An update on treatments for amyloid heart disease

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Patients with amyloid heart disease have historically been considered to have a very poor prognosis and were considered almost untreatable. However, recent therapeutic advances are encouraging and likely to have a marked effect on management across the amyloid spectrum. This message needs to be conveyed to cardiologists, not least because there is now benefit to performing an endomyocardial biopsy to determine amyloid type. We provide an update on the significant progress in managing the three most common forms of amyloid heart disease in the UK.

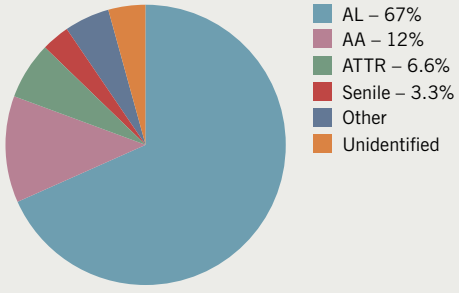
Introduction

The amyloidoses comprise a variety of proteins that are deposited in various organ systems. The major categories of amyloid seen in the UK are shown in **figure 1**,[1] although low detection rates for some types (e.g. senile systemic amyloid) may mean the breakdown in **figure 1** does not reflect the true prevalence and proportions of each amyloid type.

Without therapy, the consequences of significant heart involvement are inevitably fatal. The main variable on life-expectancy being amyloid type, extent of systemic and, particularly, heart involvement. Historically considered untreatable, this view of amyloidosis remains embedded, particularly in the mind of the cardiologist.

As with almost every cause of severe cardiomyopathy, treatments may be limited by the comorbidities of haemodynamic instability, renal, hepatic and pulmonary involvement. While the treatment of amyloid related heart failure remains fairly static,[2] considerable progress has been achieved in treating the underlying amyloidogenic process. In brief, heart failure is managed with carefully monitored use of diuretics. Combinations of loop and potassium-sparing diuretics (spironolactone or epleronone) may have an effective synergistic effect, while carefully monitoring a risk of hypotension. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta blockers and digoxin are poorly tolerated. Hypotension may necessitate compression stockings and the vasopressor alpha-agonist midodrine. There remains little evidence of benefit, in terms of survival, from the use of amiodarone or implantable defibrillators.[3,4] Mechanical dysfunction of the atria due to amyloid infiltration and often severe dilatation, either with or without atrial fibrillation, means anticoagulation with warfarin should be seriously considered. The general management of heart failure due to amyloid involvement of the heart is extensively reviewed elsewhere.[5,6]

Figure 1. Pie diagram illustrating a breakdown of amyloid type for 5,100 patients referred to the UK National Amyloid Centre over the 25-year period 1987–2012[1]

