

Recent Advances in Diagnosis and Management of Amyloidosis

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Introduction

Amyloidosis is relatively rare disease caused by tissue deposits of a fibrillar material called amyloid composed of portions of precursor proteins that self-assemble and assume a β -sheet secondary structure.^{1,2} It is not as rare as often assumed condition and is in fact half as common as chronic myeloid leukemia. AL amyloidosis has an incidence of > 1500 cases a year in the United States³ which when extrapolated to India would mean > 8000 cases a year. AL amyloidosis accounts for only one half of all types of amyloidosis and conditions such as senile cardiac amyloidosis appear to be common but no incidence studies are available⁴. More than 20 different proteins can form amyloid fibrils and cause systemic disease. The specific precursor protein determines the type of amyloid that a patient has and by consensus, in order to reduce confusion, the various types have been given abbreviated identifiers and are given in Table 1.

Amyloid Fibrils

All amyloid deposits are composed of protein fibrils. Despite the remarkable diversity of the underlying protein precursors, the structure of all amyloid fibrils is remarkably similar. X-ray diffraction analyses and electron microscopy of isolated amyloid protein fibrils revealed that all amyloid fibrils share a common core structure

consisting of anti-parallel β -strands forming sheets⁵⁻⁷ with a diameter of 7-13 nm. Amyloid like fibrils produced from pure protein precursors also have similar structure and characteristics. The specifically ordered conformation is the likely reason for the characteristic property of amyloid fibrils to demonstrate congophilia and bind other non-fibrillary components like serum amyloid P component (SAP).^{8,9} However, there is limited data about the nature of amyloid *in situ*. Infrared studies of procalcitonin¹⁰ and A β ¹¹ found the characteristic β -pleated structure. There have been more recent suggestions that the structure of amyloid fibrils may be different *in vivo* compared to the *in vitro* structure.^{12,13} The *in situ* AA fibrils have been reported to be thin filaments or tight 1-3 nm helices that are aggregated in the exterior of a micro-fibril like structure which may be derived from the extracellular matrix. The helical form seems to predominate in cryofixed tissues while the filamentous form in gluteraldehyde fixed tissues. The core seems to be composed of helically wound 30-Å chondroitin sulfate proteoglycan (CSPG) double tracked structures enclosing a pentamer of serum amyloid P component (SAP). Outside the CSPG are 45- to 50-Å heparan sulfate proteoglycans, to which the protein filaments are attached¹³. Similar structures have also been reported for transthyretin and β -2 microglobulin.^{12,14} Presumably, the filaments

Table 1 : The human amyloidoses (modified from Buxbaum 2006 ⁸⁴)

Precursor protein (Amyloid)	Systemic(S) or localized (L)	Syndrome or involved tissues
Immunoglobulin light chain (AL)	S, L	Primary; myeloma-associated, any organ involvement possible
Immunoglobulin heavy chain (AH)	S, L	Primary; myeloma-associated, any organ involvement possible
β_2 -microglobulin (β_2 M)	S ? L	Hemodialysis-associated - Joints
Transthyretin(TTR)	S ? L	Familial (nerves, heart) , Senile systemic (heart) Tenosynovium
Serum amyloid A (AA)	S	Secondary, reactive (any organ involvement possible)
Apolipoprotein AI(ApoAI)	S L	Familial (hepatic, heart, nerves, renal) Aorta
Apolipoprotein AII (ApoAII)	S	Familial
Apolipoprotein AIV(ApoAIV)	S	Sporadic, associated with aging
Gelsolin(AGel)	S	Familial (Finnish)
Lysozyme(ALys)	S	Familial
Fibrinogen α -chain (AFib)	S	Familial (renal mainly)
Cystatin C(ACys)	S	Familial
ABriPP(ABri)	S	Familial dementia, British
ADanPP(ADan) *	L	Familial dementia, Danish
A β protein precursor (A β PP)	L	Alzheimer's disease, aging
Prion protein(APrP)	L	Spongiform encephalopathies
(Pro)calcitonin (ACal)	L	C-cell thyroid tumours
Islet amyloid polypeptide(AIAPP)	L	Islets of Langerhans Insulinomas
Atrial natriuretic factor(AANF)	L	Cardiac atria
Prolactin (APro)	L	Aging pituitary Prolactinomas
Insulin (AIns)	L	Iatrogenic
Lactadherin (AMed)	L	Senile aortic, media
Kerato-epithelin (AKer)	L	Cornea, familial
Keratin	L	Lichen amyloid (sporadic) Macular cutaneous (sporadic)
Lactoferrin (ALac)	L	Cornea
A(tbn) **	L	Odontogenic tumours
Seminogelin	L	Prostate

are ordered to account for Congophilia and other specific histochemical staining, although the molecular basis for Congophilia is not clearly defined.

