REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Systemic Light Chain Amyloidosis

Vaishali Sanchorawala, M.D.

CARE OF PATIENTS WITH SYSTEMIC IMMUNOGLOBULIN LIGHT CHAIN (AL) amyloidosis has undergone transformative changes, leading to marked, steady progress in outcomes for patients over the past four decades. Substantial progress has been made through the implementation of treatments targeting the underlying plasma cell dyscrasia, mostly adapted from the treatment of myeloma. The past decade has seen remarkable advancements that have instilled hope among patients with AL amyloidosis. This review focuses on recent advances in our understanding of the pathogenesis and clinical features of amyloid fibrillogenesis, as well as risk stratification and therapeutic advances, and describes unmet needs in AL amyloidosis.

From the Amyloidosis Center, Boston University Chobanian and Avedisian School of Medicine, Boston Medical Center, Boston. Dr. Sanchorawala can be contacted at vaishali.sanchorawala@bmc.org or at Boston University Chobanian and Avedisian School of Medicine, 72 E. Concord St., K-5, Boston, MA 02118.

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CME

Amyloidosis comprises a group of diseases triggered by the misfolding of a soluble precursor protein. This misfolding leads to the formation of oligomers, aggregates, and amyloid fibrils characterized by pleated β-sheets, which are deposited extracellularly in various organs and tissues. The result is progressive organ dysfunction, organ failure, and eventual death.[1] Organ dysfunction is due to the disruption of architecture caused by amyloid deposits, direct cytotoxic effects from protein aggregates or oligomers, or both.[2]

A total of 42 soluble precursor amyloidogenic proteins that can form extracellular amyloid fibrils have been identified to date.[3] Amyloidoses are classified as systemic or localized and are further classified according to the site of the amyloid deposits and the site of precursor protein production. Systemic amyloidosis can be hereditary or acquired. The two most common forms — AL amyloidosis and wild-type transthyretin (ATTRwt) amyloidosis — are acquired. Although both these forms of systemic amyloidosis are common, ATTRwt amyloidosis is more prevalent.

AL amyloidosis is associated with a clonal plasma cell dyscrasia and is caused by abnormal or excessive production of amyloidogenic immunoglobulin light chains, which aggregate into oligomers and amyloid fibrils, leading to organ dysfunction.[4] ATTRwt amyloidosis, which affects men over the age of 70 years, is caused by the aggregation of normal transthyretin (TTR) and predominantly results in cardiomyopathy. Systemic hereditary or familial amyloidosis can also be caused by genetic mutations inherited in an autosomal dominant manner.[5] More than 120 point mutations in the gene encoding TTR, a transport protein for thyroxine and retinol-binding protein, can cause systemic amyloidosis that mainly affects the peripheral and autonomic nervous systems and the heart.[6]

PATHOGENESIS

A pathognomonic feature of systemic amyloidosis is abnormal folding of a normal soluble precursor protein (Fig. 1). In AL amyloidosis, the abnormal folding is the result of either a proteolytic event or an amino acid sequence that renders an immunoglobulin light chain thermodynamically and kinetically unstable, leading to self-aggregation.[7] These aggregates interact with glycosaminoglycan and serum

amyloid P protein, promoting fibril formation and stabilizing amyloid deposits in tissues, disrupting tissue architecture, and ultimately causing organ dysfunction. Emerging evidence from *Caenorhabditis elegans*[8] and zebrafish models[9] suggests that amyloidogenic precursor aggregates

