one ATTR patient received a liver transplant). Three AL patients showed complete remission of amyloidosis.[56]

Investigators from the Mayo Clinic described 11 patients who underwent cardiac transplantation followed by autologous STC. All subjects received conditioning chemotherapy with either high ($n=6$) or intermediate ($n=5$) dose melphalan. Two patients died of complications from STC. Of the nine survivors, the 1- and 5-year survivals were 82 and 65%. Three patients subsequently died of progressive amyloidosis at between 55 and 66 months.[57]

Investigators at the Columbia Presbyterian Medical Centre, New York, New York described their experience with cardiac transplantation in 12 patients (ten with AL and two with FAP), including eight patients with AL amyloidosis who 6 months after their cardiac transplant underwent high-dose chemotherapy with SCT. Two familial patients underwent liver transplantation in addition to heart transplantation. The 1-year survival of the group was 75%, compared to 25% in patients who were evaluated but did not receive a heart. It should be emphasized that 'extended-donor' criteria were used for the hearts transplanted into these patients.[58] Aside from these series there are limited individual cases describing patients who have responded to conventional MDex followed by cardiac transplantation.[59]

In addition to the heart, the kidney and liver are frequent targets for amyloid deposition. In patients with AL amyloidosis the survival at 1 and 5 years following liver transplantation is far poorer at 33 and 22% than compared to kidney transplantation at 95 and 67%, respectively.[60] For comparison, the survival for heart transplant patients evaluated at the same unit, over an identical follow up, was 86 and 45%.[60]

Newer disease modifying therapies

Based on their success in multiple myeloma, a large number of trials are currently reporting on the use of various combinations of thalidomide, lenalidomide (a potent analogue of thalidomide),[61–65] bortezomib,[66,67] and melphalan or cyclophosphamide,[66] in combination with dexamethasone for AL amyloidosis.[44,68] These trials include 'de novo' management, combination therapy with SCT,[67] and regimens in patients considered unsuitable for SCT,[66] or for 'salvage' therapy in relapsed cases.[43,45,64,69]

The proteasome inhibitor bortezomib has proved effective in relapsed multiple myeloma,[70] and is now being intensively studied in AL amyloidosis.[71] Bortezomib is a reversible inhibitor of the chymotryptic site in the 20S proteasome. Inhibition of the degradation of ubiquitinated proteins causes a 'jam-up' in the endoplasmic reticulum, triggering apoptosis in clonal plasma cells. The increased sensitivity of clonal plasma cells to proteasome inhibition may be due to their 'professional secretory cell' character.

Data from the studies describing the use of bortezomib in relapsed or refractory AL amyloidosis, have provided an encouraging picture of disease response.[71,72,73] In one of these studies bortezomib was used as stand-alone therapy in patients who had relapsed to other current therapies.[71,74] No patient satisfied criteria for a cardiac response; but, in patients who had relapsed on all prior conventional therapies, the results suggest that bortezomib may slow the progression of cardiac amyloid disease.[74] The predominant cardiac side effects encountered were peripheral oedema and hypotension. The incidence of peripheral neuropathy of any grade was <20% and rarely lead to discontinuation. Other studies report a prevalencemfor neuropathy of between 40–71%.[75,76] Kastritis *et al*. describe rapid and high rates of haematologic responses when bortezomib was prescribed either with or without dexamethasone. A cardiac response, in terms of a sustained improvement in functional class and less often a decrease in wall thickness, was seen in 29% of patients.[75]

An encouraging result has emerged from a small study of nine patients treated with cyclophosphamide, bortezomib and dexamethasone (CYBORD) which resulted in complete haematologic response in eight of nine patients. These patients were significant in being deemed ineligible for SCT and encouragingly suffered minimal treatment-related toxicity.[66] Similar success and tolerability has occurred with bortezomib when combined with dexamethasone as an initial therapy,[76] combined

with melphalan,[77] or with HDM and SCT.[67] A French multi-centre study using either lenalidomide, thalidomide or bortezomib, in 32 patients (17 with cardiac involvement) refractory to prior MDex, achieved an overall complete remission in 34%. The authors emphasize that bortezomib seemed the most promising of these second line therapies with a 55% complete response.[69] Other areas of research interest include drugs that might target other constituents of the amyloid deposit, including SAP,[78] and amyloid reactive antibodies.[79,80]

