

REVIEW

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Recent developments in systemic light-chain amyloidosis prognosis and treatment

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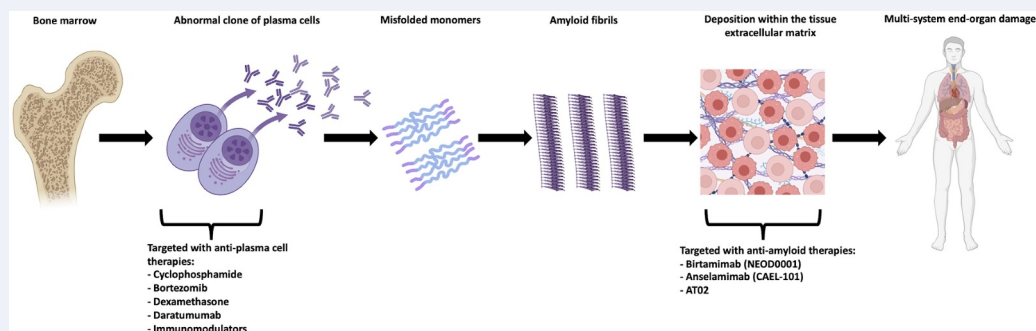
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ABSTRACT

Systemic light-chain (AL) amyloidosis is a rare clonal plasma cell disorder characterized by the production of abnormal immunoglobulin free light-chains that misfold into amyloid fibrils and deposit in the extracellular matrix of tissues. Despite being a multisystemic disease process, the presence and severity of cardiac involvement remains the main determinant of prognosis. Improved understanding of the underlying pathophysiology has resulted in transformative changes in both diagnostics and treatment. Improvements in multimodality cardiac imaging have enabled accurate diagnosis, facilitated rapid initiation of treatment and allowed the direct visualization changes in the myocardial substrate in response to chemotherapy. Significant progress has also been made through leveraging treatments that directly target the underlying abnormal plasma cell clone responsible the production of the amyloidogenic immunoglobulin free light-chains. Current treatment options successfully target amyloid production, but novel anti-amyloid therapies seek to target amyloid fibrils that have already deposited in the organs and facilitate their removal through an immune-mediated degradation process are at advanced stages of development. These treatments have the potential to induce disease regression by depleting amyloid deposits and if successful will represent a significant step forward in the treatment of systemic AL amyloidosis, especially for patients with advanced cardiac disease.

PLAIN LANGUAGE SUMMARY

Systemic light-chain (AL) amyloidosis is a rare disease. It is caused by abnormal cells in the bone marrow that make abnormal proteins. These proteins misfold into amyloid fibrils which spread throughout the body. The disease worsens rapidly and if left untreated can lead to an early death. Treatment with chemotherapy agents has resulted in significant improvements in survival. These treatments directly target the abnormal cells and slow down the production of amyloid fibrils. New treatments are being developed to help remove amyloid fibrils from the body. If successful, they will represent a significant step forward in the treatment of systemic AL amyloidosis.



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Systemic light-chain (AL) amyloidosis is characterized by the misfolding of immunoglobulin light-chains into AL-amyloid fibrils, which deposit within the extracellular matrix of various organs causing disruption to the structure, integrity, and function of each affected organ [1]. The disease process is typically rapidly progressive and historically has been associated with a poor prognosis, especially in patients with cardiac involvement [2]. Over the last few decades, treatment of patients with

systemic AL amyloidosis has undergone transformative change. Significant progress has been made through the implementation of treatments that specifically target the production of the amyloid precursor protein and this has resulted in marked improvements in patient outcomes [3]. This review will explore the recent advances in understanding the underlying pathogenesis of amyloid fibrillogenesis with a focus on diagnostics, risk stratification, and therapeutic advances.

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Article highlights

- Systemic light-chain amyloidosis is a multisystemic disease caused by the deposition of misfolded free light-chains in the form of amyloid fibrils in the extracellular matrix of tissues.
- The presence and severity of cardiac involvement is the main determinant of prognosis.
- Echocardiography can be used to raise the suspicion of cardiac amyloidosis and changes in longitudinal strain can track treatment response.
- Cardiac magnetic resonance derived extracellular volume mapping can detect multiorgan infiltration and track the multiorgan treatment response.
- A deep and rapid hematological response can be achieved using novel anti-plasma cell directed therapies and is crucial to survival.
- Novel anti-amyloid therapies directly target amyloid fibrils and seek to facilitate an immune-mediated degradation that will enable organ recovery.
- Future research should focus on earlier diagnosis, which would lead to prompt initiation of treatment and improved outcomes.

1. Pathogenesis

A pathognomonic feature of amyloidosis is the abnormal folding of a soluble precursor protein into an insoluble amyloid fibril. In the context of systemic AL amyloidosis, misfolding of the immunoglobulin free light-chains occurs as a result of either a proteolytic event or an amino acid sequence that renders the immunoglobulin light-chains thermodynamically and kinetically unstable, leading to self-aggregation [4,5]. Aggregates then interact with glycosaminoglycan and serum amyloid P protein, promoting the formation of amyloid fibrils, which are beta-pleated sheets that are stabilized within the tissues, resistant to proteolysis and histologically identifiable by apple-green birefringence when stained with Congo-Red dye and examined under cross-polarized light [1].

Systemic AL amyloidosis is associated with an underlying plasma cell disorder that results in the overproduction of abnormal immunoglobulin light-chains with abnormal lambda light-chains being responsible for 75–80% of cases and abnormal kappa light-chains being present in 20–25% of cases [6]. The abnormal plasma cells harbor cytogenetic abnormalities, with t(11:14) being most common and present in up to 50% of cases. This translocation juxtaposes the immunoglobulin heavy gene next to the oncogene cyclin D1 [7]. Although hyper-diploidy is common in multiple myeloma, it is only present in around 10% patients with systemic AL amyloidosis [8]. Somatic mutations of the immunoglobulin light-chain variable regions are also common and result in protein instability and an increased propensity to misfold into amyloid fibrils [9]. Patients with known plasma cell disorders are also at an increased risk of developing systemic AL amyloidosis. Among those with a monoclonal gammopathy of unknown significance, the relative risk of developing systemic AL amyloidosis is 8.8% with an incidence of 1%, while as many as 10–15% of patients with multiple myeloma have concomitant systemic AL amyloidosis [10,11].