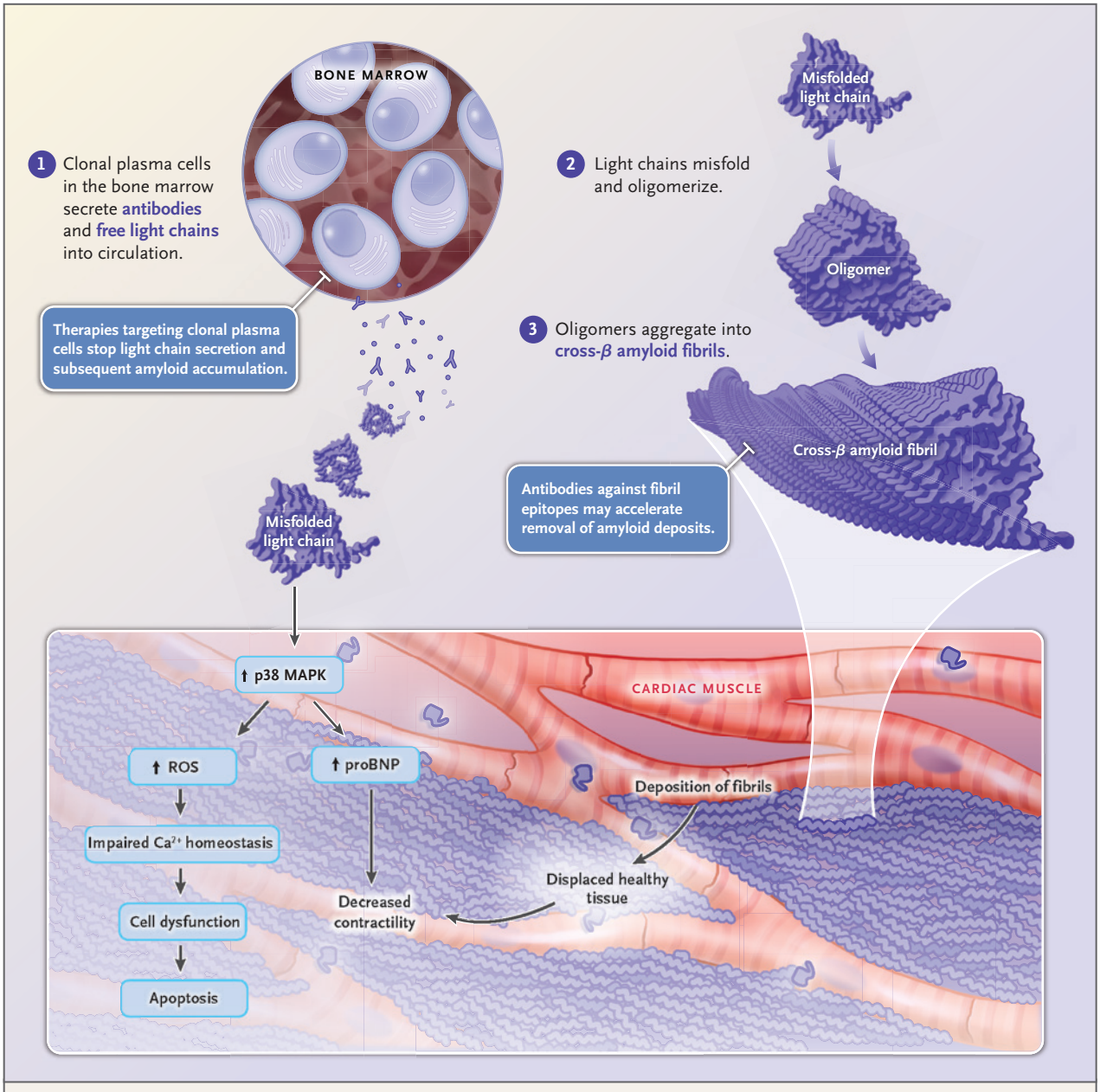

Figure 1. Pathogenesis of AL Amyloidosis.

Fibrillogenesis in immunoglobulin light chain (AL) amyloidosis is initiated from a small B-cell clone in the bone marrow that produces thermodynamically and kinetically unstable immunoglobulin light chains, which interact with the tissue microenvironment, leading to aggregation and oligomer formation. Oligomers, and the misfolded protein, have toxic effects in target organs and form highly organized, cross-β–pleated amyloid fibrils by interacting with serum amyloid P component (SAP) and glycosaminoglycans (GAGs). The accumulation of amyloid deposits in vital organs can cause mass action and disruption of the architecture. Proteotoxic effects from soluble precursor proteins and oligomers can also lead to organ dysfunction. Amyloidogenic light chains with cardiotoxic effects trigger the activation of p38 mitogen-activated protein kinase (MAPK) signaling, leading to elevated levels of reactive oxygen species (ROS) and also contributing to the transcription of pro–B-type natriuretic peptide (proBNP).

also have direct cytotoxic effects that contribute to organ dysfunction. Proteostasis, a cellular mechanism, normally ensures proper protein folding and function.[10] However, genetic mutation, impaired proteostasis due to aging, or other factors may favor misfolding and aggregation. Protein aggregates form amyloid fibrils, characterized by nonparallel cross-β fiber structures. Amyloid fibrils have a diameter of 8.0 to 10.0 nm, as determined with the use of electron microscopy.[11]

AL amyloidosis is typically associated with a plasma cell disorder that is responsible for producing lambda immunoglobulin light chains in 75 to 80% of cases and kappa light chains in the remaining 20 to 25%. AH amyloidosis, resulting from immunoglobulin heavy chains, and AH/AL amyloidosis, resulting from immunoglobulin heavy and light chains, are much less common.[12] The chromosomal translocation t(11;14), which brings together the immunoglobulin heavy-chain locus (IgH) and the oncogene cyclin D1, is characteristic of AL amyloidosis, occurring in approximately 50% of cases,[13] whereas hyperdiploidy, which is common in myeloma, is observed in approximately 10% of cases of AL amyloidosis.[14] Somatic mutations in the *IGLV* group of genes, encoding the light chain variable region, decrease protein stability, which facilitates amyloid fibril formation.[15]

RISK FACTORS

Risk factors for AL amyloidosis remain unclear, but preexisting monoclonal gammopathy and myeloma are common. Among patients with monoclonal gammopathy of unknown significance (MGUS), the relative risk is 8.8,[16] with a 1% incidence of AL amyloidosis observed in a study involving 1384 patients with MGUS. AL amyloidosis is diagnosed in as many as 10 to 15% of patients with myeloma, and 38% of patients with myeloma have Congo red–positive deposits in subcutaneous fat aspirates, bone marrow–biopsy specimens, or both.[17] An increase in monoclonal serum free light chain levels precedes the development of AL amyloidosis by more than 4 years in all patients.[18] Exposure to Agent Orange, an herbicide used in the Vietnam War, may be associated with AL amyloidosis, although the evidence is limited.[19] N-glycosylation of monoclonal kappa light chains can serve as a predictive factor for an earlier diagnosis of AL amyloidosis in patients with MGUS.[20,21]