Clinical Features

The clinical features of amyloidosis are protean. The symptoms reflect the organ or organs most prominently involved, although histologic examination will reveal some degree of amyloid deposition in virtually every organ system except the central nervous system. The initial symptoms are frequently fatigue and weight loss, but the diagnosis is rarely made until symptoms or signs referable to a particular organ often due to advanced organ dysfunction begin to appear. The kidney and the heart are the organs most commonly involved, either individually or together. Renal amyloidosis usually presents with proteinuria, often resulting in the nephrotic syndrome. Massive proteinuria with profound edema and hypoalbuminemia may occur with normal creatinine clearance, but evidence of mild renal dysfunction is frequently found. Occasionally, AL amyloidosis may present as progressive renal failure. Presence of significant hypertension raises question about the diagnosis since even in the presence of a markedly renal impairment, hypertension is uncommon. Cardiac involvement is the second commonest mode of presentation. Congestive heart failure, usually rapid in onset and progressive, may be preceded by asymptomatic electrocardiographic abnormalities. A quarter of patients present with progressive hepatic dysfunction. Asymptomatic hepatomegaly usually precedes functional hepatic involvement and is seen in 40% cases. Soft tissue infiltration is a feature of mainly AL amyloidosis and is rarely seen in other types of amyloidosis syndromes. In the presence of amyloidosis, macroglossia is nearly pathognomonic of AL amyloidosis. A history of carpal tunnel syndrome is frequently elicited and may precede other features of the disease by a year or more. Autonomic and sensory

neuropathy are seen in 10-15% cases and may be a source of major morbidity. Motor neuropathy is rare, and sensory neuropathy usually has a distal to proximal and symmetric pattern.

Each hereditary amyloidosis syndrome has a typical pattern of organ distribution. Transthyretin (TTR) generally causes neuropathy (peripheral and autonomic) and cardiac involvement. Fibrinogen alfa chain amyloidosis has an almost exclusively renal presentation. Apolipoprotein A1 (ApoA1) amyloidosis presents with hepatic, cardiac and neuropathic presentation. Lysozyme amyloidosis causes progressive, often asymptomatic, hepatosplenic amyloidosis.¹⁵ Organ rupture (liver or spleen), presumably due to the enzymatic effects of Lysozyme of the collagen framework, is a typical complication in this variant and is rare in other types of amyloidosis. Gelsolin amyloidosis causes cranial neuropathy and renal involvement. Cystatin -C amyloidosis presents with intracranial bleeding. Senile transthyretin presents with progressive cardiac failure and 40% cases may have additional carpal tunnel syndrome, though other organ system involvement has not been described.

