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RESEARCH ARTICLE

Amyloid Protein in AL-Amyloidosis. Natural History and Potential for Regression

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ABSTRACT:
Amyloid light chain amyloidosis is the most commonly seen form of systemic amyloidosis and is characterized by the accumulation of circulating monoclonal immunoglobulin light chain precursors arising from an abnormal clone of plasma cells. These light chain precursors demonstrate a propensity for misfolding, aggregation and deposition as highly stable fibrillar cross-linked beta sheets in various tissues and organs in a manner characteristic of other forms of systemic amyloidosis. There have been great advances in the treatment of the underlying plasma cell dyscrasia with improved long-term survival but the persistence of extracellular amyloid deposits in the tissues of vital organs, particularly the heart and kidney remains a significant cause of morbidity and mortality even in those patients in whom a hematological complete response has been achieved. This review focuses on the importance of early diagnosis and treatment on limiting the extent of amyloid protein accumulation and organ dysfunction and the current state of knowledge on the potential for resorption and clearance of these amyloid deposits in patients with amyloid light chain amyloidosis. The status of current novel anti-fibrillar agents is reviewed and future strategies for effectively intervening to improve organ function and survival these individuals is discussed.

Introduction

Systemic amyloidosis comprises a number of rare but distinct disorders characterized by an autologous misfolding protein with a propensity for aggregation and extracellular accumulation as highly organized fibrils (amyloid) in multiple organ systems. These fibrils stabilize as dense expanding beta-sheet structures that are resistant to proteolysis and resorption. Progressive organ dysfunction occurs as a result of both the cytotoxicity of the prefibrillar species as well as the direct structural and functional impact of the end organ accumulation of amyloid protein [1].

Of these disorders, the most common form is amyloid light chain (AL) amyloidosis comprising 65% - 90% of total cases in most series [2,3]. where the precursor protein is a misfolded immunoglobulin light chain. Other forms of systemic amyloidosis include transthyretin derived (ATTR) amyloidosis (hereditary and wild types) and serum amyloid A protein derived (AA) amyloidosis which is typically associated with chronic inflammatory disease. This targeted review will focus on AL-amyloidosis and examine the current state of knowledge on the process of amyloid protein deposition in the heart and other organs, its clinical importance, the natural history of amyloid accumulation in tissues, the potential for regression and strategies that are being investigated that may act to facilitate tissue amyloid protein clearance.

Clinical presentation and diagnosis of AL-amyloidosis

The clinical presentation of AL-amyloidosis is highly variable, as it can affect many different organ systems. Up to 75% of patients have evidence of cardiac involvement at the time of diagnosis, 60% have renal involvement, 50% have hepatic involvement, 20% have signs of autonomic neuropathy and 10-20% show other less common manifestations such as macroglossia, periorbital purpura, peripheral neuropathy and gastrointestinal involvement [4,5]. Because of this variable presentation, often with a constellation of symptoms that may include dyspnea, fatigue, anorexia, weight loss, diarrhea and postural dizziness, a high index of suspicion is essential for the appropriate identification, investigation and early diagnosis of these patients.

Confirmation of the diagnosis of AL-amyloidosis allows for the early aggressive treatment of the underlying plasma cell dyscrasia with the aim of eliminating the circulating clonal light chain protein. Achievement of a hematological complete response (HCR) is the most effective way of limiting the progressive amyloid burden and cumulative organ damage which accounts for the high early mortality in these patients. One of the unmet challenges remains our inability to meaningfully impact on amyloid deposits that have already accrued, particularly for patients with advanced cardiac involvement, who account for the majority of deaths in the first year.

Abnormal findings that may serve as clues to the diagnosis include elevation of cardiac biomarkers (troponin T and NT-proBNP), echocardiographic evidence for unexplained left ventricular hypertrophy in the absence of hypertension and comparatively low voltage QRS complexes on routine ECG. Echocardiographic evidence of diastolic impairment and abnormal longitudinal strain measurements in basal and mid-ventricular segments with apical sparing are characteristic and typically manifest before there is a measurable drop in ejection fraction. Negative Tc99-DPD or Tc99-pyrophosphate scintigraphy can be helpful in excluding the ATTR variety when systemic amyloidosis is suspected. While serum and urine immunoelectrophoresis and serum free light chain levels are typically abnormal in symptomatic AL-amyloidosis patients, definitive diagnosis additionally requires tissue biopsy demonstration of characteristic 'apple green' birefringence under polarized light after Congo Red staining and only then can specific therapy be initiated.