EPIDEMIOLOGY

Epidemiologic data on AL amyloidosis are limited, primarily because of the absence of comprehensive population databases. The prevalence of this disease tends to increase with advancing age. In the Olmsted County Project in Minnesota, the overall incidence rate of AL amyloidosis was 8.9 cases per 1 million person-years between 1950 and 1989, 10.5 cases per 1 million person-years between 1970 and 1989, and 12.0 cases per 1 million person-years between 1990 and 2015.[22] A calculated crude incidence rate of 10.4 cases per 1 million person-years was reported across 38 countries. As of 2018, approximately 74,000 cases of AL amyloidosis had been diagnosed globally in the preceding 20 years. The estimated incidence was 10 cases per 1 million population, and the estimated 20-year prevalence was 51 cases per 1 million population.[23] A real-world study based on a U.S. health care claims database showed a significant increase in the prevalence of AL amyloidosis, from 15.5 cases per 1 million population in 2007 to 40.5 cases per 1 million population in 2015, whereas the incidence rate remained steady, ranging from 9.7 to 14.0 cases per 1 million person-years.[24]

CLINICAL PRESENTATIONS

In the majority of cases, AL amyloidosis is characterized as a rapidly progressive disease with various clinical syndromes (Fig. 2). Common nonspecific symptoms include fatigue and weight loss; however, organ-specific symptoms often lead to the diagnosis. Diagnostic delays occur because of low awareness among clinicians.[25] The kidneys are commonly affected in AL amyloidosis (in 60 to 70% of patients); kidney effects typically manifest as nephrotic-range proteinuria, hypoalbuminemia, secondary hyperlipidemia, and edema. In some cases, kidney failure occurs in the absence of proteinuria, as a result of interstitial or vascular amyloid deposition.[26]

The heart is also frequently involved (in 70 to 80% of patients), and cardiac involvement is the leading cause of death. Early signs include low voltage on electrocardiography and concentric ventricular thickening on echocardiography, along with diastolic dysfunction. Poor atrial contractility occurs even in sinus rhythm, and patients with

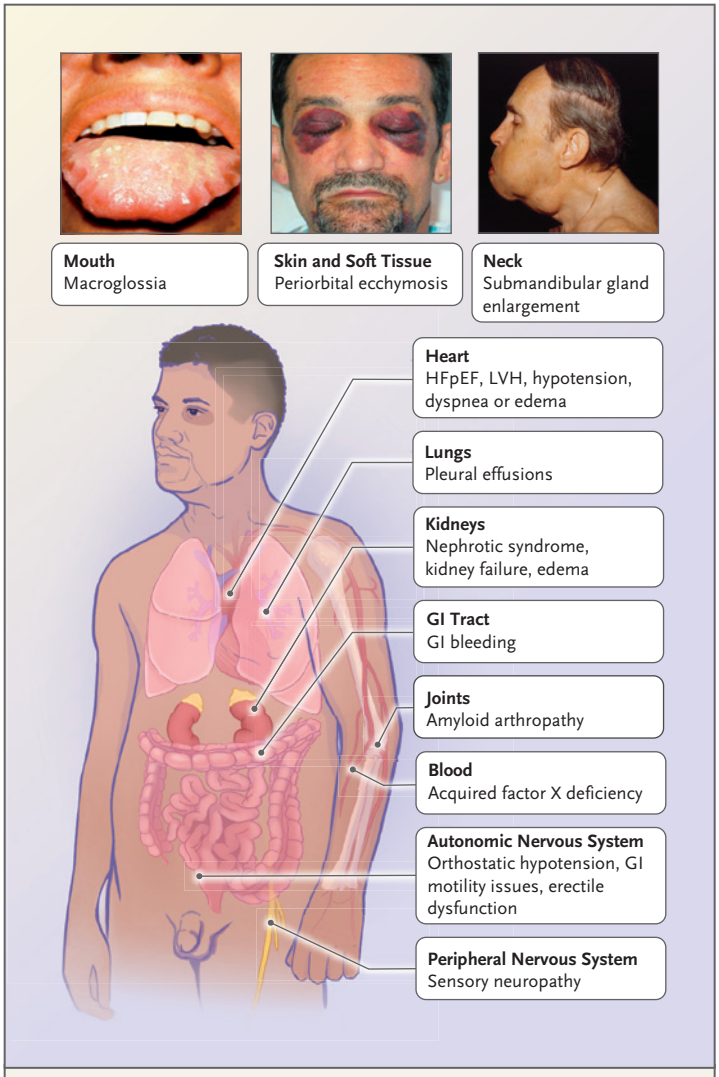

Figure 2. Clinical Presentation of AL Amyloidosis.