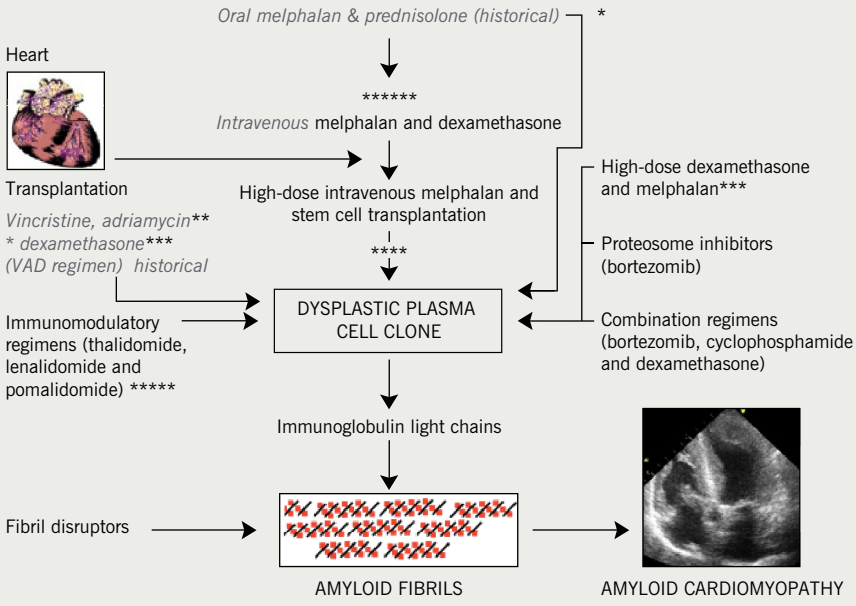


Key: AA = secondary amyloid; AL = immunoglobulin light chain amyloid; Senile = senile systemic amyloid (wild-type transthyretin); ATTR = transthyretin amyloid; Other = includes amyloid due to mutations of fibrinogen and apolipoprotein; Unidentified = includes 4% of cases not definitively typed

Immunoglobulin light-chain AL amyloidosis

Amyloid light-chain (AL) amyloidosis is caused by the deposition and assembly of immunoglobulin light chains into a fibrillar amyloid matrix. Treatment of the disease process and dissolution of amyloid is now feasible.[7] However, when the heart is involved, several months may elapse following therapy before measureable benefit is evident.

Figure 2. Schematic illustrating the development of therapies in light chain AL amyloidosis and certain caveats from a cardiac aspect



*Original therapy and now reserved for more palliative patients unable to tolerate aggressive regimens; **adriamycin is cardiotoxic; ***dexamethasone in high dose may exacerbate heart failure; ****stem cell transplantation is not tolerated well in patients with significant cardiac involvement; *****immunomodulatory regimens are associated with an as yet unexplained rise in cardiac biomarkers (NT-pro BNP); ******intravenous melphalan is toxic and now rarely used, as oral melphalan is equally effective. Therapies in grey italic text are now largely historical.

Introduction to the treatment of AL amyloidosis

Disease-modifying therapies in AL amyloidosis continue to follow advances seen in the field of multiple myeloma. AL amyloidosis is frequently a rapidly fatal disease. Crucial to management is a therapy that will quickly remove amyloidogenic precursor proteins. This produces immediate benefit as component immunoglobulin light chains are inherently cytotoxic. Circulating amyloidogenic free light chains and serum N-terminal natriuretic peptide type B are shown to decrease simultaneously in association with improvement of survival in AL amyloidosis.[8] Regardless of the type of chemotherapy used, a reduction in amyloidogenic free light chains (FLC) of more than 50% results in a substantial survival benefit.[9]

High-dose chemotherapy and autologous stem cell transplantation

High rates of haematological, and organ response, have now been achieved by multiple centres. Median survivals of over a decade, for high-dose melphalan (HDM) and autologous stem cell transplantation (ASCT), are reported in patients achieving complete haematological response (CR).[10-12] The Boston University group reported on 312 patients and described a median survival, in those achieving a CR, in excess of 10 years, compared with 50 months in those who did not.[13] The Mayo Clinic describe 434 patients treated with HDM and ASCT over 14 years, demonstrating a CR in 39%. A median survival was not reached for CR patients but was 107 months in partial responders, compared with 32 months in non-responders.[14]

Actual regression of cardiac amyloid involvement, has been reported in patients achieving CR undergoing treatment with HDM and ASCT.[15,16] The Boston 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 ASCT. Patients without a complete haematologic response (n=34) showed an increase in wall thickness of 0.37 ± 2.21 mm (p=0.0018).[15]

In 2007, the obvious success of HDM and ASCT therapy was challenged by the results from a French study. In 100 patients from 29 centres, the haematological results were similar when patients treated with HDM and ASCT were compared with conventional oral melphalan and dexamethasone (67% *vs.* 68%). Moreover, overall survival was superior in the conventional chemotherapy cohort.[17] Several reasons have been proposed for these findings, but are beyond this brief review.[18] These findings have resulted in the USA favouring HDM and ASCT, and Europe (with the possible exception of Germany) favouring combination chemotherapy.

New therapies and triple-therapy regimens

Treatment regimens consisting of high-dose steroid (usually dexamethasone) and alkylating agents (usually melphalan or cyclophosphamide and, more recently, bendamustine) are being increasingly challenged (**figure 2**).