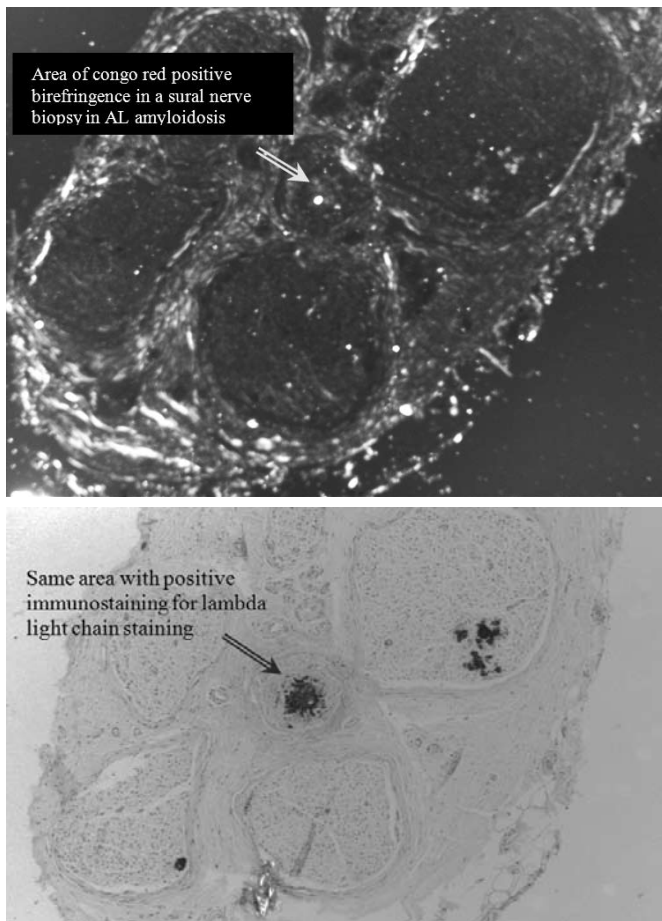
A Diagnostic Pathway For Amyloidosis

Cong Red staining still remains the gold standard for the diagnosis of any type of amyloidosis. However, it is not easy to perform reliably and not reproducible across the laboratories, especially when only small numbers of samples are studied in smaller centres. The diagnostic pathway for any suspected case of amyloidosis is described below.

Confirmation of amyloid deposition

All patients will need a tissue biopsy for confirmation of the diagnosis. Congo red staining should be done (Figure 1) and fresh tissue should be available for electron microscopy. Amyloid fibrils have a distinctive appearance by electron microscopy (EM) of fibrils 7 to 10 nM in diameter. Confirming amyloid deposition is often the easy part of diagnosis.

Figure 1 : Immunostaining for amyloid deposits: Immunostaining of sural nerve deposits in a case of AL amyloidosis with lambda light chain staining



Determining the type of amyloid fibril and the underlying nature of problem causing amyloidosis

Once a diagnosis of amyloidosis has been established, the next key step is to determine the fibril type. This is an area that has advanced enormously over the last 5 years.

Immuno-histochemical staining for the fibril type

All patients should have immunohistochemical studies in the first instance as this can be done on fixed tissue sections. Monoclonal antibodies are available for staining AA amyloid deposits and are very accurate and reliable (Figure 1). AL amyloidosis is more difficult to type and kappa and

lambda staining is positive in only 50% of the cases. Antibodies are also available for transthyretin, Apo-A1 and Lysozyme staining.