The heart, kidneys, liver, gastrointestinal (GI) tract, peripheral and autonomic nervous systems, and soft tissues are commonly affected vital organs. Pathognomonic presentations of AL amyloidosis are spontaneous periorbital ecchymosis (raccoon eyes), submandibular gland enlargement, macroglossia, and acquired factor X deficiency. Clinical symptoms and signs associated with vital organ involvement can be vague and nonspecific.

cardiac AL amyloidosis are at risk for the development of atrial thrombi and thromboembolic complications. Elevated levels of serum cardiac troponin, N-terminal pro–B-type natriuretic peptide (NT-proBNP), or both are common.[27] Bradyarrhythmias often precede terminal cardiac decompensation.[28]

Nervous system symptoms include small-fiber neuropathy and autonomic dysfunction, manifested as gastrointestinal motility disturbances, early satiety, dry eyes and mouth, orthostatic hypotension, and neurogenic bladder. Macroglossia is seen in approximately 10 to 20% of patients. Liver involvement causes cholestasis and hepatomegaly. Hyperbilirubinemia can occur as a terminal event in patients with liver involvement. Splenic involvement manifests as functional hyposplenism rather than splenomegaly. "Easy bruising" may occur as a result of amyloid deposits or clotting factor X deficiency. Cutaneous ecchymoses, nail dystrophy, alopecia, and amyloid arthropathy may also occur. The presence of a multisystemic illness that is unexplained by common diseases or general fatigue along with any of these clinical syndromes should prompt testing for amyloidosis.

The precise mechanisms governing organ tropism in AL amyloidosis remain unclear. Certain features of the light chain variable region genes elevate the risk of specific organ involvement. For instance, the germline gene *IGLV6-57* is more prevalent among patients with kidney manifestations, whereas *IGLV1-44* is associated with a higher risk of cardiac involvement. Most cases of systemic AL amyloidosis are attributed to lambda light chains, but the kappa light chain of the *IGKV1-33* germline mutation targets the liver.[29,30]

DIAGNOSIS

Nonspecific symptoms linked to AL amyloidosis often contribute to diagnostic delays. Consideration of AL amyloidosis is crucial in patients with unexplained proteinuria, restrictive cardiomyopathy, peripheral neuropathy with autonomic features, carpal tunnel syndrome in both wrists, or hepatomegaly without imaging abnormalities and in any patient with a monoclonal gammopathy or multiple myeloma with atypical manifestations such as macroglossia or raccoon eyes. A high index of suspicion is essential to prevent delays in diagnosis.

The diagnosis of AL amyloidosis requires evidence of amyloid deposits in tissue (target or surrogate) and evidence of a plasma cell dyscrasia. Tissue amyloid deposits show green birefringence when stained with Congo red dye and viewed with the use of polarized light microscopy. Fine-needle aspiration of abdominal fat is a simple procedure that is positive for amyloid deposits in approximately 70 to 75% of patients

with AL amyloidosis.[31] Other tissues that allow for relatively noninvasive biopsy procedures are the minor salivary glands, gingiva, rectum, and skin. However, if the clinical index of suspicion is high and abdominal fat-pad aspiration is negative for Congo red staining, biopsy of an affected organ may be necessary to establish the diagnosis of amyloidosis. Examination of specimens from both abdominal fat and bone marrow biopsies identifies 85% of patients with AL amyloidosis.[31]

After a tissue diagnosis of amyloidosis has been established by means of biopsy of a surrogate or target organ, confirmation of AL amyloidosis requires demonstration 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, the presence of lambda or kappa restricted plasma cells in a bone marrow biopsy specimen, or all three. Immunofixation electrophoresis should be performed on serum and urine specimens because in AL amyloidosis, unlike multiple myeloma, the concentration of the monoclonal component is often too low to be detected by protein electrophoresis.

Even if a monoclonal immunoglobulin light chain is identified in serum or urine, bone marrow aspiration and biopsy are mandatory to assess the plasma cell burden and to rule out multiple myeloma and other, less common disorders that can be associated with AL amyloidosis, including B-cell lymphoproliferative disorders such as chronic lymphocytic leukemia, indolent lymphoma, and Waldenström's macroglobulinemia.[32]

If amyloid deposits are detected in biopsy specimens, accurate identification of the precursor protein is crucial for guiding treatment. Such identification is feasible with the use of immunohistochemical studies [33] in highly experienced laboratories and with the use of immunogold electron microscopy.[34] The accuracy of immunohistochemical studies is dependent not only on laboratory expertise but also on an extensive panel of antibodies for reporting. This is not the method of choice for accurate amyloid fibril typing, although immunofluorescence staining of a kidney-biopsy specimen may have sufficient accuracy for establishing a tissue diagnosis of amyloidosis. However, a mass spectrometry–based analysis of the amyloid-containing tissues is now considered the best approach, with a reported sensitivity of 88% and a specificity of 96%.[35,36] Although not widely available, mass spectrometry is performed in some reference laboratories to unequivocally confirm the protein subunit. It is particularly important to distinguish between AL amyloidosis and V122I ATTR variant amyloidosis, especially in Black patients, because of the high prevalence of the variant form and a clinical presentation that may resemble AL amyloidosis. Both conditions can involve monoclonal gammopathy, making accurate diagnosis and management essential for appropriate treatment.[37]

Cardiac imaging is a critical component of a comprehensive cardiac assessment in patients with AL amyloidosis.[38,39] Echocardiography — specifically, strain imaging and Doppler techniques — aids in identifying early signs of cardiac amyloidosis, such as restrictive ventricular filling patterns. Cardiac magnetic resonance imaging contributes valuable information on myocardial thickness, late gadolinium enhancement, and T1-weighted mapping for extracellular volume. Positron-emission tomography with the use of radiotracers such as 18F-florbetapir targets amyloid deposits, especially in the myocardium. In contrast, bone scintigraphy can be useful in diagnosing ATTR cardiac amyloidosis. The integration of these advanced imaging techniques allows for a more nuanced understanding of cardiac involvement in AL amyloidosis.