A product that delivers one of the most rapid responses is the reversible proteosome inhibitor bortezomib (Velcade). Kastritis *et al.* describe a high rate 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, in some, a decrease in wall thickness, was seen in 29% of patients.[19] A later study, in patients who had relapsed on all prior conventional therapies, suggested bortezomib slowed the progression of cardiac amyloid disease.[20] Bortezomib can be used as a stand-alone therapy or within combinations. Patients with Mayo Clinic class III high-risk cardiac amyloidosis have achieved rapid haematological responses to the combination of bortezomib, cyclophosphamide and dexamethasone (VCD or CYBORD regimens).[21,22] Moreover, bortezomib alone or with dexamethasone has also proved successful as consolidation therapy following ASCT.[23] Second-generation proteosome inhibitors are also being developed, including the irreversible product carfilzomib and the agent MLN9708.

A combination of cyclophosphamide, thalidomide and dexamethasone (CTD) has been demonstrated to deliver a response rate in AL amyloidosis higher than that previously reported for non-transplant (ASCT) regimens and with a lower treatment-related mortality.[24]

Immuno-modulatory products, initially comprising thalidomide, but lately the derivatives lenalidomide and pomalidomide, are now being used. Among several combinations, a trial in 35 patients (50% with significant cardiac involvement) using lenalidomide with cyclophosphamide and dexamethasone achieved an overall haematological response of 60%.[25] Pomalidomide in combination with dexamethasone has also produced very encouraging results, including in previously treated patients (48% had relapsed to prior treatment) and in whom 82% had cardiac involvement.[26] Toxicity, particularly peripheral neuropathy and thromboembolic events, remain a considerable issue with thalidomide and its derivatives.

These latest drug combinations have proved so effective that discussion now centres on which to use as first-line therapy.

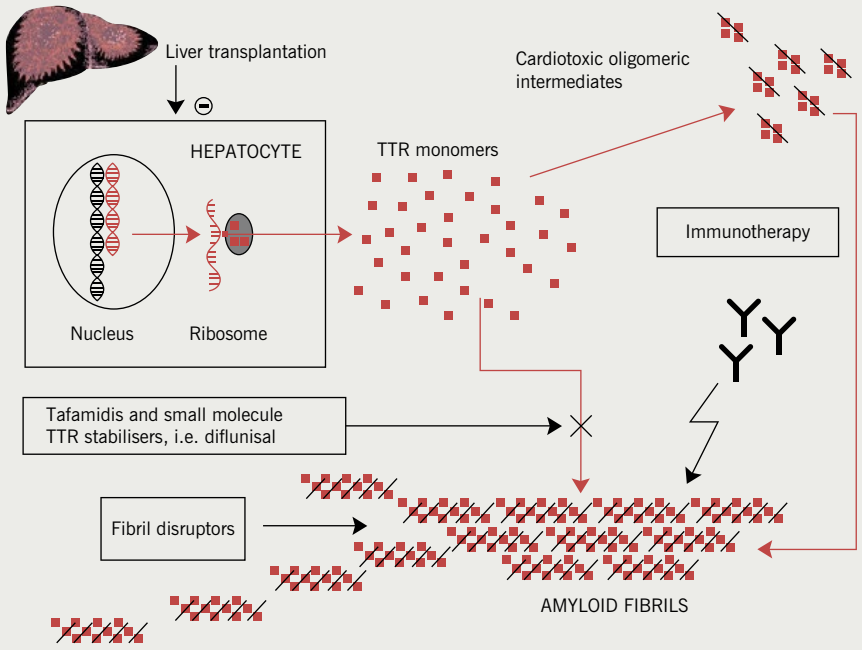
Novel therapeutic approaches

One approach is to target the 'chaperone' glycoprotein, serum amyloid P (SAP), found in abundance in amyloid deposits, and likely crucial to amyloid assembly.[27] To date, approaches have used the bis-d-proline compound CPHPC, which binds to circulating SAP and forms complexes that are cleared by the liver. Having depleted the supply of circulating SAP, tissue-bound SAP can then be targeted with anti-SAP monoclonal antibodies.[28] A fully humanised version of anti-SAP monoclonal antibody is under investigation.