2. Clinical presentation

Systemic AL amyloidosis is a rapidly progressive disease process, and due to being a multisystem disease, it can present with a wide variety of symptoms and clinical signs. Cardiac amyloidosis occurs when amyloid fibrils deposit within the myocardial extracellular space, causing interruption and distortion of myocardial contractile elements, impaired ventricular relaxation, and subsequent systolic/diastolic dysfunction. Cardiac involvement occurs in 70–80% of cases and the clinical presentation can range from patients being minimally symptomatic to rapidly progressive heart failure, a sign of advanced end-stage disease. Although this is a multisystem disease process, the presence and severity of cardiac involvement remains the main determinant of morbidity and mortality [12]. Common extra-cardiac sites of involvement include the kidneys, causing nephrotic syndrome and renal failure, the liver causing hepatomegaly, cholestasis and hepatic failure, the gastrointestinal tract causing bowel disturbance and malabsorption, and the nerves causing autonomic/peripheral neuropathy. Soft tissue infiltration can result in macroglossia and periorbital bruising, but despite being pathognomonic, these signs only occur in a minority of patients [13].

The precise mechanisms that determine organ tropism remain unclear, but increasing evidence suggests that features within the light chain variable region govern the likelihood of organ involvement, for example, the germline gene immunoglobulin light chain lambda variable 6–57 is more prevalent among patients with kidney involvement, whereas immunoglobulin light chain lambda variable 1–44 is associated with cardiac involvement [14].

The multi-systemic nature of systemic AL amyloidosis and its diverse clinical phenotype, combined with a low index of suspicion outside of specialist amyloidosis centers, often leads to significant diagnostic delays. Consideration of systemic AL amyloidosis within the differentials is crucial in patients with a restrictive cardiomyopathy, unexplained proteinuria, or a peripheral neuropathy, especially when found in conjunction with a monoclonal gammopathy or multiple myeloma. A high index of suspicion is essential to avoiding diagnostic delays.

3. Diagnosis

The diagnosis of systemic AL amyloidosis requires histological evidence of amyloid deposits within the tissue along with evidence of a plasma cell dyscrasia according to the presence of a monoclonal protein as determined by serum or urine immunofixation electrophoresis, immunoglobulin free light chain assay, or the presence of lambda or kappa restricted plasma cells in a bone marrow biopsy specimen. Following the detection of amyloid deposits, accurate identification of the amyloid precursor protein is essential to confirming the type of amyloidosis and guiding subsequent treatment. Immunohistochemistry was previously used to identify the amyloid type, but more recently mass spectrometry-based analysis has been considered the best approach with the

highest diagnostic accuracy [15,16]. Many of the systemic amyloidoses have an overlapping clinical phenotype, and therefore, distinguishing systemic AL amyloidosis from other forms of amyloidosis through histological examination is crucial [17].

4. Imaging

Imaging is a critical component of the comprehensive assessment in all patients with suspected or confirmed systemic AL amyloidosis. In many cases, cardiac imaging represents the first clinical investigation that raises a suspicion of cardiac amyloidosis and prompts subsequent specialist confirmatory diagnostic investigations. Advances in multimodality cardiac imaging have improved diagnostic accuracy and also enriched our understanding of the underlying pathophysiology, provided a noninvasive assessment of each individual patient's cardiac amyloid load and facilitated the assessment of the response to treatment [18].

5. Transthoracic echocardiography

Echocardiography is a widely available cardiac imaging modality and is often the initial imaging modality used to investigate patients presenting with symptoms of heart failure. It is the only cardiac imaging modality that can characterize cardiac structure while also providing an assessment of systolic/diastolic function. Cardiac amyloidosis typically presents with biventricular wall thickening and impaired relaxation, which results in diastolic dysfunction.

There is a typical pattern of amyloid fibril accumulation within the myocardium. Deposition begins at the base of the heart and spreads to the apex creating a gradient of amyloid deposition, and it also begins in the endocardial layer and spreads to the epicardium as the disease progresses [19]. The myocardial fibers responsible for longitudinal contraction are typically situated in the endocardium and the fibers responsible for radial contraction in the mid-wall, and hence, longitudinal contraction is impacted early in the disease process, whereas radial contraction remains preserved until more advanced disease stages [19]. The gradient of amyloid accumulation also typically results in an apical sparing strain pattern, which if detected increases the suspicion of cardiac amyloidosis. Apical sparing can occur in other diseases that present with a hypertrophic phenotype and therefore the diagnostic accuracy of this sign is highly dependent on the patient population [20,21]. The septal apical-to-base strain ratio has demonstrated superior diagnostic accuracy [22], and when used in conjunction with other imaging characteristics linked with cardiac amyloidosis, it can produce a specificity of 98% [23].

Despite there being reported differences in the structure and function of different types of cardiac amyloidosis, there remains a significant overlap in the imaging phenotype, and therefore echocardiographic features used in isolation are not able to accurately differentiate between the different types [17,24].

6. Serum amyloid P component scintigraphy

This is a nuclear imaging modality that utilizes the intravenous injection of ^{123}I -labeled purified human serum amyloid P component (SAP). This tracer has an extremely high binding affinity to all types of amyloid fibrils. Following the administration of radiolabeled SAP, gamma camera acquisition enables a visual qualitative assessment of the amount of amyloid present in the visceral organs (liver, spleen, and kidneys) [25]. However, unfortunately SAP scintigraphy is unable to assess the amyloid burden in hollow or small structures such as the gastrointestinal tract, skin, nerves, and most critically in the heart. There are many plausible factors that may account for the inability of SAP scintigraphy to image amyloidotic heart muscle, including movement artifact, ventricular blood-pool content, and most importantly, the lack of a fenestrated endothelium in the myocardium, hindering access of the large 127 kDa SAP tracer to the amyloidotic interstitium within the available timescale of the short half-life ^{123}I isotope [26]. SAP scintigraphy scans have been corroborated with biopsy samples from patients with different forms of amyloidosis and this has confirmed that this imaging technique can identify visceral organ amyloid infiltration with a high degree of sensitivity and specificity. Despite the impressive diagnostic accuracy of this imaging technique, SAP scintigraphy remains only available in a select minority of highly specialized amyloidosis centers [25].