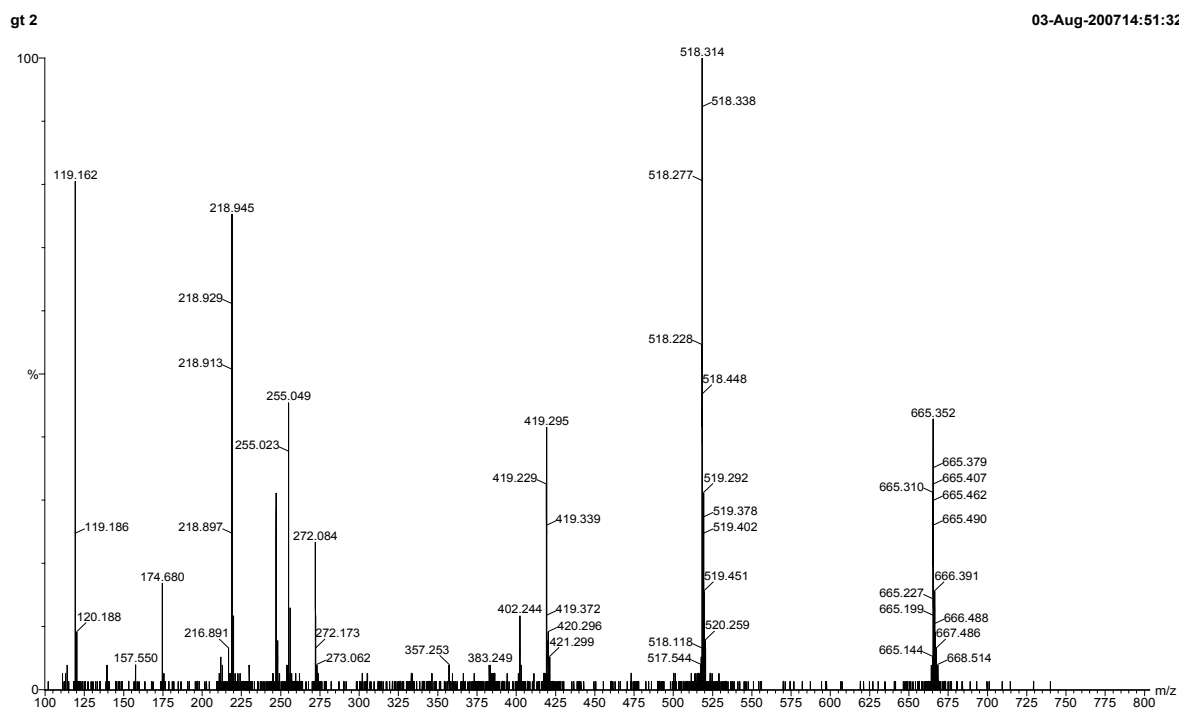
Immuno-gold electron microscopy

This is a very reliable technique and often gives better results than standard immunostains.¹⁶⁻²² This is particularly useful for AL amyloidosis and has been pioneered by the Italian Amyloidosis group. The high electron density of the gold particles coupled with the ease with which different particle sizes can be used for examination at different magnifications make this an ideal method. More recently, however, it has become clear that the strong emission of secondary electrons and backscattered electrons from gold particles make the gold probes ideal for study of surface antigens and macromolecules in the scanning electron microscope (SEM). Gold probes are available in sizes ranging from 1-40 nm for electron microscopy. While the resolving power of a scanning electron microscope is, with secondary electron imaging, better than 1 nm, the possibility of ambiguity between small gold particles and tissue structures indicate that larger particle sizes are preferred and are best visualized by backscattered electron imaging. While all sizes of gold probe may be used to label tissue proteins, the sizes most commonly employed for SEM studies are 20-30 nm.

Laser micro dissection capture of amyloid deposits

This is relatively new technique which allows for micro-dissection of the actual amyloid deposit from the histology sections.²³⁻²⁶ In laser capture micro dissection, a laser microbe am of near-infrared power (at a temperature below 70°C) does not cut the tissue, but rather melts a thermoplastic ethyl vinyl acetate membrane that overlays the tissue. The melted membrane sticks to the selected cells, which can then be lifted and secured in a microfuge tube containing the appropriate extraction solution. The surrounding tissue remains unchanged. Amyloid deposits in complex tissues can easily be sampled without damage to the morphology of the selected zone and the surrounding tissue. The

Figure 2: Mass spectrometry showing transthyretin from a patient with amyloidosis due to mutant transthyretin



dissected deposits can then be used for sequencing the fibril.

Fibril typing by proteomics

There have been advances in the proteomic techniques over the years and use of advanced mass spectrometry will allow for detection of a single amino-acid change. Figure 2 depicts detection of mutant transthyretin amyloid fibril protein in a patient with isolated cardiac amyloidosis due to mutant TTR.

Gene sequencing to determine the underlying mutant protein in non-AL and non-AA type of amyloidosis

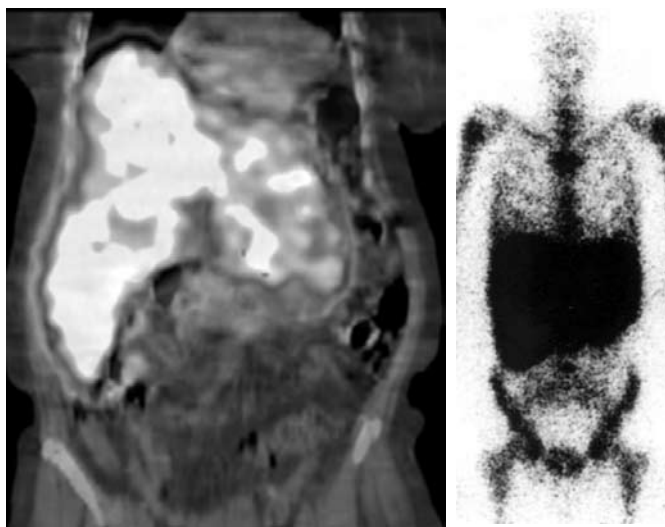
Patients whose amyloid deposits cannot be typed as AA or AL amyloidosis often have a hereditary amyloidosis syndrome due to mutant proteins.²⁷ The commonest are TTR (familial amyloid polyneuropathy), fibrinogen alfa chain mutations and Apo-A1 amyloidosis.²⁸ Table 1 shows the major manifestations of various types of mutant protein amyloidosis and directed gene sequencing has to be

undertaken based on the clinical presentation. Genes that are routinely sequenced in the laboratory at the UK National Amyloidosis Center are transthyretin, fibrinogen alfa chain, Apo-A1, Apo-A2, Lysozyme, Gelsolin, serum amyloid A and Cystatin-C.