Heart transplantation and concomitant therapies

Cardiac transplantation, for amyloid heart involvement, has been plagued by recurrence in the graft, as well as with continued systemic deposition. Attempts to prevent this have resulted in many units using modified regimens of melphalan and ASCT following cardiac transplantation (**figure 2**), with reasonable success. Recent UK data show that of 14 patients receiving heart transplants, the five-year survival was 45%. Eight patients had subsequent ASCT with a median survival of 9.7 years.[29] Heart transplantation can also be pre-treated with a 'risk-adapted' therapeutic approach, followed-up with consolidation therapy after transplantation, utilising many of the new therapies described above. However, chemotherapeutic consolidation and continuation maintenance therapies have to be balanced against the risk of developing secondary neoplastic disease from these drugs.

Figure 3. Schematic illustrating extracellular targets in the treatment of transthyretin (TTR) amyloidosis



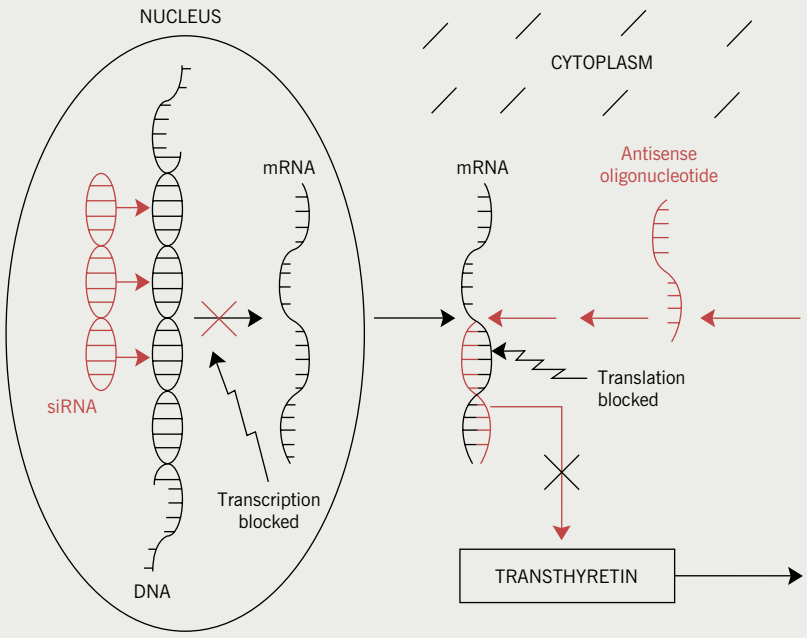
Hereditary amyloidosis

Most cases of hereditary amyloidosis (ATTR) are caused by one of over a hundred known mutations of the protein transthyretin (TTR). Without treatment this is a lethal disease, although, with a life-expectancy considerably longer than for AL amyloidosis. Death is usually within 10 years of symptom onset, and frequently due to significant heart involvement.

Transthyretin is a tetrameric protein, produced predominantly from the liver, and responsible for transporting thyroxine and retinal binding protein. Of the 75 mutations currently known to express a clinical phenotype, around 44 (59%) result in cardiomyopathy.[30] Of particular interest is a mutation of TTR (Val122Iso) almost exclusively reported in Afro-Caribbeans and with a predilection for the heart. Around 4% of Afro-Caribbeans may carry the genotype.[31] A report from the UK indicated that 10% of such patients, attending with cardiomyopathy and heart failure, possessed this Val122Iso mutation.[32] Patients with the Val122Iso mutation have a median survival of three to five years, reduced to between 27 and 36 months when cardiomyopathy and heart failure are apparent.[32-33] One centre reports a worse survival of 50% at 11 months in patients with this mutation presenting with cardiomyopathy.[34]