7. Bone scintigraphy

Bone scintigraphy was repropounded following the incidental finding of myocardial uptake of technetium-based bone-avid radiotracers in patients with cardiac amyloidosis, with subsequent studies demonstrating the diagnostic potential of bone scintigraphy in identifying transthyretin amyloid cardiomyopathy [27]. However, it is increasingly recognized that cardiac uptake of bone-avid radiotracers can also occur in up to 40% of patients with cardiac AL amyloidosis [28]. These observations contributed to the development of a non-biopsy diagnostic algorithm for transthyretin amyloid cardiomyopathy, which combined the impressive sensitivity of bone scintigraphy with serum free light chains (FLCs) and serum and urine immunofixation electrophoresis to exclude systemic AL amyloidosis [29]. It is important to note that bone scintigraphy cannot be used in isolation to diagnose transthyretin amyloid cardiomyopathy and also has a low sensitivity for detecting cardiac AL amyloidosis.

8. Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) provides a comparable structural and functional assessment to echocardiography, alongside providing complimentary data about the myocardial substrate through deep tissue characterization. This additional benefit enables CMR to accurately differentiate between cardiac amyloidosis and other disease processes responsible for a hypertrophic phenotype. Administration of gadolinium-based contrast agents gives rise to pathognomonic patterns of late gadolinium enhancement across a variety of

cardiovascular diseases. In cardiac amyloidosis, gadolinium kinetics are altered due to amyloid infiltration expanding the extracellular space. This leads to rapid myocardial gadolinium uptake and early enhancement, often resulting in the myocardium appearing brighter than the blood pool on late gadolinium enhancement imaging. The pattern of late gadolinium enhancement is typically subendocardial or transmural, with an increasing transmurality of enhancement as the disease progresses [30].

The main disadvantage of late gadolinium enhancement imaging is that does not provide a quantitative assessment of the amyloid burden, but this can be overcome with the use of multiparametric mapping. Pre-contrast native T1 mapping provides a measure of the myocardial relaxation time and this is typically increased in patients with cardiac amyloidosis. Native T1 mapping has demonstrated diagnostic utility in patients referred with a suspicion of cardiac amyloidosis and therefore can be of value in patients with a high pretest probability [31]. However, native T1 mapping measures a composite signal from both the intracellular and extracellular space, and therefore native T1 mapping cannot differentiate between the different underlying disease processes that are responsible for its elevation.

Gadolinium-based contrast agents accumulate in the extracellular matrix and, hence, enable isolation of the signal from the extracellular space. Amyloidosis is the exemplar interstitial disease, with amyloid fibrils accumulating in the extracellular space and the extracellular volume (ECV) providing a surrogate measure of the amyloid burden. Myocardial ECV becomes elevated following early cardiac infiltration, even before the development of late gadolinium enhancement and before changes in cardiac structure and function, making ECV a sensitive marker of early cardiac amyloid infiltration [30].

Routine CMR examinations have also demonstrated the ability to detect liver and spleen amyloid infiltration. A novel approach involving liver and spleen ECV measurements has demonstrated a good diagnostic performance, as compared with SAP scintigraphy, and enables a multiorgan assessment of the amyloid load through a single imaging modality. Multiorgan ECV measurements can help refine the diagnostic differentials, with the detection of extra-cardiac amyloid infiltration possibly impacting on treatment decisions [32].

Multiparametric mapping has significantly improved the understanding of the underlying pathophysiology of cardiac amyloidosis. Myocardial T2 mapping provides a surrogate measure of myocardial edema and following corroboration with histological samples, this noninvasive imaging modality demonstrated that myocardial edema occurs in patients with systemic AL amyloidosis, seemingly owing to the direct impact light-chain toxicity on the heart and subsequent myocardial injury [33].

Quantitative stress perfusion mapping has demonstrated that cardiac amyloidosis results in impaired coronary blood flow, which is comparable to the that is observed in patients with flow-limiting triple vessel coronary artery disease. The reduction in stress myocardial blood flow and myocardial perfusion reserve correlated with the myocardial ECV as a marker of amyloid burden. These findings were also validated against endomyocardial biopsies, which demonstrated

amyloid infiltration at the level of mural arterioles and refraction of the capillaries. Chronic hypoxic conditions also led to an upregulation of vascular endothelial growth factor [34]. Microvascular obstruction is also a common phenomenon in patients with cardiac amyloidosis and correlates with the magnitude of amyloid infiltration and severity of the cardiac phenotype as evidenced by serum cardiac biomarkers and structural and functional cardiac imaging parameters [35].

Developments in multiparametric mapping have increased the diagnostic accuracy of CMR, while also improving understanding of the underlying disease pathophysiology and enabling noninvasive measurements of the multiorgan amyloid burden [36].

9. Positron emission tomography

Multiple amyloid-binding positron emission tomography (PET) tracers have been assessed in several studies. ^{11}C -Pittsburgh compound B (PIB) accurately detects cardiac amyloid deposits in patients with systemic AL amyloidosis [37], but the requirement of a local cyclotron for its production limits the use of PIB [38]. ^{18}F -florbetapir is a stilbene derivative that has a high binding affinity for amyloid fibrils and a longer half-life than PIB. Ex-vivo studies of myocardial tissue demonstrated that ^{18}F -florbetapir colocalised well to amyloid deposits [39], and in-vivo studies of patients with systemic AL amyloidosis have confirmed its diagnostic utility [40]. Furthermore, the magnitude of uptake also seems to reflect the cardiac amyloid load. Patients with established cardiac amyloidosis have the greatest uptake, while the those without cardiac amyloidosis, as per the conventional diagnostic criteria, have the lowest uptake. Therefore, ^{18}F -florbetapir may be able to detect early cardiac infiltration before structural and functional changes are seen on other cardiac imaging modalities [41].