STAGING SYSTEM AND RISK STRATIFICATION

The survival of patients with systemic AL amyloidosis is dependent on the severity of cardiac dysfunction at the time of diagnosis. Patients who receive a diagnosis late in the clinical course of the disorder (when heart damage is often advanced) have a median survival of 3 to 6 months, whereas patients without cardiac involvement can survive for many years. The current staging systems for risk stratification and prognostication use the biomarkers of plasma cell dyscrasia and cardiac and kidney involvement (Table 1).

The Mayo Clinic 2004 staging system is based on the levels of NT-proBNP and cardiac troponins[40] and was modified by European investigators to identify and classify patients at very high risk — that is, those with an NT-proBNP level exceeding 8500 pg per milliliter.[41] This cardiac staging system is the most widely used to predict early death. The system was modified in

Table 1. Staging Systems for AL Amyloidosis.*

System, Criteria, and Stage	Treatment Effect
Mayo Clinic, 2004	
Troponin T level >0.035 ng/ml, NT-proBNP level >332 pg/ml	Hazard ratio for death (95% CI)
Stage I: Neither marker above cutoff	1.0 (reference)
Stage II: 1 marker above cutoff	2.5 (1.9–3.5)
Stage III: both markers above cutoff	6.7 (6.0–9.1)
Mayo Clinic, 2012	
Troponin T level ≥0.025 ng/ml, NT-proBNP level >1800 pg/ml, dFLC >180 mg/liter	Hazard ratio for death (95% CI)
Stage I: 0 markers above cutoff	1.0 (reference)
Stage II: 1 marker above cutoff	1.7 (1.2–2.3)
Stage III: 2 markers above cutoff	4.1 (3.1–5.5)
Stage IV: 3 markers above cutoff	6.3 (4.8–8.3)
European modification, 2013	
NT-proBNP level >8500 pg/ml, troponin T level >0.035 μg/liter, NT-proBNP level >332 pg/ml	Hazard ratio for death (95% CI)
Stage I: neither marker above cutoff	1.0 (reference)
Stage II: 1 marker above cutoff	2.5 (1.9–3.5)
Stage IIIa: both markers above cutoff, NT-proBNP level ≤8500 pg/ml	4.9 (3.6–6.8)
Stage IIIb: both markers above cutoff, NT-proBNP level >8500 pg/ml	11.1 (8.1–15.4)
Boston University, 2019	
Troponin I level >0.1 ng/ml, BNP level >81 pg/ml, BNP level >700 pg/ml	Median overall survival
Stage I: 0 markers above cutoff	>12 yr
Stage II: 1 marker above cutoff	9.4 yr
Stage IIIa: both markers above cutoff, BNP ≤700 pg/ml	4.3 yr
Stage IIIb: both markers above cutoff, BNP >700 pg/ml	1 yr
Renal staging	
eGFR <50 ml/min/1.73 m^2, urinary protein excretion >5 g/24 hr	2-yr risk of dialysis
Stage I: both criteria below cutoff	0–3%
Stage II: one criterion above cutoff	11–25%
Stage III: both criteria above cutoff	60–75%

* BNP denotes B-type natriuretic protein, CI confidence interval, dFLC difference between involved and uninvolved circulating free light chain, eGFR estimated glomerular filtration rate, and NT-proBNP N-terminal proBNP.

2012 to include the clonal burden, assessed as the difference between involved and uninvolved circulating free light chain (dFLC, with a cutoff value of 180 mg per liter), which is a predictor of survival.[42] The Mayo Clinic 2012 staging system predicts late survival more accurately than the Mayo Clinic 2004 staging system, and the Mayo Clinic 2004 staging system with the European modification predicts early death more accurately than the 2012 system. In the current era of effective treatments against the plasma cell clone in patients with AL amyloidosis, the dFLC appears to be less prognostic in these staging systems.[43] Boston University investigators introduced a staging system incorporating BNP and troponin I, which also predicts survival.[44,45] Patients with AL amyloidosis who have a very low dFLC level (<50 mg per liter) have a substantially better outcome, irrespective of the cardiac stage, than those with higher dFLC levels.[46,47,48]

A renal staging system has also been developed, which uses biomarkers of 24-hour urinary

protein excretion and the estimated glomerular filtration rate to predict the risk of progression to dialysis at 2 years and the annual risk.[49] Other biomarkers, such as von Willebrand factor,[50] D-dimer,[51] and growth differentiation factor 15,[52] have been shown to predict outcomes and survival but have not yet been incorporated in staging systems.

MANAGEMENT

Substantial increases in survival rates have been observed among patients with AL amyloidosis. A longitudinal natural history study spanning 40 years revealed a consistent improvement in survival over time, with 5-year overall survival increasing from 15% in the mid-1980s to 48% in the mid-2010s.[53]

The treatment of AL amyloidosis typically involves a multidisciplinary approach and should be provided by a medical team that is experienced in treating this rare condition, since the approach can vary according to the extent and severity of organ involvement.[54] The three principles of treatment are to rapidly and sustainably reduce causative amyloidogenic monoclonal protein production; to individualize therapy on the basis of organ involvement, anticipated toxic effects, and the extent of disease; and to provide organ-specific supportive care in order to minimize treatment-related complications, reduce the risk of death, and maximize the quality of life.