Nature of the underlying clonal dyscrasia in AL amyloidosis

All patients with AL amyloidosis have an underlying clonal dyscrasia. 94% have a plasma cell dyscrasia while 6% have a lymphoid clone, usually a lymphoplasmacytoid clone. Recent data suggest that use of expression microassays can be useful for determining the nature of the plasma cells,²⁹ which are often closer to monoclonal gammopathy of uncertain significance but may be myelomatous in 10-15% cases. These plasma cells have the recurrent chromosomal translocations that have been described in other types of gammopathies or myeloma though translocation affecting the cyclin gene with translocation t(11;14) seem to be particularly common.³⁰ Only 80% patients have a monoclonal protein detectable by standard

Figure 3 : SPECT-CT scintigraphy (right hand panel) and whole body scanning (left panel) with I123 labelled serum amyloid P showing intense uptake in the liver in a patient with asymptomatic hepatomegaly and minor abnormalities of the liver function tests. The bony uptake on SAP scan as seen on the left panel is characteristic of AL amyloidosis



electrophoresis or immunofixation of the urine or serum.³¹ The availability of the serum free light chain assay (Freelite™) has been one of the most significant advances in the diagnosis and monitoring of AL amyloidosis patients with 98% patients having a detectable abnormality³¹ which can be tracked monthly by monitoring for response to treatment.

Determining the extent of amyloid deposition

Amyloid deposits can affect any organ and all patients need a global functional assessment by standard tests of organ function. Serum amyloid P scintigraphy which was developed in the laboratory at our center in the last decade³² has now become the standard of care in UK for determining the extent and monitoring serially the extent of amyloid deposits in routine clinical practice. This depends on the binding of SAP (a normal plasma protein) to the amyloid deposits and I¹²³ labelled SAP is used for imaging. The recent development of SPECT-CT techniques have allowed very precise imaging of amyloid deposits (Figure 3). Impedance

cardiography (ICG) appears to be a very sensitive technique to determine autonomic involvement. Cardiac magnetic resonance imaging is promising for the evaluation of the heart in amyloidosis.³³ We are studying the role PET-CT in imaging amyloid deposits. Tc99m labeled aprotinin appears to be a sensitive means of cardiac imaging in some cases.³⁴