Whole-body PET imaging has an additional advantage of imaging the extracardiac organs. In the context of systemic AL amyloidosis ^{18}F -florbetapir PET detected widespread multiorgan amyloid infiltration and was able to identify early amyloid deposition before the development of symptoms and clinical signs [42].

^{124}I -evuzamitide is an amyloid radiotracer which has a high binding affinity for amyloid fibrils from multiple different amyloid precursor proteins. In the context of systemic AL amyloidosis, ^{124}I -evuzamitide identifies cardiac amyloid deposits with a comparable diagnostic accuracy to ^{18}F -florbetapir, with the magnitude of cardiac uptake correlating with biomarkers and imaging parameters that are reflective of disease severity [43]. Similar to ^{18}F -florbetapir, ^{124}I -evuzamitide has also demonstrated utility in detecting extracardiac amyloid infiltration (Table 1) [44].

Targeted amyloid-binding PET tracers are likely to have an increasingly important role in the diagnosis of systemic AL amyloidosis and are likely to facilitate earlier diagnosis by potentially detecting cardiac amyloid deposits before patients have undergone structural and functional changes. However, these PET tracers remain at an early investigational stage and larger multi-center trials are needed to assess their diagnostic capabilities [36].

Table 1. Summary of cardiac imaging modalities utilized in the diagnosis and monitoring of patients with systemic AL amyloidosis.

	Transthoracic echocardiogram	Cardiac magnetic resonance	Positron emission tomography
Availability	Widely available	Only available at tertiary centers	Not clinically available yet
Clinical information	– Assessment of systolic and diastolic function – Valvular assessment – No tissue characterization	– Detailed tissue characterization – Assessment of systolic function and chamber size – Limited information on valvular function – No information on diastology	– Accuracy in identifying cardiac amyloid infiltration
Diagnostic capabilities	– Can identify structural and functional features of cardiac amyloidosis – May not be able to differentiate between different causes of a hypertrophic phenotype – Unable to detect early cardiac infiltration before structural and functional changes occur	– Can detect early cardiac infiltration with a high sensitivity – Can accurately differentiate between different causes of a hypertrophic phenotype – Can detect liver and spleen amyloid infiltration	– Can detect early cardiac infiltration with a high sensitivity – Can identify extra cardiac amyloid infiltration
Ability to track treatment response	– Improved longitudinal strain indicates a favorable cardiac response to treatment	– Reduction in myocardial native T1 and ECV indicates cardiac disease regression – Reduction in liver ECV indicates hepatic disease regression – Reduction in spleen ECV indicates splenic ECV regression	– Further studies are needed to assess the ability to track treatment response
Time required	20–30 minutes	40–60 minutes	40–60 minutes
Advantages	– Safe in pregnancy – No requirement for vascular access – No ionizing radiation	– Unaffected by body habitus – No exposure to ionizing radiation	– Unaffected by body habitus – Not operator dependant – Can be used in patients with metalwork such as cardiac devices – Can be used in patients with renal impairment
Disadvantages	– Variable image quality – Highly operator dependant – High intra and inter observer measurement variability	– Image quality is affected by breathing and arrhythmias – Requires gadolinium contrast – Contraindicated in patients with non-MRI safe metalwork – Not safe in pregnancy – Requires vascular access	– Not safe in pregnancy – Not safe in breastfeeding – Involves exposure to ionizing radiation – Requires vascular access

ECV = extracellular volume; MRI = magnetic resonance imaging.

10. Stratifying prognosis

The prognosis of patients with systemic AL amyloidosis is highly dependent on the severity of cardiac involvement at the time of diagnosis and therefore measures of the cardiac amyloid burden are highly prognostic. The current staging systems utilize widely available cardiac biomarkers to stratify patients into prognostic categories.

In 2004, the Mayo Clinic developed a staging system that utilized both NT-proBNP and troponin T [45] and this was later modified by a group of European investigators in 2013 to identify patients at a high risk of early mortality by adding a second NT-proBNP cutoff of 8500ng/L [46]. In 2012, the Mayo Clinic modified the staging system to include the clonal burden, which is measured using the difference between involved and uninvolved circulating free light chain (dFLC) [47]. The 2012 Mayo Clinic staging system is able to predict late survival more accurately, whereas the Mayo Clinic 2004 staging system with the European modification is able to predict early mortality more accurately. It is also likely that in the current era of efficacious plasma cell directed therapies the prognostic importance of the dFLC has been diminished [48]. A team of investigators at Boston University also developed a staging system in 2019 using serum BNP and troponin I, which predicts survival and has a high concordance with the Mayo staging system [49].

A renal staging system has also been developed in 2014 and this leverages both 24-h proteinuria and estimated glomerular filtration rate at the time of diagnosis to predict the risk of progression to dialysis (Table 2) [50].

Although serum cardiac biomarkers form the foundations of all the staging systems for systemic AL amyloidosis, abnormal increases in cardiac biomarkers represent the final common pathway of several mechanisms integrating cardiac and renal function, volume status, and neurohormonal activation, rather than providing a direct measure of the cardiac amyloid load. Therefore, imaging-based parameters that reflect the degree of amyloid accumulation are being increasingly utilized to refine risk stratification. Echocardiographic longitudinal strain is an independent prognostic marker that remains associated with mortality after adjusting for the Mayo staging system with the European modification, wall thickness, and systolic blood pressure. The prognostic nature of longitudinal strain is likely related to the pattern of amyloid infiltration, which begins in the endocardial layer, where the fibers responsible for longitudinal contraction are located. Therefore, imaging-based metrics that reflect longitudinal systolic function, such as longitudinal strain, reflect the entire spectrum of cardiac disease, from early cardiac deposits to end-stage disease [51].