Table 2. Supportive Therapies in Patients with AL Amyloidosis.*

Clinical Presentation	Supportive Measures†
Fluid retention	Salt restriction Loop diuretics
Orthostatic hypotension	Behavioral modifications Thigh-high stockings Midodrine, pyridostigmine, or droxidopa
Neuropathy	Gabapentin or pregabalin Serotonin–norepinephrine reuptake inhibitors (duloxetine or venlafaxine) Analgesic agents
Diarrhea	Loperamide or diphenoxylate–atropine Tincture of opium Octreotide Testing to rule out small-bowel intestinal bacterial overgrowth
Malnutrition	Nutritional supplements Parenteral nutrition with a consultation from a nutritionist
Renal failure	Dialysis Kidney transplantation in selected cases
Heart failure	Loop diuretics Salt restriction Mineralocorticoid receptor antagonists Digoxin (used with extreme caution) ACE inhibitors and ARBs (used with caution) Heart transplantation, LVADs, or pacemakers or AICDs in selected cases
Bleeding complications	FFP Recombinant factor VIIa Prothrombin complex concentrate

* ACE denotes angiotensin-converting enzyme, AICD automatic implantable cardioverter–defibrillator, ARB angiotensin-receptor blocker, FFP fresh-frozen plasma, and LVAD left ventricular assist device.
† All these measures can be used exclusively or in combination.

SUPPORTIVE THERAPY

Supportive care, which requires collaboration among specialists (Table 2), aims to alleviate symptoms and preserve organ function.[55] Treatment for amyloid cardiomyopathy includes sodium restriction, careful diuretic use, and possible use of angiotensin-converting–enzyme (ACE) inhibitors for afterload reduction. Digoxin is generally not beneficial except in certain cases of atrial fibrillation.[56] Caution is needed with anticoagulation because of the risk of bleeding. Calcium-channel blockers are typically avoided. Recurrent syncope may warrant a pacemaker, whereas ventricular arrhythmias are treated with amiodarone or implantable defibrillators in some instances.

Orthostatic hypotension can be managed with various measures. Fludrocortisone is often not a good option because of associated fluid retention. Supportive treatment for amyloid-associated kidney disease includes salt restriction, diuretics, and management of hyperlipidemia. ACE inhibitors or angiotensin-receptor blockers may help with proteinuria if they are not contraindicated by hypotension. Hemodialysis and peritoneal dialysis are options for end-stage renal disease. The role of sodium–glucose transport protein 2 (SGLT2) inhibitors is being explored for kidney and cardiac involvement. Diarrhea is an incapacitating problem for patients with autonomic nervous system involvement and can be managed with certain medications. Adequate oral or intravenous feeding is essential for undernourished patients. Neuropathic pain may be managed with gabapentin, duloxetine, or pregabalin. Non-nephrotoxic analgesic agents may be used as adjuvant therapy. Bleeding complications are common and may warrant various interven-

Table 3. Hematologic and Organ Response Criteria.

Response	Criteria*
Hematologic	
Complete response	Absence of monoclonal protein in serum and urine on IFE and either a normal FLC ratio or an uninvolved FLC concentration that is greater than the involved FLC concentration, with or without an abnormal ratio
Very good partial response	dFLC <40 mg/liter
Partial response	>50% Reduction in dFLC
No response	≤50% Reduction in dFLC
Organ	
Cardiac response	
Complete response	Nadir NT-proBNP ≤350 pg/ml or BNP ≤80 pg/ml
Very good partial response	>60% Reduction in NT-proBNP or BNP
Partial response	31–60% Reduction in NT-proBNP or BNP
No response	≤30% Reduction in NT-proBNP or BNP
Renal response	
Complete response	Nadir value for proteinuria ≤200 mg/24 hr
Very good partial response	>60% Reduction in proteinuria to nadir value >200 mg/24 hr
Partial response	31–60% Reduction in proteinuria
No response	≤30% Reduction in proteinuria
Hepatic response	≥50% Decrease in abnormal alkaline phosphatase value or decrease in radiographic liver size by ≥2 cm

* For patients with a dFLC value between 50 and 20 mg per liter, a hematologic response other than a complete response (ungraded) is reached when the dFLC value falls below 10 mg per liter. FLC denotes free light chain, and IFE immunofixation electrophoresis.

tions, including splenectomy for acquired factor X deficiency, as well as clotting-factor replacements. Iron deficiency due to chronic blood loss in patients with a bleeding diathesis or gastrointestinal involvement should be monitored and corrected with iron infusions.