Treatment

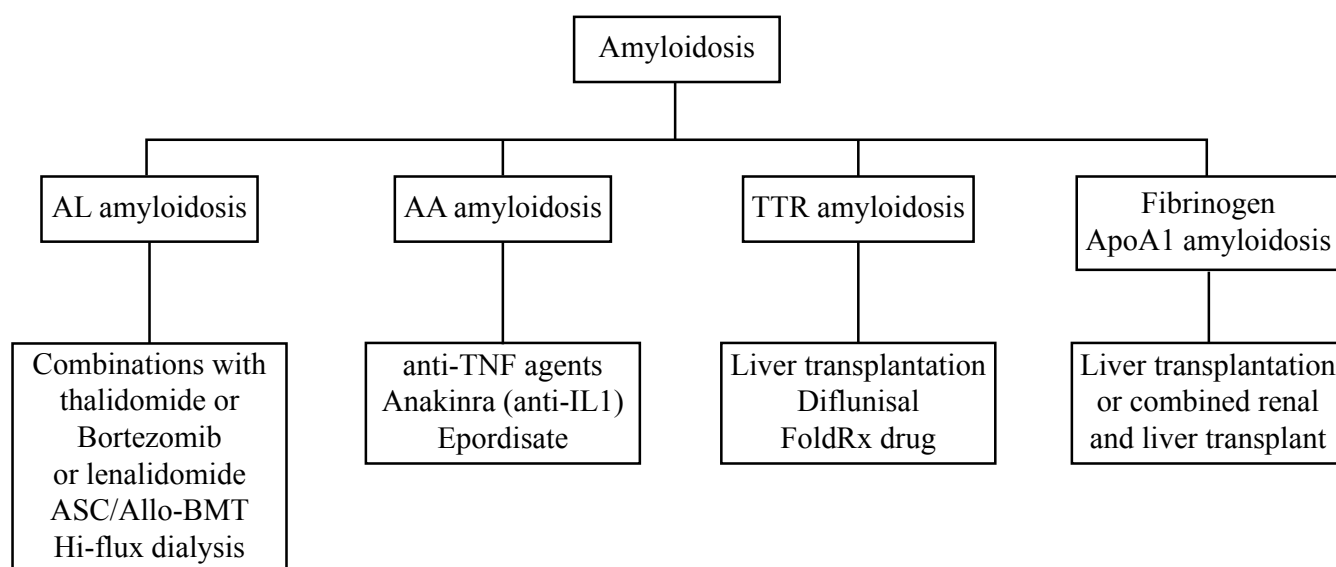
The care of all patients with amyloidosis has to be stratified by function and degree of involvement of the organ systems by amyloid deposits. Supportive care for cardiac failure, renal dysfunction and autonomic neuropathy is needed along the standard treatment pathway and is critical to patient survival. This often needs to be done in a multidisciplinary setting as these patients have advanced involvement of many organ systems. The clinical management of all types of amyloidosis is presently focused on reducing amyloid formation by suppressing production of the respective fibril precursor protein (Figure 4). Thus, treatment of AL amyloidosis comprises chemotherapy that targets the underlying clonal B cell dyscrasia with the aim of reducing production of amyloidogenic light chains, coupled with appropriate supportive measures. The treatment of AA amyloidosis is based on suppression of the underlying inflammatory problem. In case of hereditary amyloidosis, the situation is more complex and where the synthesis of the abnormal protein is predominantly in the liver (like fibrinogen, ApoA1 and TTR), liver transplantation is the treatment of choice.

Recent advances in treatment of AL amyloidosis

Treatment regimens for AL amyloidosis have essentially been adapted from those developed in multiple myeloma, though most patients with AL amyloidosis have a low grade plasma cell dyscrasia and small clonal burden.³⁵

Chemotherapy in AL amyloidosis

Various recent studies suggest improved clonal

Figure 4 : An approach to treatment of amyloidosis

response rates and better outcomes following 'intermediate' dose chemotherapy regimens as compared with "low dose" oral alkylators. Oral melphalan and dexamethasone (Mel-dex) was reported by Palladini and colleagues who treated 46 AL patients and achieved hematologic combined complete and partial response rates of 67%, and which occurred in a median of 4.5 months.³⁶ The regimen was well tolerated and this group recently reported an impressive 4.9 year median duration of clonal remission among 9/15 patients who achieved complete responses.³⁷ A recent randomised trial yielded similar results.³⁸ Combination regimens such as VAD and intermediate dose intravenous melphalan (25 mg/m²) and dexamethasone (IDMD) achieved hematologic combined CR and PR rates and median survival were 65% and 80 months respectively for 229 cases treated with VAD,³⁹ and 54% and 40 months respectively for 144 patients with more advanced disease who were treated with IDMD.⁴⁰

The advent of immunomodulatory drugs has ushered a new era in the treatment of plasma cell disorders. We recently reported the use of risk adapted cyclophosphamide, thalidomide and dexamethasone (CTD) in AL amyloidosis.⁴¹ This

regimen achieved combined hematologic CR and PR rates of 74%, which is amongst the highest of any reported non-ASCT regimen; moreover, all clonal responses occurred within 3 months and resulted in organ responses in 31% of cases.⁴¹ Three year survival among complete responders was 100% and median survival of the whole cohort was 41 months.

Bortezomib shows early promise in patients with AL amyloidosis who have relapsed or refractory clonal disease with 77% achieving CR or PR although the median progression free interval of their clonal disease was only 6 months⁴² and one third developed grade 3 toxicity or needed to discontinue bortezomib treatment. The preliminary results of an ongoing dose escalating phase I/II study of bortezomib in AL amyloidosis in Europe and North America reports a lower response rate and more manageable toxicity, possibly reflecting the lower drug dosages used for the early patients;⁴³ further results are eagerly awaited. In myeloma, bortezomib combination chemotherapy⁴⁴⁻⁴⁶ appears to be highly effective, raising the possibility of this approach in AL amyloidosis. Phase II results for lenalidomide with dexamethasone in AL amyloidosis are encouraging with 67% overall

clonal response rates.^{47,48} Severe fluid retention and other problems that can complicate treatment of cardiac amyloidosis with thalidomide,⁴⁹ seem not to be common with lenalidomide. Skin toxicity appears to be much more frequent in patients with AL amyloidosis receiving this agent for reasons as yet unclear⁵⁰ but is usually not an indication for discontinuing therapy.