Cardiac magnetic resonance (CMR) imaging is of particular value in characterizing amyloid deposition in the heart and its impact on structure and function by providing a means for accurate and reproducible estimates of LV and RV mass, chamber volumes and ejection fraction as well as by depicting the spatial distribution of amyloid deposits in cardiac tissue [6]. The inability to null the normal myocardium on late gadolinium enhancement images is an important marker for cardiac infiltrative disorders and can be helpful in defining the pattern and extent of cardiac amyloid deposition. T1 mapping analysis can also allow for estimation of extracellular volume (ECV), an accurate means of serially quantifying amyloid deposition and clearance. T2 mapping analysis is useful for evaluating myocardial edema, a frequent finding in patients at the time of presentation [7].

Treatment of AL-amyloidosis

Because the prognosis of AL-amyloidosis is highly dependent on extent of amyloid deposition in vital organs, particularly the heart and kidneys, the overriding treatment goals are to arrest the process of amyloid deposition through the elimination of circulating clonal amyloid-forming light chains as

rapidly and completely as possible. Melphalan and prednisone had been the de facto treatment of choice for AL-amyloidosis from the late 1970's and remained so for two decades. However, its efficacy in achieving at least a very good hematological response was limited and in the range of 10% or less in many series [8,9].

With the emergence of autologous stem cell transplantation (ASCT) in the late 1990's as a treatment option, typically preceded by a course of high dose melphalan (HDM). the potential for achieving a HCR improved dramatically with as many as 70% achieving a complete or partial hematological response, but patients with moderate or advanced cardiac amyloid involvement were often ineligible because of high morbidity and mortality [10]. While transplant related mortality has fallen with experience and with the refinement of treatment protocols, there has been a parallel improvement in chemotherapy alone that has prompted a reconsideration of the appropriate role of ASCT in managing AL-amyloidosis.

Advances such as the inclusion of proteasome inhibitors such as bortezomib [11] and more recently daratumumab, a specific human CD38-targeting antibody in treatment protocols of patients with AL-amyloidosis, have been associated with markedly improved survival and have resulted in a paradigm change in the management of AL-amyloidosis patients. In January 2021 and based on the results of the ANDROMEDA study [12], the FDA granted approval for the use of subcutaneous daratumumab in combination with cyclophosphamide–bortezomib–dexamethasone (Dara-CyBorD) for the treatment of newly diagnosed AL amyloidosis patients. This treatment was shown to produce a HCR in 53% of treated patients at a median follow up of 11.4 months, an almost three-fold improvement over the standard cyclophosphamide–bortezomib–dexamethasone (CyBorD) control group. The addition of daratumumab also resulted in a roughly two-fold increase in the likelihood of a cardiac as well as a renal response at 6 months (as determined by improvement in NT-proBNP, NYHA class, proteinuria and eGFR) [12].

Despite these paradigmatic therapeutic advances, early mortality in AL-amyloidosis has remained high. In ANDROMEDA, an impact on early mortality and major organ deterioration was only apparent after 6 months post-initiation of treatment. Early mortality was largely seen in patients with advanced cardiac involvement at diagnosis. Reliable and effective achievement of an organ response in more advanced AL-amyloidosis remains an unmet challenge.

Long term survival and quality of life in treated AL-amyloidosis patients depends on both the durability of the hematological response as well as the natural history of tissue amyloid deposition and clearance, particularly in the heart and kidneys. With improving treatment of the underlying plasma cell dyscrasia, we may expect to see substantially higher numbers of patients with HCR's that are deep and sustained. Available data on AL-amyloidosis patients with cardiac involvement suggest a previously unrealized potential for meaningful regression of tissue amyloid. An understanding of the factors that impact on amyloid deposition and clearance is a vitally important adjunct to the management of these patients and will continue to direct research in this area.