Transthyretin amyloidosis

Transthyretin (TTR) is a tetrameric protein which functions to transport retinol binding protein and thyroxine. More than 100 different mutations that can cause familial or hereditary amyloidosis have been described. Many can involve the heart to some degree.[81] The Val30Met is the commonest mutation of transythretin seen clinically with heart involvement. This mutation abounds and now represents 85% of TTR mutations reported to the Familial Amyloid Polyneuopathy World Transplant Registry (FAPWTR).[82]

Around 98% of all transthyretin is synthesized by the liver. Orthotopic liver transplantation (OLT) has thus been proposed as a curative procedure for this condition. First performed in 1990, more than 1500 such surgical procedures have now been performed in 70 centres around the world.[83] Removing the liver from such patients has the effect of eliminating more than 95% of variant transthyretin from the circulation.[83] Ninety eight percent of patients in the FAPWTR were subjected to isolated liver transplantation.[82]

Initial impressions that this procedure might 'cure' the condition[84–86] have been tempered byseveral reports of progressive disease occurring after OLT.[87–91] Unfortunately, it is cardiac progression that seems to be most evident,[87,89–92] and in several cases the patient may have had

no evidence of cardiac involvement prior to their OLT.[91] It appears this is due to continued deposition of native wild-type transthyretin, analogous to that occurring in senile systemic amyloidosis (SSA).[91,92–95] Several studies show that wild-type transthyretin is preferentially deposited in the myocardium of patients with FAP who have undergone OLT, both with a Val30Met variant[93] and with the non-Val30Met variants.[93,94] Whilst some reports suggests that OLT is generally successful in patients with the most common TTR Met30 variant;[95–100] there are now several studies showing progression of heart involvement in these patients.[90,100–105] A recent French study of 53 patients with FAP, confirmed a worse outcome in non-Met30 TTR patients undergoing OLT than in Met30 TTR patients.[106]

The Mayo clinic reported similar outcomes for 11 patients undergoing liver transplants for either Met30 or non-Met30 variants. One- and three-year survival rates were 100% for patients with the Met30 variant and 100 and 85.7% for the non-Met30 patients. However, five of seven non-Met30 patients in this study also needed to undergo heart transplantation.[98] The World transplant registry shows that in the non-Val30Met mutation group 11% of patients also received a heart transplant.[82]

In 2008, a Japanese study showed that OLT can result in regression and in some cases disappearance of amyloid in abdominal fat aspirates for patients with the common TTR Met 30 variant.[93] The long-term outcome in 108 Swedish patients with FAP has also shown

increased survival when compared to 33 patients not transplanted. Particular benefit was seen in those with early onset disease, defined as disease onset at <50 years of age.[107] In 2010, Yamashita *et al.* reported a 100% survival at 10 years for 32 patients undergoing OLT, with the Val30Met mutation.[100] The general consensus is that a patients prognosis is improved if the OLT is performed earlier in the disease, with good nutritional status[85,91,96] and when the non-Met30 variants with heart involvement are excluded.[98,106] The International experience after 10 years of performing OLT for FAP (539 patients) produced an overall 5-year survival of 77%, which is comparable to results of OLT performed for other liver disorders. A breakdown of these results show a value of 80% for TTR Met 30 variants and 59% for other variants ($p < 0.001$).[108] Because cardiovascular complications account for 39% of deaths following OLT, many centres now implant pacemakers in patients with evidence of cardiac autonomic involvement prior to surgery.[83,106]

Senile systemic amyloidosis

In SSA the constituent monomer unit is wild-type (unmutated) transthyretin. Inexplicably, it is almost exclusively a disease of elderly men and as such is probably frequently overlooked. The echocardiographic appearance is typical and indistinguishable from other forms of amyloidosis. Current management remains symptomatic, with diuretics, cardiovascular medications and anticoagulation for atrial fibrillation. High-degree AV block occasionally occurs and, if pacing is needed, strong consideration should be given to bi-ventricular pacing in order to

prevent further decrease in stroke volume by right ventricular stimulation.