Stem cell transplantation for AL amyloidosis

Autologous stem cell transplantation

A number of studies have reported the efficacy of high dose melphalan followed by autologous stem cell transplantation in AL amyloidosis.^{51,52} Anecdotal reports^{53,54} were followed by small studies⁵⁵ reporting efficacy of ASCT in AL amyloidosis. A major problem in patients with amyloidosis is limited eligibility and a very high treatment related mortality of 20-40% amongst patients, especially when treated in less experienced transplant centres.⁵⁶⁻⁵⁸ Use of a risk adapted approach further reduces the TRM to < 5%⁵⁹ but the reduction in melphalan dose probably compromises its efficacy.⁶⁰ ASCT achieves the highest rates of complete clonal response among the current treatments for AL amyloidosis – 35-41% CR with a single ASCT⁵¹ and tandem approach achieved a remarkable 67% complete response rate.⁶¹ Greater than 90% suppression of aberrant FLC was reported in 56% of cases who underwent ASCT in a recent study.⁶² Median overall survival appears to be close to 5 years for ASCT recipients⁵¹ and, more impressively, the median survival has not yet been reached after 10 years in the cohort who were in complete hematological remission and alive at year 1 after ASCT.⁶³ In the UK, median survival of patients who survived beyond day +100 after ASCT was 8.5 years.⁶⁴

Allogeneic stem cell transplantation in AL amyloidosis

Isolated case reports indicate that allogeneic transplantation has been performed rarely in AL amyloidosis, the first successful case being reported in 1998 from our center.⁶⁵ In a recent EBMT report, overall and progression free survival at 1 year

among 19 cases were 60% and 53% respectively;⁶⁶ but the overall TRM was substantial at 40%, and even higher at 50% among those who received total body radiation. Reduced intensity allogeneic (RIC) transplantation is more appealing in AL amyloidosis since early morbidity and TRM are markedly lower than the traditional full intensity methods and there are a few case reports of RIC allografts in AL amyloidosis,^{67,68} but systematic data of any kind is lacking.

Comparison between stem cell transplantation and chemotherapy

This is a matter of unresolved and poorly informed debate. A study from France is the only prospective randomised controlled trial that has been reported. The Mayo group reported superior outcome of their transplant cohort compared with historical chemotherapy controls.⁶⁹ In one study patients who were eligible for ASCT but had actually been treated with chemotherapy had median overall survival of 42 months.⁷⁰ A recent trial in France,³⁸ the only prospective randomised comparison between chemotherapy and ASCT, casts some doubt on the role of ASCT as first line therapy in AL amyloidosis. ASCT failed to demonstrate superiority over oral Mel-Dex chemotherapy either in terms of patient survival (48 versus 56 months respectively) or clonal response rates (64% versus 65% respectively). TRM was 24% in the ASCT group (comparable with older multicenter series of ASCT but substantially higher than more recent single center reports) versus 2% among patients receiving Mel-Dex. A key limitation of the study was the small number of patients with only 50 patients in each arm. A larger study with adequate sample size is required to investigate this further.

Newer treatments in AA amyloidosis

Anti-cytokine treatment

All patients with AA amyloidosis have an underlying inflammatory disorder and the suppression of inflammation is the key to achieving good outcomes. Data from our group suggests that serial serum amyloid A measurement is a very sensitive method

of monitoring patients with AA amyloidosis and patients who achieve SAA level of < 10 mg/L have the best long term outcomes.⁷¹ Anti-cytokine therapy has made a large impact in treating patients with refractory auto inflammatory disorders. Using anti-TNF agents (infliximab, etanercept and adalimumab) is strongly recommended in patients whose inflammation cannot be controlled with standard therapy.⁷¹⁻⁷³ Anti-IL1 (Anakinra™) is very effective in patients refractory to anti-TNF agents.⁷⁴