ASSESSMENT OF TREATMENT RESPONSE

Criteria for hematologic and organ responses in patients with AL amyloidosis are unified and formalized (Table 3). An international group established and validated hematologic and organ response criteria.[57] The criteria for organ response, which previously were binary, have been graded and can predict survival and longer-term clinical outcomes.[58,59] Refinements in hematologic response criteria have been suggested, with an iFLC (involved free light chain) value of less than 20 mg per liter and a dFLC value of less than 10 mg per liter predicting longer survival.[60,61] Emerging data indicate the importance of measurable residual disease, which may be responsible for residual organ dysfunction despite a high-quality hematologic response.[62,63,64] An early and deep hematologic response has been found to lead to significantly prolonged survival, and therefore the hematologic response should be measured every month during treatment.[65] Improved organ function may be evident only 6 to 12 months after treatment, although delayed responses, occurring up to 24 months after treatment, may also occur.[59,66] The time from initiation of treatment directed against the plasma cell dyscrasia to the best organ response can vary: 24 months for a cardiac response, 29 months for a renal response, and 35 months for a hepatic response.[59]

TREATMENT OF NEWLY DIAGNOSED AL AMYLOIDOSIS

High-dose intravenous melphalan and autologous peripheral-blood stem-cell transplantation (SCT) have been used as a treatment since the mid-1990s for selected patients with AL amyloidosis. Numerous single-center and multicenter studies of SCT have shown its efficacy in AL amyloidosis.

SCT leads to a hematologic complete response in 40% of patients, and the median duration of a complete response is 12.3 years.[67] With a median follow-up of 8 years, the median event-free survival and overall survival are prolonged, at 3.3 and 7.6 years, respectively.[67] Patients with a hematologic complete response had a median overall survival of 15 years, and 30% of these patients survived for more than 20 years.[67] However, only 10 to 20% of patients with newly diagnosed AL amyloidosis are eligible for SCT because of factors such as poor performance status, advanced organ dysfunction, and multiorgan disease. The expanding therapeutic landscape is another reason for the limited role of SCT.

The International Society of Amyloidosis Working Group, comprising a collaborative effort with representation from six countries, has published guidelines for SCT in AL amyloidosis. These guidelines cover eligibility criteria, indications for induction therapy, stem-cell mobilization and collection, risk-adapted melphalan dosing, and supportive care after SCT.[68]

Patients who are ineligible for SCT (approximately 80%) receive treatment with the combination of cyclophosphamide, bortezomib, and dexamethasone (CyBorD) plus daratumumab, which is the preferred first-line therapy on the basis of 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). CyBorD alone or bortezomib–melphalan–dexamethasone is used when access to daratumumab is limited. Daratumumab–CyBorD yields high percentages of hematologic response, with 78% of patients having a very good partial response or better and approximately 50 to 55% having an organ response 18 months after treatment.[69]

Certain patient characteristics should be considered in choosing a regimen. For example, treatment with the combination of bortezomib, melphalan, and dexamethasone[70] can overcome the effects of both 1q21 gain (which confers a poorer outcome with oral melphalan and possibly daratumumab)[71] and t(11;14) (which confers a poorer outcome with bortezomib).[13] Patients with high-risk disease account for approximately 20% of all patients with AL amyloidosis, and they represent a challenge owing to advanced cardiac disease (stage IIIb) or severe heart failure (New York Heart Association class III or IV).[72]

TREATMENT OF RELAPSE AND PROGRESSION AFTER INITIAL THERAPY

No consensus has been established on the criteria for commencing second-line therapy in patients with progressive disease after initial therapy.[73,74] Patients with relapsed disease can be treated by repeating first-line therapy if the response lasted for more than a year, although such patients have a shorter time to relapse without a reduction in overall survival than patients who are treated with a different therapy for relapsed disease.

The potential options available for the treatment of relapsed systemic AL amyloidosis include proteasome inhibitors,[75,76] anti–CD-38 monoclonal antibodies,[77,78] immunomodulatory agents,[79] venetoclax for patients with t(11;14),[80] bendamustine,[81] high-dose melphalan with autologous SCT,[82,83] bispecific antibodies,[84,85] and even chimeric antigen receptor T-cell therapy.[86] Although it is not possible to be prescriptive regarding the sequencing of therapies, the two guiding considerations are the depth and duration of the initial response and the choice of a class of agents not previously used. The limitations imposed by a patient's reduced level of fitness or frailty and end-organ damage must also be considered. Enrollment in clinical trials is encouraged.

ANTIFIBRIL MONOCLONAL ANTIBODIES

Chemotherapy targets plasma cell dyscrasia and the production of amyloidogenic precursor protein, yet it does not directly resorb or degrade amyloid deposits in tissues. Although markers of organ dysfunction improve with amyloid precursor suppression, two antibodies, birtamimab and anselamimab, are currently being investigated as antifibril agents. Dezamizumab (an anti–serum amyloid P component antibody), once under consideration, is no longer being researched. Antifibril antibodies have the potential to remove amyloid fibrils from organs by activating immune cells for chemical and enzymatic degradation and inducing antibody-dependent phagocytosis.[87]

Birtamimab (NEOD0001) is a fully humanized monoclonal antibody that targets a cryptic epitope on serum amyloid A protein that is revealed when misfolded. This agent cross-reacts with immunoglobulin light chain amyloid fibrils and reportedly activates macrophage-mediated degradation and clearance of light chain fibrils.[88]

A nonprespecified post hoc analysis of data from the VITAL study (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 AL Amyloidosis; ClinicalTrials.gov number NCT02312206), which was terminated early on the basis of an interim futility analysis, showed a survival benefit with birtamimab in patients with Mayo Clinic 2012 stage IV advanced cardiac AL amyloidosis. The international AFFIRM-AL study (A Study to Evaluate the Efficacy and Safety of Birtamimab in Mayo Stage IV Patients with AL Amyloidosis; NCT04973137), a randomized, double-blind, placebo-controlled phase 3 trial designed to confirm this finding, is ongoing.