The kinetics of amyloid deposition and clearance in AL-amyloidosis

Light chain immunoglobulins consist of adjacent constant and variable domains, the latter defining the unique antigenic affinity of the immunoglobulin as well as its susceptibility to the specific misfolding alterations that lead to amyloid formation. Most clonal light chain disorders manifest simply as an asymptomatic monoclonal gammopathy of unknown source (MGUS), and only a small percentage will go on to develop more serious light chain diseases including myeloma and AL-amyloidosis [13].

Clonal light chains with these amyloidogenic misfolding alterations are typically cytotoxic as are their prefibrillar oligomeric aggregates. Evidence for this cytotoxicity has been shown in a study of 51 treated patients followed for a median of 12.4 months where cardiac response as measured by a fall in NT-proBNP levels were contemporaneous with the free light chain (FLC) response. These improvements in NT-proBNP, seen as early as 3 months after initiation of chemotherapy were also accompanied by clinical improvement in heart failure and occurred in a timeframe too short to implicate changes in tissue amyloid burden in a causal role, suggesting that the cardiac response was due to disappearance of the circulating FLC and its oligomers.

Similarly, in ANDROMEDA, robust improvements in organ function were seen at 6 months in the Dara-CyBorD group, again speaking to the impact of lower levels of cytotoxic FLC species in this group [12]. However, overall mortality was similar in both groups at 12 months, with most deaths related to amyloidosis-related cardiomyopathy. This finding

underscores the existing gap in therapy vis a vis an inability to meaningfully impact on the clearance of amyloid deposits from vital organs in patients with advanced disease.

Any discussion of therapies aimed at enhancing the ability for clearance of amyloid deposition requires first an understanding of the natural history of tissue amyloid deposition and the potential for amyloid protein breakdown and resorption. In-vitro studies have demonstrated a lag phase whereby misfolded light chain slowly aggregate into oligomeric forms followed by a more accelerated phase once these precursors undergo a conformational change and begin to organize as insoluble fibrils with binding sites that allow for nucleated polymerization and further seeding [15]. This ability to self-propagate is fundamental to the pathophysiology of amyloidosis in general and in AL-amyloidosis, the process proceeds in a rapid auto-catalytic fashion as long as there is available substrate in the form of circulating FLC and its oligomeric forms. This underscores the importance of achieving an HCR, thus removing protein substrate as rapidly and completely as possible to arrest the process of tissue amyloid deposition. The persistence of tissue amyloid deposits also explains why patients with a hematological relapse are at risk for seeded aggregation with rapid resumption of end organ amyloid accumulation and resulting organ dysfunction [16].

Clinical studies showing spontaneous regression in AL-amyloidosis

Because of the propensity for vital organ involvement (heart and kidneys) and the fact that in the presence of circulating clonal light chain, the accrual of amyloid fibrils far outpaces the potential for clearance, there have been few opportunities to study the natural history of tissue amyloid deposits in AL-amyloidosis patients. Indeed, such patients have historically had a median survival of only 14.7 months as described in a 1975 series by Kyle and Bayrd [17]. and as a result, data on the fate of amyloid deposition over time has been unavailable.

It would be instructive to utilize animal models of AL-amyloidosis to gain an understanding of the potential for amyloid clearance, but investigators have been unable to develop reliable in vivo animal models that may serve as a surrogate for the progression and potential for regression of AL-amyloidosis as seen in humans. The challenge appears to be the difficulty in predicting whether any given light chain amino acid sequence predisposes to aggregation and amyloid formation because such properties are dependent on multiple mutations within the variable domain of the light chain. Thus, investigators have had to rely on murine models where human AL-amyloidosis-related tissue extracts were injected into mice. In studies on such models, the capacity for rapid clearance of these amyloid deposits has been demonstrated in immunocompetent mice [18] whereas in humans, those same amyloid deposits tend to be inert, incapable of generating an immune response and seemingly resistant to proteolysis, phagocytosis and clearance. Because of the limitations in drawing meaningful conclusions from these in vivo animal model observations, most of the data on spontaneous regression of tissue amyloid deposits have by necessity been reliant on human clinical observations and have only become feasible in the past 2 decades with the advent of more effective therapies and longer patient survival.