Until very recently, the accepted treatment was orthotopic liver transplantation (OLT) to remove the main source of the mutant protein (**figure 3**). Over 1,900 OLTs have now been performed in over 70 centres worldwide.[35] Initially considered a curative procedure, it is now appreciated that progression of the disease can occur, due to deposition of wild-type transthyretin. Unfortunately, the heart is a particularly avid target for this process.[36] Liver transplantation appears a

Figure 4. Schematic of hepatocyte illustrating therapeutic targets for small interfering RNA (siRNA) and oligosense antinucleotides, in preventing transcription and translation of DNA and messenger RNA (mRNA), respectively



reasonable therapy, if performed early in the disease, in well-nourished patients and in patients possessing the genotype for the most common (worldwide) mutation of TTR (Val30Met).[37] On the negative side, liver transplantation is an expensive procedure, requires an organ donor, is not without risk and necessitates life-long administration of immunosupressants.

Transthyretin stabilisers as treatments for hereditary amyloidosis

A major advance in amyloid therapy has been the development of molecules that will stabilise circulating transthyretin, preventing a conformational change that would have resulted in auto-aggregation to form amyloid deposits (**figure 3**). Around 99% of the thyroxine receptors on TTR molecules are vacant and occupancy of these sites imposes kinetic stability.[38] Foremost among these is the orally administered product, tafamidis meglumine (Vindaqel). A study of 128 patients showed a greater proportion of tafamidis-treated patients exhibiting no disease progression, compared with placebo.[39] Currently, tafamidis is approved for use in Europe, but is only indicated for the treatment of neuropathic aspects of ATTR.[40] A recent trial demonstrated tafamidis to stabilise TTR in most patients with mutant (including the common Val30Met and also non-Val30Met mutations) or wild-type TTR, resulting in less neurological or cardiac deterioration and a maintained quality of life.[41] The non-steroidal anti-inflammatory diflunisal has also been demonstrated to prevent dissociation of TTR and fibril formation (**figure 3**).[42] An ongoing trial in ATTR patients is due to report in early 2013, but is currently showing diflunisal to be well tolerated.[43] In contrast the UK amyloid centre report a high proportion of adverse events from diflunisal (250 mg twice daily), despite the routine co-prescription of proton-pump inhibitors. The outcome results, of overall efficacy, are awaited.[44]

Oligosense anti-nucleotide and interfering RNA treatments for TTR amyloidosis

Anti-sense oligonucleotides (ASOs) have been engineered to target both 'wild' and all known mutant forms causing ATTR (**figure 4**). Maximal antisense-mediated reductions of target mRNA levels are typically greater than 90% of control levels, with animal and phase I human studies demonstrating dramatic reductions in circulating mutant and wild-type TTR levels.[45] Phase II placebo-controlled clinical studies in ATTR patients are in progress.

Small-interfering RNA (siRNA) (also known as short-interfering-RNA or silencing-RNA) are double-stranded RNA molecules that cause post-transcriptional gene silencing (**figure 4**). They are administered in lipid nanoparticles that target wild and mutant TTR synthesis in the liver. In pre-clinical studies, a highly specific siRNA (ALN-TTR) resulted in almost complete regression of human mutant TTR protein accumulation from peripheral tissues of transgenic mice.[46] A phase I, multi-national trial conducted in 32 patients with hereditary amyloidosis, has also demonstrated TTR lowering.[47]

Other proposals as treatments for TTR amyloidosis

A catechin component of green tea (epigallocatechin-3-gallate) has recently been shown, in a small study, to halt the progression of TTR-related cardiomyopathy. After 12 months of consuming green tea, 14 of 19 evaluable patients showed no increase in left ventricular (LV) wall thickness or mass on echo. A smaller subgroup undergoing cardiac magnetic resonance imaging (MRI), all showed a decrease in LV myocardial mass.[48] Curcumin, a yellow pigment found in tumeric, has also been demonstrated in mice to considerably increase plasma TTR stability and decrease TTR deposition.[49] Another nutraceutical that appears to inhibit TTR amyloidogenesis, by inhibiting transthyretin tetramer dissociation, is the natural product genistein found in soy.[50] Genistein is orally active, indicating that patients could benefit from increasing their intake of soy products.