Combined liver and heart or liver and kidney transplantation

The poor prognosis after isolated liver transplantation in the non-Met30 patients, due to progressive heart involvement lead several units to consider combined organ transplant procedures in these patients.[109,110] The combination of OLT and heart or combined liver and kidney transplantation has now become recognized as practical when these organs are severely disrupted by amyloid infiltration. Some authors suggest this be reserved for patients with non-Val30Met variants of TTR amyloidosis.[111,112] At least one patient, with a TTR Tyr77 variant, has now undergone heart, liver and kidney transplantation.[108] One incidental advantage to result from OLT in patients with FAP is the provision of a donor organ to be transplanted into a second recipient; the so called 'Domino procedure'.[98,113] However, there is now evidence for transmission of transthyretin amyloidosis to recipients of such grafts.[114] Of note, the UK and Spain report a total of four patients receiving heart transplants for SSA.[49,50] The two UK patients presented before the age of 60 and one has now survived 19 years since the transplant. As such, cardiac transplantation appears a reasonable approach in patients with severe wild-type cardiac amyloidosis who present at a sufficiently young age.

Additional therapies in TTR amyloidosis

A recent advance has been the development of tafamidis, an orally administered small molecule that stabilizes both wild-type and mutant transthyretin. By preventing the dissociation of the tetrameric structure of transthyretin it appears to prevent misfolding of the protein and the formation of amyloidogenic TTR fibrils. Tafamidis meglumine (Fx-1006A) may be the first true disease modifying drug for use in TTR amyloid neuropathy.[115] An open label study is currently running with tafamidis being used in patients with TTR-associated cardiomyopathy. A recent trial including 128 patients showed a greater proportion of tafamidis-treated patients showing no disease progression when compared to placebo.[116] Tafamidis has shown promise in the treatment of SSA. Further trials of its clinical efficacy in ATTR (and SSA) are in progress and several similar, and possibly more potent, agents are in development.[117] Similarly to tafamidis, diflusinal has been found to stabilize the tetrameric structure of TTR.[118] Other small molecule ligands that stabilize native tetrameric TTR to prevent fibrillogenesis are also under active investigation for prophylaxis and therapy in TTR amyloidosis.[119] Gene therapy with small interfering RNAs and antisense oligonucleotides, the latter engineered to bind to TTR mRNA and promote premature destruction of transthyretin, appear promising.[120,121]

Fibrinogen amyloidosis

In the fibrinogen based amyloidoses, nine mutations have been identified to date.[122] The predominant variant is of the α-chain, the most common being the Glu526Val mutation. Classically, patients will present with nephropathy, leading to renal failure but heart involvement may also be severe. When isolated, renal transplantation is performed but there is usually very rapid recurrence of amyloid in the graft. The 10-year renal graft survival is only 6%.[123] The liver is the source for at least 98% of the circulating mutant fibrinogen.[124] However, unlike in transthyretin derived amyloidosis, the liver may also be a major target for deposition of fibrinogen based amyloid. OLT is effective and appears to be a potentially curative treatment.[125]

Combined liver and kidney transplantation

In one reported case, combined hepatic and renal transplantation proved highly successful in patient with not only renal failure but also progressive liver failure from hepatic amyloid deposition.[126] In the largest series to date, nine patients received combined liver and kidney transplantation with six surviving (67% survival). These patients had good allograft function and no amyloidosis at a median of 67 months follow-up.[127] Four successful domino liver transplant procedures also followed from this study. The authors indicate that cardiovascular amyloid involvement may preclude this option. They suggest that pre-emptive solitary liver transplantation be used to prevent subsequent liver, vascular, cardiac and particularly renal involvement,[127] an opinion supported at the First International Workshop on hereditary renal amyloidosis in 2008.[123] In 2010 a consensus statement supported, albeit despite limited experience, isolated kidney transplantation in older patients with kidney failure and combined liver and renal transplantation in younger patients to eliminate the pre-cursor amyloidogenic protein.[128] To date, no patient has undergone combined liver and heart transplantation for this condition.