There have been rare earlier reports of AL-amyloidosis patients who have demonstrated specific organ-tropism such that the heart and kidneys have been spared leading to longer survival and the opportunity for tissue amyloid assessment over a longer period of follow up [19]. Such organ-tropism is likely a result of the heterogeneous nature of AL-amyloidosis whereby the abnormality in the precursor light chain is variable domain-dependent and unique, resulting in differential organ involvement in different patients.

An example of this is illustrated in a case report from 1989 of a 56 year old woman with AL-amyloidosis and biopsy-proven amyloid deposition confined to liver, bone and subcutaneous fat with apparent cardiac and renal sparing, a pattern of disease that allowed for longer patient survival. In this patient, an excellent hematological and organ response was achieved with melphalan, prednisone and colchicine treatment. Follow up to 96 months which included repeat biopsies of bone marrow and subcutaneous fat, as well as imaging studies of the liver, showed evidence for amyloid regression [19].

In the past 2 decades, there have many more reports that illustrate the potential for tissue amyloid regression after treatment of the underlying plasma cell dyscrasia. In a 2009 paper, Van Gameren and colleagues addressed this issue by studying 120 consecutive patients with AL-amyloidosis in whom fat aspiration and FLC measurements were obtained every 3 to 6 months. Using a validated 4 grade semiquantitative scoring system for amyloid deposition in fat tissue and over a median follow up of 19 months, the authors observed an improvement of at least 2 grades in 25 patients, each of which were amongst the 30 in whom an HCR was achieved [20].

Katoh and colleagues reported on a 52 year old woman with AL-amyloidosis treated with HDM and ASCT in whom an HCR was achieved. They observed a marked regression in hepatic amyloid protein in serial liver biopsies obtained before and 14 months after treatment was initiated [21].

There is also mounting evidence that regression in amyloid protein is achievable in cardiac tissues in the setting of an HCR. Early case reports and series of patients studied after HDM and ASCT showed evidence for regression of LV wall thickness with serial echocardiography in patients in whom an HCR was achieved [22,23]. In a subsequent case report, Brahmanandam and colleagues demonstrated a substantial reduction in late gadolinium enhancement by CMR but without a notable decrease in LV mass in a 52 year old man before and 2.5 years after successful ASCT [24].

In a letter to the editor and a subsequent abstract, Martinez-Navarro and colleagues reported on a series of 31 consecutive patients with AL-amyloidosis who had undergone CMR evaluation prior to and a mean of 20 months after chemotherapy [25,26]. ECV was estimated by T1 mapping images and was used as a surrogate for myocardial amyloid content. Regression in amyloid protein was defined by a fall of greater than 2 SD or 22% in ECV between the 2 studies and was noted in 13/31 patients. This extent of regression was largely confined to patients in whom an HCR was achieved.

Our group recently published a case report of a 67 year old male who exhibited a greater than 50% reduction in left ventricular mass by CMR and a parallel decline in the extent of late gadolinium enhancement over 8 years of follow up in the setting of a deep and sustained HCR. It is worth noting that he had maintained a high level of activity throughout his treatment and recovery [27]. This unprecedented extent of cardiac amyloid clearance points to a far greater potential for recovery of normal cardiac function in patients than previously thought and indicates a potential adjunctive role for regular exercise in these patients.

Ioannou and colleagues recently reported on a series of 171 patients with AL-amyloidosis who underwent both CMR-based ECV mapping as well as serum amyloid P-component (SAP) scintigraphy and were re-evaluated at 6, 12 and 24 months. The authors found evidence of regression of amyloid protein in liver and spleen but to a lesser degree in the heart at 6 months. By 12 and 24 months, the degree of cardiac amyloid regression had 'caught up' and was similar to that seen in liver and spleen [28]. Regression was principally seen in patients with an HCR and the degree of regression seen at 6 months was a strong predictor of mortality.