Deep tissue characterization through use of multiparametric mapping techniques provides additional information to the structural and functional parameters. Myocardial ECV acts as a direct noninvasive measure of extracellular expansion secondary to amyloid accumulation and represents an independent predictor of prognosis. Hepatic and splenic ECV measurements reflect the visceral organ amyloid load, and in addition, liver ECV measurements remain independently prognostic after adjusting for the components of the Mayo staging criteria, the myocardial ECV, and the splenic ECV [32].

Table 2. Staging systems for systemic AL amyloidosis. Adapted from Fontana M, et al. JACC Cardiovasc imaging 2025 [36].

Staging systems for systemic AL amyloidosis	
Mayo 2004 NT-proBNP threshold of 332ng/L Troponin-T threshold of 35ng/L	I: both variables below the cutoffs II: one variable above the cutoff III: both variables above the cutoff
European modification of Mayo 2004 NT-proBNP thresholds of 332ng/L and 8500ng/L Troponin-T threshold of 35ng/L	I: both variables below the cutoffs II: one variable above the cutoff IIIa: NT-proBNP between 332–8500 and troponin-T above cutoff IIIb: NT-proBNP > 8500 and troponin-T above cutoff
Mayo 2012 NT-proBNP threshold of 1800ng/L Troponin-T threshold of 25ng/L dFLC threshold of 180 mg/L	I: both variables below the cutoffs II: one variable above the cutoff III: both variables above the cutoff
Boston University 2019 BNP threshold of 81ng/L Troponin-I threshold of 10ng/L	I: both variables below the cutoffs II: one variable above the cutoff III: both variables above the cutoff
Renal staging 2014 eGFR threshold of 50 ml/min/1.73 m ² Urinary protein excretion threshold of 5 g/24 hr	I: both variables below the cutoffs II: one variable above the cutoff III: both variables above the cutoff

BNP = B-type natriuretic peptide; dFLC = difference between involved and uninvolved circulating free light chain; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-b-type natriuretic peptide.

11. Management

The treatment of patients with systemic AL amyloidosis typically involves a multidisciplinary approach with care being provided by clinicians who are experienced in managing patients with this rare condition. Treatment decisions are often dictated partly by the extent and severity of organ involvement, with supportive therapy being administered to minimize the toxic effects of amyloid accumulation and minimize the anticipated side effects of disease modifying therapy, while cytotoxic chemotherapy is utilized to target the abnormal clone of plasma cells and achieve a deep and rapid suppression of the amyloidogenic free light-chains.

12. Supportive therapy

In the context of cardiac amyloidosis, the mainstay of supportive management revolves around meticulous volume control through fluid restriction and loop diuretics. It is unclear whether conventional heart failure therapies such as beta-blockers and renin–angiotensin system blockers are of benefit and should be used cautiously because they may be poorly tolerated in some patients, especially those with advanced disease and hypotension [52]. Common cardiac complications include atrial fibrillation, which requires anticoagulation for stroke prophylaxis, and conduction disease, which often requires implantation of a permanent pacemaker. Patients are also at risk of ventricular arrhythmias, and despite amiodarone being commonly prescribed as a prophylactic antiarrhythmic, there is a lack of good data to support its use. Sudden cardiac death is common in patients with cardiac amyloidosis and is challenging to treat. Studies suggest there is a lack of benefit from implantable cardioverter-defibrillators and even in patients where appropriate shocks have been delivered, there does not appear to be an overall survival benefit [53,54].

Orthostatic hypotension is also common and is often caused by autonomic neuropathy but may be exacerbated

by cardiac amyloidosis. Fludrocortisone is often poorly tolerated because it can exacerbate fluid retention. Midodrine is an alpha-1 agonist, which acts to increase vascular tone and in turn increase blood pressure. Midodrine can be effective in patients with orthostatic hypotension but can also increase supine blood pressure [55]. Alternative pharmacological agents include pyridostigmine and droxydropa [52].

Renal impairment and nephrotic syndrome are also common. Edema often requires high-dose loop diuretics and in resistant cases may also require use of thiazides and potassium sparing diuretics. Renin–angiotensin system blockers may be utilized to reduce urinary protein excretion, and hypercholesterolemia should also be treated with statins. Patients with a low serum albumin are at risk of venous thromboembolism and prophylactic anticoagulation should be considered. End-stage renal failure can be treated with dialysis and treatment with dialysis is associated with improved outcomes especially in those without cardiac amyloidosis [56].

Gastrointestinal involvement through either direct amyloid deposition or autonomic dysfunction causing gut motility issues can present with intractable diarrhea or constipation due to gastroparesis and malabsorption. Supportive measures include adequate nutritional supplementation, medications to treat diarrhea such as loperamide and octreotide, as well as testing for bacterial overgrowth. Neuropathic pain may be managed with gabapentin, pregabalin, and duloxetine [52,55]. Bleeding complications can also occur due to factor X deficiency and can be treated with clotting factors [57].

13. Monitoring treatment response

A two-pronged approach is utilized to evaluate the efficacy of chemotherapy and consists of measuring the decrease in amyloidogenic free light-chains in response to chemotherapy and the direct impact of this reduction on the affected organs.

An international collaboration has established and validated both the hematological response and the end organ response criteria. The criteria for organ response were previous binary but more recently have been refined with the addition of various grades that accurately predict survival and longer term clinical outcomes [58]. Refinements in hematological response criteria have also been suggested, with involved free light chain value of less than 20 mg/L and a dFLC value of less than 10 mg/L predicting improved survival [59,60].

More recently, multimodality cardiac imaging has become an important adjunct that enables noninvasive measures of the changes in amyloid load in response to chemotherapy [61,62]. Serial echocardiographic assessments have demonstrated that patients who achieved a complete hematological response were more likely to experience favorable changes in longitudinal strain, and a clinically meaningful improvement was independently associated with increased survival [51].