Apolipoprotein AI amyloidosis

In apolipoprotein AI (ApoAI) amyloidosis there are now 19 variants identified.[129] Around 50% of the Apo AI monomer unit is synthesized by the liver.[123] ApoAI disease is a systemic disease often resulting in severe renal as well as hepatic and cardiac involvement. However, long-term restoration of organ function can be achieved by kidney, heart or liver transplantation, despite ongoing production of the amyloidogenic protein from extra-hepatic sources.[122]

The extensive systemic character of this disease type has resulted in few liver transplants having been performed due to concerns around disease progression. In the first case described, a male with the ApoAI Gly26Arg mutation underwent combined hepatic and renal transplantation for end stage renal failure and progressive liver dysfunction. The plasma level of variant ApoAI fell by 50% after transplantation with resultant regression, on serum amyloid P scintigraphy (SAP scan), of pre-operative sub-clinical deposits in his spleen and heart.[130] Australian and French teams report successful outcomes from individual cases with the ApoAI Gly26Arg mutation undergoing hepatic and renal transplantation.[131,132] Encouraging long-term results are also described for combined cardiac and renal transplants performed in patients with hereditary apolipoprotein A1 amyloidosis.[49] An excellent outcome was reported for 9 of 10 patients with ApoAI amyloidosis transplanted in 2006, four of whom had dual liver and cardiac transplants.[133] Even though liver transplantation may be curative, a primary indication for this procedure in ApoAI amyloidosis is for amyloid liver failure.[123] As a result, sequential 'Domino' liver transplant procedures with organs obtained from certain mutations of ApoAI donors may be too extensively involved with parenchymal disease to be suitable for use.[134]

Secondary (AA) amyloidosis

In secondary (AA) amyloidosis the constituent monomer unit to amyloid formation is serum amyloid A protein (SAA). Although cardiac deposits are often present on histology, echocardiographic abnormalities and clinical symptoms of cardiac AA amyloidosis are extremely rare, occurring in ~2% of cases. Deposition in the heart may sometimes be massive which can result in severe heart failure.[135] The prognosis is substantially better than in cases of AL amyloid.[136] Renal dysfunction is the predominant disease manifestation with amyloid burden and mortality related to SAA concentration.[137] Treatment involves suppressing the underlying inflammatory or chronic infective disease state with disease modifying or antibiotic drugs, respectively. In chronic inflammatory diseases, such as rheumatoid arthritis or Crohns disease, suppression of SAA levels to below 10 mg/l (normal basal value <3 mg/l) should be attempted.[138] Despite the rare occurrence of symptomatic heart involvement, no patient has yet been described who has undergone heart transplantation for secondary (AA) amyloidosis.

Isolated atrial amyloid

The pre-cursor protein in isolated atrial amyloid (IAA) is atrial natriuretic peptide (ANP). Synthesized locally by atrial myocytes, it can be deposited locally within the atria as amyloid. It may be important in the development of atrial conduction abnormalities and atrial fibrillation, particularly after cardiac surgery. Mutations of ANP have recently been genetically linked to patients with familial atrial fibrillation,[139,140] and to the even rarer condition of persistent atrial standstill.[141] Both are clinical features common to amyloid heart disease but as yet not intrinsically linked to the development of IAA. IAA is a disease of the elderly, with a female preponderance that contrasts with senile TTR amyloid. There are no clinical or distinguishable echocardiographic features of IAA. The prevalence of IAA in elderly hearts is high, with one autopsy study describing IAA in 91 of 100 hearts.[142] No specific therapy exists to treat IAA and management centres on controlling rhythm disturbance.

Conclusions

Disease modifying therapies in AL, TTR and other hereditary types of amyloidosis that can be used in patients with significant cardiac involvement remain to some degree an elusive goal. Unless the amount of amyloid-forming protein is reduced below the threshold for toxicity and fibril deposition, the disease progresses. In addition, unlike the liver, cardiac amyloid deposits are not mobilized without consequence. Scarring and both functional and conduction system abnormalities regularly occur in those with cardiac amyloid successfully treated years and decades later. Generally, however, amyloid specialists are optimistic that the newer drugs currently being tested will have a major impact on the amyloid disease spectrum.

Many new therapies are currently being developed, including inhibitors of various amyloid constituents such as SAP,[143] and glycosaminoglycans. Kinetic stabilization by small molecules that

prevent the conformational change permissive to amyloid assembly show particular theoretical promise.[144]

Conflict of interest: S.W.D. has received payment from Johnson & Johnson pharmaceuticals for studies into the use of Velcade (Bortezomib). R.L.C. consults for Millenium Pharmaceuticals, Elan and Onyx and receives research support from Celgene and Millenium.

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