There are limited data to demonstrate regression of amyloid deposits in the kidneys. Zhang and colleagues reported on a case of AL-amyloidosis in a 46 year old woman in whom an HCR was achieved at 2 months after CyBorD chemotherapy. Renal biopsy was performed pre-chemotherapy and repeated 9 months later because of persistent proteinuria and in spite of the HCR, progression rather than regression of renal amyloid deposition was seen [29].

Taken in its totality, there is mounting evidence that amyloid clearance from most tissues is in fact a common occurrence in patients although largely confined to those in whom an HCR can be achieved and maintained. The observation that an HCR is necessary before one can expect to see signs of regression of amyloid protein speaks to the need for removal of all precursor protein from the equation such that no further accrual of amyloid can occur. In such a circumstance, the evidence for amyloid breakdown and resorption becomes more apparent. The time course and the ultimate capacity for regression appears to be organ-dependent, occurring faster in some tissues such as subcutaneous fat, liver and spleen and more gradual in cardiac muscle. However, the capacity for cardiac amyloid regression appears to be substantially greater than was once believed and the extent of patient activity may play a role. Regression of amyloid tissue in the kidneys may be possible but has not yet been convincingly demonstrated.

Specific therapy directed at the amyloid fibril

The persistently high early mortality in AL-amyloidosis, 35-60% in the first 12 months, points to the need for a more effective and targeted approach to amyloid deposits particularly in the heart, as the extent of cardiac involvement appears to be the principal determinant of early mortality. Closing this treatment gap requires an effective means of triggering or enhancing the removal of amyloid fibrils from tissues beyond what can be achieved by eliminating the circulating substrate protein alone. Such approaches are currently under investigation and include therapies that target serum amyloid P component and those that target specific epitopes on the misfolded FLC aggregate.

Serum amyloid P (SAP) is a circulating plasma glycoprotein that has a unique capacity for tightly

binding as a calcium-dependent ligand bond to specific determinants shared by all types of amyloid fibrils. Thus SAP is an invariable component of amyloidosis deposits irrespective of the precursor protein and has been used as a substrate for amyloid body imaging. SAP may serve to mask amyloid fibrils from immune recognition and as such, may be a particularly attractive target for specific anti-fibril therapy [30].

A therapeutic approach developed by Pepys and colleagues involved a combination of miridesap to deplete circulating SAP followed by dezamizumab to target SAP binding sites and impact on amyloid resorption and clearance. Miridesap is a competitive inhibitor of the SAP binding site to amyloid fibrils as well as directly altering SAP in a manner which leads to its rapid hepatic clearance with a marked reduction in circulating SAP. Miridesap was shown to be safe and free of adverse effects while reducing circulating SAP by 95% [31]. Dezamizumab is a humanized IgG1 anti-SAP monoclonal antibody that showed the capacity for binding and eliminating amyloid bound SAP. In a Phase 1 open label study of 16 patients with systemic amyloidosis (8/16 had AL-amyloidosis) , the combination of miridesap and deszmizumab resulted in a liver response accompanied by evidence of a significant reduction in hepatic amyloid protein without serious adverse effects [32]. However, a subsequent Phase 2 trial was terminated because of the concern of the development of abdominal large vessel vasculitis as well as evidence of limited uptake of and response to dezamizumab in cardiac tissues. As a result, this combination therapy is no longer under investigation [33].

Another agent being studied is birtamimab, a humanized form of a murine monoclonal antibody with affinity for an epitope derived from the cleavage site of SAP. Birtamimab has been shown to have affinity for both kappa and lambda-based amyloid fibrils and in vitro studies have shown effective binding to both soluble and insoluble light chain aggregates extracted from patients with AL amyloidosis resulting in increased macrophage activity and phagocytic clearance [34]. An initial phase I/II trial suggested a high cardiac (57%) and renal (60%) response rate by biomarker criteria [35]. This led to 2 independent double blind placebo-controlled trials, one a Phase IIb trial of 129 patients with persistent cardiac dysfunction after achieving at least a partial hematological response (PRONTO - NCT02632786) [36] and the second a Phase III trial of 260 patients receiving bortezomib-based chemotherapy (VITAL - NCZT02312206) [37]. While birtamimab appeared to be safe in both trials, there was no evidence of a cardiac or other organ response in the PRONTO trial and the VITAL study was terminated soon afterwards, based on a futility analysis. However, there were data in a non-prespecified sub-analysis that demonstrated a significant survival benefit in the birtamimab arm in patients with Mayo stage IV disease at baseline, and this has led to a new Phase III trial on Mayo stage IV AL amyloidosis patients that is expected to be completed in June, 2024.