The glycosaminoglycan heparan sulphate appears to be integral to the aggregation of TTR monomer units and may represent a further target for treatments in preventing transthyretin fibrillisation.

As in AL amyloidosis, the compound CPHPC, which binds circulating SAP and eventually removes SAP from amyloid deposits,[27] might also be efficacious in ATTR. Subsequent

anti-SAP antibody therapy might also be applicable.[28]

A combination of the anthracine IDOX (4'-iodo-4'-deoxydoxorubicin) and the bile acid TUDCA (tauroursodeoxycholic acid) was recently trialled in 20 patients with ATTR and demonstrated stable neuropathy impairment scores and, importantly, no progression of cardiac involvement.[51]

Further proposals for therapy include immunisation against specific amyloidogenic TTR variants.[52]

Senile systemic amyloidosis: wild-type transthyretin amyloid

Senile systemic amyloidosis (SSA) is caused by the deposition of wild-type transthyretin. This predominantly occurs within the heart. SSA is almost exclusively a disease of elderly men, and as such is probably frequently overlooked. While present in around 80% of hearts in those over 80 years,[53] it clinically affects around 25% of this age group.[54] A recent study of 102 patients with SSA showed that 96% were male, congestive heart failure was the presenting feature in 86% and the median age-adjusted survival (without disease-modifying therapy) was 4.6 years.[55] Development of heart failure is slow but insidious and atrial fibrillation is not infrequent. Unlike AL amyloidosis, patients with SSA may tolerate ACE inhibitors or angiotensin receptor blockers. Atrioventricular block will respond to pacing, and strong consideration should be given to bi-ventricular devices. SSA is not associated with other significant organ involvement making heart transplantation a reasonable proposition when there is severe cardiac involvement.[56,57]

Novel therapies in the treatment of senile systemic amyloidosis

With SSA, the main issue has been identifying these patients, largely compounded by extremes of age and a reluctance by physicians to perform cardiac biopsies. Many of the approaches described for the management of ATTR will also be applicable in SSA. With this in mind, and the potential to use stabilising molecules, including tafamidis and diflunisal, the justification of determining a diagnosis by endomyocardial biopsy has increased. In units familiar with this procedure, the complication rate (perforation, tamponade, valve damage, fistulae formation and arrhythmia) is low, with mortality estimates of 0–0.4%.[58] A Japanese report from a total of 214 institutes reported a mortality of 10 cases in 19,964 (0.05%) cardiac biopsy procedures.[59]

Conclusion

Considerable advances have been made in the treatment of amyloid types affecting the heart. An early diagnosis of the disease, and an exact diagnosis of amyloid type, is critical to achieve any chance of success. Resolution of cardiac amyloid may take several years but patients now have treatment options that may permit this

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Conflict of interest

SWD has received payment from Johnson & Johnson Pharmaceuticals for studies into the use of Velcade (Bortezomib) and is funded by ISIS Pharmaceuticals in an advisory role on a Data Safety and Monitoring Board for an antisense oligonucleotide study in TTR amyloidosis.

Key messages

- Amyloid deposits can be 'resorbed' and organ function (including the heart) can be restored
- Advances in treatment in all three amyloid types support performing cardiac biopsies to determine amyloid type
- Heart transplantation for senile systemic amyloidosis appears a successful approach in patients who present at a sufficiently young age
- Small molecule kinetic stabilisation of transthyretin, preventing conformational change permissive to amyloid assembly, shows particular promise
- The impact of treatment in AL amyloidosis can be measured using serum free light chain estimates
- Serum amyloid P (SAP) scans allow whole body amyloid load to be monitored
- Biomarkers (NT-Pro-BNP and troponin) allow cardiac response to be monitored

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