Anselamimab (CAEL-101) is a chimeric monoclonal antibody targeting a cryptic epitope on immunoglobulin light chains that is exposed when the light chains are misfolded. It binds to misfolded free immunoglobulin light chains, as well as amyloid fibrils deposited in organs. It is hypothesized that CAEL-101 opsonizes the amyloid fibrils and misfolded light chains, thereby attracting and activating macrophages that degrade the complex through phagocytosis, enzymatic and chemical proteolysis, or both.[89] Two randomized, double-blind, phase 3 trials, which have completed enrollment, are designed to evaluate the efficacy and safety of coadministering CAEL-101 with standard treatment for plasma cell dyscrasia in patients with AL amyloidosis and severe cardiomyopathy in stages IIIa and IIIb (A Study to Evaluate the Efficacy and Safety of CAEL-101 in Patients with Mayo Stage IIIa AL Amyloidosis [NCT04512235] and A Study to Evaluate the Efficacy and Safety of CAEL-101 in Patients with Mayo Stage IIIb AL Amyloidosis [NCT04504825]) (Fig. 3).

FUTURE DIRECTIONS

The progress that has been made in treating AL amyloidosis is unprecedented. Future efforts should focus on increasing early diagnosis through

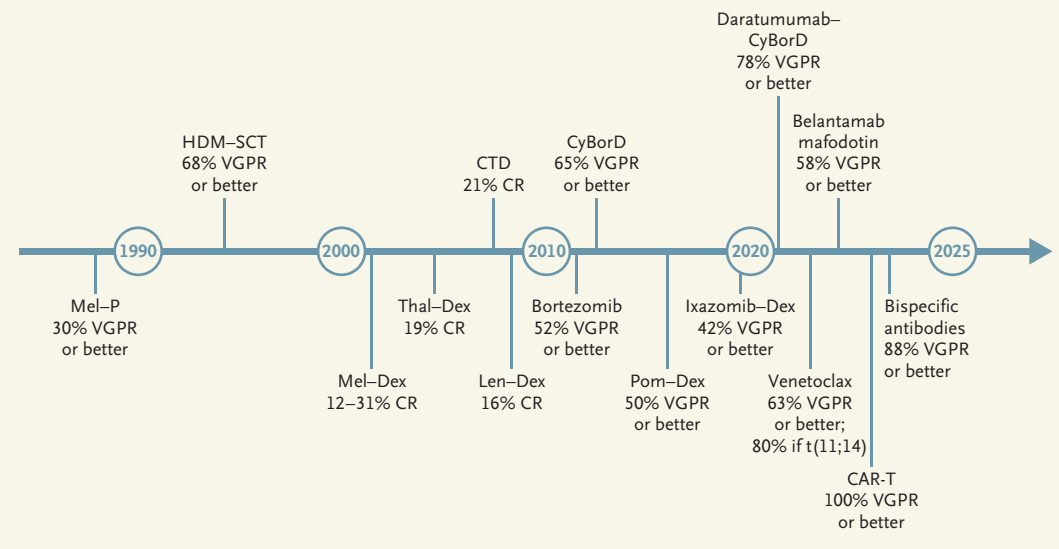

Figure 3. Therapeutic Landscape of AL Amyloidosis.

The therapeutic landscape of AL amyloidosis has seen substantial expansion in the past three decades. The majority of treatment regimens are adapted from myeloma therapies, with a focus on targeting the underlying plasma cell clone. Hematologic response has improved significantly with more effective and contemporary treatments, contributing to an overall increase in survival and a reduction in the rate of early death. CAR-T denotes chimeric antigen receptor T-cell therapy, CR complete hematologic response, CTD cyclophosphamide–thalidomide–dexamethasone, CyBorD cyclophosphamide–bortezomib–dexamethasone, HDM–SCT high-dose melphalan and stem-cell transplantation, Ixazomib–Dex ixazomib–dexamethasone, Len–Dex lenalidomide–dexamethasone, Mel–Dex melphalan–dexamethasone, Mel–P melphalan–prednisone, Pom–Dex pomalidomide–dexamethasone, Thal–Dex thalidomide–dexamethasone, and VGPR very good partial hematologic response.

professional education, defining the standard of care for patients with advanced cardiac disease, defining hematologic or organ progression that warrants additional treatment, evaluating new techniques to assess the hematologic response more stringently, investigating new clone-directed therapies, and developing treatments that target misfolded light chains[90] and amyloid fibril deposits.

CONCLUSIONS

Promising treatments are available for patients with AL amyloidosis. Prompt diagnosis and appropriate referral have the potential to improve survival and outcomes for these patients. Including AL amyloidosis in the differential diagnosis for patients being evaluated for a variety of syndromes, particularly patients with nephrotic-range proteinuria, unexplained nonischemic cardiomyopathy, peripheral neuropathy, unexplained hepatomegaly, or atypical multiple myeloma, should improve diagnostic efficiency. Despite improvements in the diagnosis and treatment of AL amyloidosis, continued basic and clinical research efforts are needed to brighten the future for patients with this disorder.

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