One particularly promising agent current under investigation is anselamimab or CAEL-101, a monoclonal IgG1 antibody which targets a cryptic eptitope on the variable portion of misfolded light chains as well as those sequences within tissue amyloid fibrils. CAEL-101 has been shown to accelerate the breakdown of AL amyloid deposits in the in vivo murine model [38] and appears to be safe and free of toxicity at doses that have been shown to produce biomarker-based evidence for cardiac and to a lesser degree, renal responses [39]. A recent abstract / poster presentation suggested improved overall survival and organ response in 22 patients with relapsed or refractory AL-amyloidosis at a median follow up of 81.3 months when compared with historical controls [40]. Two separate Phase III randomized placebo-controlled clinical trials are currently underway to determine whether CAEL-101 is effective in facilitating organ recovery in patients with advanced organ damage in AL-amyloidosis.

Synopsis and future directions

The prognosis of patients with AL-amyloidosis has improved substantially over the past 25 years and what was once a disease with an abysmal prognosis and median survival of 14.7 months is now eminently treatable with the prospects of long-term survival and improved quality of life in a high percentage of patients.

Early diagnosis is critical to achieving a good outcome and requires a high index of suspicion because of the variable and non-specific nature of its presentation. Expedited and aggressive treatment of the underlying plasma cell dyscrasia with the aim of eliminating the circulating clonal light chain protein is critical and the advent of Dara-CyBorD has allowed for the achievement of an HCR in over 50% of patients. The utilization of ASCT, an advanced and effective therapy but with unacceptably high levels of treatment related morbidity and mortality in patients with advanced stage cardiac amyloidosis, has been reduced but not eliminated by these improvements in chemotherapy and immunotherapy.

Multiple studies have shown that with a deep and sustained hematological response and removal of the circulating monoclonal FLC precursors, an environment is provided where clinically meaningful regression of tissue amyloid deposits can spontaneously occur. It remains unknown why such regression occurs to differential extents in different organ systems in different patients. Lifestyle interventions such as prescribed physical activity may play a role in improving organ response in patients with cardiac amyloidosis who have sufficient cardiac reserve to follow such a protocol. In our own recently published case report [27], we demonstrated a profound cardiac response at 8 years of follow up in a very active individual in whom a sustained HCR was achieved. Physical activity has been shown to have myriad beneficial effects on cardiovascular health [41, 42] and it is interesting to speculate on the impact of exercise-induced increases in coronary blood flow, myocardial energetics and other biological effects on the susceptibility of cardiac amyloid deposits to breakdown and resorption. These observations will require further investigation but an interim recommendation of encouraging regular physical activity seems prudent.

The potential role of anti-fibril therapy in ameliorating the effects of tissue amyloid deposition and resulting dysfunction is intriguing and while early phase I and II trials have shown promise, these benefits have not yet been confirmed in appropriately designed placebo-controlled trials. A number of clinical trials are in progress that may shed light on the clinical impact of these agents on accelerating organ response and impacting on patient survival and quality of life.

Conclusions

AL-amyloidosis is a complex systemic disorder characterized by the aggregation and deposition of misfolded immunoglobulin light chain proteins as amyloid fibrils in various tissues and organs. Despite advances in treating the underlying cause of the disease, the persistence of extracellular amyloid deposits in the tissues of vital organs remains a significant challenge. Future research efforts should focus on developing therapies that can enhance the clearance of these deposits, potentially improving outcomes for individuals with this condition.

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