Patients who achieve a deep and rapid hematological response are also more likely to attain myocardial ECV regression, with a global reduction in ECV in response to treatment representing a reduction in amyloid burden. Reductions in myocardial ECV were followed by favorable changes in cardiac structure and function, and changes in myocardial ECV were independently associated with prognosis [63]. Multiorgan ECV measurements have also been effective in tracking the hepatic and splenic response to treatment. Changes in liver and spleen ECV were corroborated with changes in amyloid load seen on SAP scintigraphy scans, and changes in liver ECV were also corroborated with changes in liver function tests that reflect the hepatic amyloid load. The changes in liver and spleen ECV in response to treatment were associated with prognosis, with changes in the liver ECV remaining

independently associated with mortality even after adjusting for the hematological response, changes in NT-proBNP and changes in both the myocardial and splenic ECV [32].

Changes in myocardial native T1 measurements are also able to track the myocardial response to chemotherapy. A reduced myocardial native T1 was associated with favorable changes in cardiac biomarkers and cardiac structure and function. The myocardial native T1 measurements reflect a composite signal that is influenced by the intra and extracellular space, and therefore, changes in myocardial native T1 reflect changes in the amyloid burden and myocardial edema, and importantly remained independently associated with prognosis after adjusting for the hematological response and changes in NT-proBNP (Table 3) [64].

14. Treatment of newly diagnosed systemic AL amyloidosis

The treatment of systemic AL amyloidosis has evolved over the past few decades and substantial progress has been made by directly targeting the underlying plasma cell dyscrasia, mostly through adapting treatments licensed for myeloma. There has been a dramatic improvement in survival rates with 5-year survival increasing from 15% in the 1980s to 45% in 2010s [65].

In the 1990s, melphalan and prednisolone were shown to be beneficial, but hematological responses were often slow, taking a median of 9–12 months [66]. Response rates were improved through the use of dexamethasone, which has since become the steroid of choice for treatment of systemic AL amyloidosis [67]. Studies investigating the use of immunomodulators such as thalidomide and lenalidomide in

Table 3. Summary of the hematological and organ responses to treatment in systemic AL amyloidosis.

Haematological and organ response criteria		Criteria
Response		
Haematological response		
	Complete response	Absence of a monoclonal protein in serum and urine on immunofixation and either a normal serum free light chain ratio or an uninvolved free light chain concentration that is greater than the involved free light chain concentration
	Very good partial response	dFLC < 40ng/L
	Partial response	Reduction in dFLC > 50%
	No response	Reduction in dFLC ≤ 50%
Organ biomarker response		
Cardiac response		
	Complete response	Nadir NT-proBNP ≤ 350ng/L or BNP ≤ 80ng/L
	Very good partial response	Reduction in NT-proBNP or BNP > 60%
	Partial response	Reduction in NT-proBNP or BNP between 31–60%
	No response	Reduction in NT-proBNP or BNP ≤ 30%
Renal response		
	Complete response	Nadir proteinuria ≤ 200 mg/24 hr
	Very good partial response	Reduction in proteinuria > 60%
	Partial response	Reduction in proteinuria between 31–60%
	No response	Reduction in proteinuria ≤ 30%
Hepatic response		
Cardiac imaging response		
Echocardiographic longitudinal strain		
		Improvement ≥ 2%
CMR derived myocardial native T1		
		Reduction ≥ 50 ms
CMR derived myocardial ECV		
		Reduction ≥ 5%
CMR derived liver ECV		
		Reduction ≥ 10%
CMR derived spleen ECV		
		Reduction ≥ 10%

BNP = B-type natriuretic peptide; dFLC = difference between involved and uninvolved circulating free light chain; ECV = extracellular volume;

NT-proBNP = N-terminal pro-B-type natriuretic peptide.

combination with dexamethasone also demonstrated efficacy, but the response rates still remained suboptimal [68,69].

The widespread use of bortezomib began following studies that demonstrated its ability to achieve remarkably rapid hematological responses, and more recently, the combination of cyclophosphamide-bortezomib-dexamethasone (CyBorD) has emerged as a highly efficacious chemotherapeutic regime [70,71]. The current preferred first-line therapy for systemic AL amyloidosis utilizes daratumumab in combination with CyBorD. This recommendation follows the ANDROMEDA trial (A Study to Evaluate the Efficacy and Safety of Daratumumab in Combination with CyBorD Compared to CyBorD Alone in Newly Diagnosed Systemic AL Amyloidosis), which demonstrated that the addition of daratumumab to the standard of care resulted in significantly more patients achieving a complete hematological response or very good partial hematological response [72]. There is emerging data to suggest that in patients with advanced disease treatment modifications can be considered to reduce the risk of toxicity related to chemotherapy. A small phase 2 trial of 40 patients demonstrated that daratumumab monotherapy induced an early and deep hematological response in the majority of patients without any safety concerns and therefore could be considered as an alternative [73]. The AQUARIUS (A Study of Daratumumab-Based Therapies in Participants With Amyloid Light Chain (AL) Amyloidosis) trial is a phase 3 trial comparing treatment with daratumumab CyBorD upfront to daratumumab monotherapy initially followed by the delayed addition of CyBorD in patients with Mayo stage II and stage IIIa disease [74].

The rapidity and depth of the hematological response is crucial to improving outcomes and is particularly important in patients with a significant cardiac amyloid burden. The primary goal of treatment is to achieve a complete hematological response. In patients with a myocardial ECV > 40% achieving a deep hematological response at 1-month was associated with better survival than achieving a deep hematological response at 6-months; whereas in those with an ECV < 40%, a deep hematological response at 1-month did not translate to better outcomes. Furthermore, in patients with a myocardial ECV > 40%, survival was highly dependent on achieving a complete hematological response at 6-months; whereas in patients with an ECV < 30% survival was independent of the hematological response and in patients with an ECV 30%–40%, survival was dependent on achieving at least a partial hematological response. CMR with ECV mapping can help define the hematological response targets for each individual patient and potentially inform treatment strategies [75]. However, a complete hematological response does not always translate to a favorable organ response. Next-generation flow cytometry has been used to detect minimal residual disease. Patients with minimal residual disease positivity have reduced rates of organ response and increased rates of relapsed disease. Therefore, testing for minimal residual disease should be considered in patients with a complete hematological response especially if not accompanied by organ response [76].