Targeting glycosaminoglycans in AA amyloidosis

Eprodisate (Kiacta®, Neurochem Inc, Canada) is a negatively charged, sulfonated molecule of low molecular weight that has structural similarities to heparan sulfate.⁷⁵ Eprodisate is thought to inhibit the formation of AA amyloid fibrils by inhibiting their interaction with glycosaminoglycans.⁷⁶ and in a landmark recent phase II/III placebo controlled trial in AA amyloidosis.⁷⁷ treatment with this novel agent was associated with reduction by 54% of the risk of doubling serum creatinine ($p = 0.027$), and a halving of the risk of a 50% reduction in creatinine clearance ($p = 0.011$). Glycosaminoglycans are a universal constituent of amyloid deposits and inhibiting the interaction between GAGs and amyloid fibrils remains a promising therapeutic approach in all types of amyloidosis.

Treatment approaches to hereditary amyloidosis

The treatment of hereditary amyloidosis is more difficult since it is often not possible to remove or reduce to affected amyloidogenic protein. In many cases, the disease is relentlessly progressive with death due to progressive organ dysfunction over few years. Liver is the sole site of synthesis of transthyretin and fibrinogen and partial synthesis of Apo A1. Liver transplantation offer surgical gene therapy for these patients with removal of the liver producing the mutant protein by a liver producing a normal protein. Patients who have more than one organ involvement can be considered for combined organ transplantation – liver and heart

for TTR patients; liver and kidney for fibrinogen; liver/kidney or liver/heart or liver alone for ApoA1 patients⁷⁸.

Novel Approaches to Amyloid Treatment

Enhancing regression – Targeting serum amyloid P component (SAP)

SAP binds to amyloid fibrils *in vitro* and protects them from degradation by phagocytic cells and proteolytic enzymes.⁷⁹ R-1-[6-[R-2-carboxypyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC) is a drug developed in our unit in collaboration with Roche, which cross-links pairs of SAP molecules *in vivo*⁸⁰ and triggers their prompt and virtually complete clearance from the blood. Phase I/II clinical studies indicate that CPHPC is extremely well tolerated and safe, and that it results in sustained depletion of circulating SAP and substantially depletes SAP from amyloid deposits. Larger randomized controlled trials will be necessary to determine efficacy.

Immunotherapy

All amyloid fibrils share common structural motifs and an attractive strategy under investigation is development of therapeutic antibodies to enhance their clearance. This approach has proved successful in a mouse model of AL amyloidosis, and a potentially therapeutic chimeric antibody will shortly enter the first phase of clinical study.⁸¹ Plasma cell antigens such as CD32B may also be promising targets for immunotherapy in AL amyloidosis, and phase I trials of a humanised monoclonal antibody directed against this antigen are due to begin shortly.⁸²

Stabilising amyloid fibril precursor proteins

Relative instability of fibril precursor proteins is a key property that potentiates amyloid fibrillogenesis. *In vitro* studies support the hypothesis that amyloid fibril precursor proteins can be stabilised by drugs that bind to them, thereby inhibiting amyloid fibril formation. Whilst this concept is yet to be developed in AL amyloidosis, two randomized

placebo controlled trials using agents to inhibit TTR amyloid fibril formation in familial amyloid polyneuropathy are in process, one using diflunisal, a non-steroidal anti-inflammatory drug⁸³ and the other Fx-1006A under the sponsorship of the US company FoldRx Pharmaceuticals Inc (www.foldrx.com).

Summary

Amyloidosis was an orphan disease with a poor prognosis, median survival < 1 year and no treatment option. Over the last few years there has been tremendous progress. New methods allow the use of microscopic amounts of tissue to be obtained and analysed with molecular precision for accurately determining the amyloid type, so that an individualised treatment plan can be devised. New and rapidly effective chemotherapy regimes allow treatment of patients with very treatment related mortality and morbidity and rapid improvement in organ function. While systemic amyloidosis is rare, amyloid deposits are a part of the pathogenesis of a number of very common diseases including diabetes mellitus, Alzheimer's disease and osteoarthritis. A number of novel approaches directly targeting the amyloid fibrils or the processes of amyloidogenesis show very promising early clinical or pre-clinical results. There is real possibility of achieving a cure for amyloidosis in the near future and cure of this relatively rare disease may eventually have enormous public health implications.

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