15. Treatment of relapsed disease

No consensus recommendations have been established regarding the criteria for reinitiating chemotherapy once patients experience a relapse in disease following initial therapy. The choice of second-line agents often depends on the nature of the response to first-line therapy, which agents were used in first-line therapy and also the local availability of second-line agents. There may also be limitations imposed by the organs involved in the disease process and the severity of end-organ damage, and also the patient's general level of fitness or frailty. Possible second-line agents include and are not limited to daratumumab (if not used first line) and immunomodulatory agents such as lenalidomide and pomalidomide [77,78].

Bispecific antibodies are emerging as promising novel therapies for patients with relapsed disease. Teclistamab, a bispecific T-cell engager (B cell maturation antigen [BCMA] × CD3) antibody, has been demonstrated to achieve a deep and rapid hematological response in patients with relapsed or refractory disease [79].

Chimeric antigen receptor T-cell (CAR T) therapy also represents a novel therapy utilizing T-cells that are genetically engineered to target and destroy cells expressing an antigen. A phase 1a/b study of 11 patients was the first proof of concept that anti-BCMA CAR T cell therapy is safe and further studies are required to assess efficacy in patients with systemic AL amyloidosis [80].

Venetoclax is a selective B-cell lymphoma 2 (BCL-2) inhibitor, which has been used in patients with t(11;14), who have a high expression of BCL-2. A multicenter registry of 26 patients with relapsed or refractory disease demonstrated that treatment with venetoclax was safe and achieved high rates of hematological response [81]. Another retrospective analysis of 43 previously treated patients demonstrated that the best responders harbored t(11;14) [82].

16. Autologous stem cell transplant

High-dose intravenous melphalan and autologous peripheral-blood stem-cell transplantation (HDM-ASCT) have been used in selected patients with systemic AL amyloidosis since the 1990s, with numerous studies demonstrating that if successful it can result in a prolonged remission lasting for greater than 10 years [83]. However, the vast majority of patients are deemed ineligible for HDM-ASCT because of either a poor performance status, advanced organ dysfunction, or multiorgan disease. HDM-ASCT remains high risk with a significant treatment-related mortality, and therefore, patient selection remains paramount to its success. Current data suggests that between 10% and 20% of patients with systemic AL amyloidosis could be considered eligible for HDM-ASCT and it should be reserved for patients who are young, who have not had previous amyloid-related gastrointestinal bleeding or clinically significant autonomic disease, who have a good performance status, who do not have advanced renal failure, and who have favorable serum cardiac biomarkers [84].

17. Anti-amyloid therapies

Chemotherapy targets the underlying abnormal plasma cell clone to reduce the production of the amyloidogenic precursor proteins and hence reduce the formation of amyloid fibrils, but chemotherapy does not accelerate removal of fibrils that have already deposited within the myocardium. The removal of amyloid fibrils represents a significant unmet clinical need, especially for those with advanced cardiac disease. This represents a significant area of ongoing research with several anti-amyloid therapies at multiple different stages of development.

Birtamimab (NEOD0001) is a fully humanized monoclonal antibody that is designed to target and neutralize soluble toxic light chain aggregates and deplete insoluble amyloid fibrils that have already deposited within the organs by activating macrophage-mediated degradation. The efficacy of birtamimab was assessed in the VITAL trial (A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, 2-Arm, Efficacy and Safety Study of NEOD001 Plus Standard of Care Versus Placebo Plus Standard of Care in Subjects With Light Chain (AL) Amyloidosis) whereby patients with systemic AL amyloidosis were randomized to birtamimab + standard of care or to placebo + standard of care. The trial was terminated early following a futility analysis, but there was a numerical trend favoring birtamimab in the analysis of the primary composite end point of all-cause mortality and cardiovascular hospitalization in the overall population and it was hypothesized to be driven by a treatment effect in the most advanced patients (Mayo stage IV). A subsequent post-hoc analysis confirmed a significant improvement in survival in Mayo stage IV patients who received birtamimab [85]. The AFFIRM-AL study (A Study to Evaluate the Efficacy and Safety of Birtamimab in Mayo Stage IV Patients with AL Amyloidosis) is a randomized, double-blind, placebo-controlled phase 3 trial that has been designed to confirm this finding and is currently ongoing.

Anselamimab (CAEL-101) is a chimeric monoclonal antibody that targets a cryptic epitope on light-chains that becomes exposed when the light-chains are misfolded, and hence targets both misfolded free light-chains and amyloid fibrils that have already deposited in organs. It opsonizes the misfolded light-chains and amyloid fibrils and, in turn, activates a macrophage-mediated degradation process. A small phase 1a/b study demonstrated that following 4-weeks of treatment with anselamimab there was a significant reduction in NT-proBNP, with the majority of patients demonstrating an NT-proBNP response (8/12); and a significant improvement in global longitudinal strain [86]. The efficacy of anselamimab is currently being assessed in two randomized, double-blind, phase 3 trials that are designed to evaluate the additive benefit of anselamimab to the standard of care in patients with advanced cardiac amyloidosis (A Study to Evaluate the Efficacy and Safety of CAEL-101 in Patients with Mayo Stage IIIa AL Amyloidosis and A Study to Evaluate the Efficacy and Safety of CAEL-101 in Patients with Mayo Stage IIIb AL Amyloidosis).

AT-02 is a fusion protein that consists of a humanized immunoglobulin monoclonal antibody with an amyloid binding peptide genetically fused to the light-chain. This peptide binds to multiple different amyloid fibrils with a high affinity and the

immunoglobulin promotes a macrophage-mediated degradation process. Preclinical studies have demonstrated that AT-02 binds with a high affinity to amyloid fibrils and subsequently induces macrophage-mediated phagocytosis [87]. A phase 1 study will assess the safety, tolerability, and pharmacokinetics of rising doses of AT-02 in healthy volunteers and patients with systemic amyloidosis (A Three-part, Phase 1, Single-ascending, and Multiple-ascending Dose Escalation Study in Healthy Volunteers and Subjects With Systemic Amyloidosis to Assess the Safety, Tolerability, and Pharmacokinetics of AT-02) and a phase 2 open-label extension study will evaluate the long-term safety, tolerability, and clinical activity of AT-02 in patients with systemic amyloidosis by measuring the changes in cardiac biomarkers and cardiac imaging parameters (A Phase 2, Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of AT-02) (Table 4).

18. Conclusions

An improved understanding of the pathophysiology responsible for systemic AL amyloidosis has resulted in transformative changes in diagnostics, risk stratification, and treatments, all of which have contributed to improved outcomes. Developments in cardiac imaging have played a key role in enhancing understanding of the underlying disease process and are able to inform treatment decisions and treatment targets at diagnosis. Cardiac imaging enables a noninvasive measure of the cardiac amyloid burden, which in turn allows direct visualization of the treatment effects and will be crucial in determining the efficacy of anti-amyloid therapies that seek to facilitate the removal of amyloid fibrils and induce disease regression. Despite these improvements, many patients with systemic AL amyloidosis are still diagnosed at a late disease stage, and therefore, future research must focus on improving earlier detection of this disease process to facilitate prompt initiation of treatment.

19. Future perspectives

Unprecedented progress has been made in treating systemic AL amyloidosis and the leveraging of targeted anti-plasma cell therapies has resulted in improved survival. However, many patients are still being diagnosed with advanced or even end-stage cardiac disease. Future efforts should focus on earlier diagnosis, which in turn would enable the prompt initiation of chemotherapy. Earlier diagnosis could be facilitated by improvements in the diagnostic accuracy of cardiac imaging investigations. The use of artificial intelligence and more specifically convolutional neural networks has already begun to revolutionize multiple areas of cardiovascular medicine and could play a key role in earlier diagnosis in systemic AL amyloidosis. Artificial intelligence-based diagnostic algorithms could utilize either artificial intelligence-derived measurements in multiparametric diagnostic scoring systems or an artificial intelligence-based deep learning model to flag a suspicion of cardiac amyloidosis from routine echocardiograms and potentially result in more patients being diagnosed earlier in the disease process [88].

Table 4. Summary of anti-amyloid therapies.

Drug	Mechanism of action	Stage of approval	Route of administration	Phase 3 clinical trial	Inclusion criteria	Intervention	Primary end point	Trial outcomes
Birtamimab (NEOD0001)	Humanized monoclonal antibody that binds directly to a conserved epitope in misfolded light chains	Under investigation	Intravenous infusion	A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, 2-Arm, Efficacy and Safety Study of NEOD001 Plus Standard of Care Versus Placebo Plus Standard of Care in Subjects With Light Chain (AL) Amyloidosis (NCT02312206)	- Treatment naïve patients with cardiac AL amyloidosis - NT-proBNP ≥ 650 and ≤ 8500 ng/L - eGFR ≥ 30 mL/min per 1.73 m^2	Patients were randomized 1:1 to receive birtamimab + SOC or placebo +SOC	Time to composite of all-cause mortality or cardiac hospitalization	- In the overall population there were no significant differences in primary outcome between the two groups. - Post-hoc analysis of patients with Mayo stage IV disease demonstrated a significant improvement in all-cause mortality with birtamimab compared with placebo.
Ansalamimab (CAEL-101)	Chimeric monoclonal antibody targeting a cryptic epitope on immunoglobulin light chains that is exposed when the light chains are misfolded	Under investigation	Intravenous infusion	A Study to Evaluate the Efficacy and Safety of Birtamimab in Mayo Stage IV Patients with AL Amyloidosis (NCT04973137) A Study to Evaluate the Efficacy and Safety of CAEL-101 in Patients With Mayo Stage IIIa AL Amyloidosis (NCT04512235)	- Treatment naïve patients with cardiac AL amyloidosis - Mayo stage IV disease - NT-proBNP ≤ 8500 ng/L - Treatment naïve patients with cardiac AL amyloidosis - Mayo stage IIIa based on the European Modification of the 2004 Standard Mayo Clinic Staging	Patients were randomized 2:1 to receive birtamimab + SOC or placebo +SOC	Time to composite of all-cause mortality	Trial currently ongoing.
AT-02	Pan amyloid removal technology using a single-chain fusion protein to stimulate immunological removal of amyloid	Under investigation	Intravenous infusion	A Study to Evaluate the Efficacy and Safety of CAEL-101 in Patients with Mayo Stage IIIb AL Amyloidosis (NCT04504825)	- Treatment naïve patients with cardiac AL amyloidosis - Mayo stage IIIb based on the European Modification of the 2004 Standard Mayo Clinic Staging	Patients were randomized 2:1 to receive ansalamimab + SOC or placebo +SOC	Hierarchical combination of time to All-cause mortality and frequency of cardiovascular hospitalizations Hierarchical combination of time to All-cause mortality and frequency of cardiovascular hospitalizations	Trial currently ongoing. Small phase 1 and phase 2 trials are currently ongoing.

eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-b-type natriuretic peptide; SOC = Standard of care.

The elimination of manual contouring also allows the artificial intelligence software to provide precise and robust measurements that are not subject to intra- and inter-observer variability. These advantages have the potential to improve the utility of cardiac imaging in tracking the response to treatment and may even uncover additional parameters that can be used to track the treatment response [61]. The application of artificial intelligence to cardiac imaging modalities such as echocardiography and CMR also has important implications on work flow with the increased efficiency and reduced reporting time enabling more scans to take place.

Considering the development of several novel agents that promote disease regression by stimulating macrophage-mediated degradation of amyloid fibrils, the ability to non-invasively track changes in the amyloid burden is of increasing importance [85–87]. CMR with multiparametric mapping has already demonstrated utility in tracking changes in the multiorgan amyloid load, and although many amyloid-specific PET tracers are currently at early investigational stages, preliminary data suggest that these tracers are also able to track changes in the amyloid load in response to treatment. Multimodality imaging studies are needed to optimize the precision of each imaging technique and also to decipher which imaging modality is most suited to tracking changes in the amyloid load over time.

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