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STATE-OF-THE-ART REVIEW

AL Amyloidosis: Current Chemotherapy and Immune Therapy Treatment Strategies

JACC: CardioOncology State-of-the-Art Review

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ABSTRACT

Immunoglobulin light chain (AL) amyloidosis is an incurable plasma cell disorder characterized by deposition of fibrils of misfolded immunoglobulin free light chains (FLC) in target organs, leading to failure. Cardiac involvement is common in AL amyloidosis and represents the single most adverse prognostic feature. A high index of clinical suspicion with rapid tissue diagnosis and commencement of combinatorial, highly effective cytoreductive therapy is crucial to arrest the process of amyloid deposition and preserve organ function. The clinical use of molecularly targeted drugs, such as proteasome inhibitors and immunomodulatory agents, monoclonal antibodies such as daratumumab, and risk-adjusted autologous stem cell transplant in eligible patients, has radically changed the natural history of AL amyloidosis. Here, we review the state-of-the-art treatment landscape in AL amyloidosis with an eye toward future therapeutic venues to impact the outcome of this devastating illness. (J Am Coll Cardiol CardioOnc 2021;3:467–487) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Amyloidoses are a heterogeneous group of diseases characterized by organized deposition of a misfolded protein in repetitive β-pleated sheets in target organs. The identity of the precursor protein distinguishes the various amyloidoses and guides organ tropism and the therapeutic approach (1). In immunoglobulin light chain (AL) amyloidosis, the amyloidogenic protein is a misfolded immunoglobulin (Ig) free light chain (FLC), typically produced by clonal plasma cells (PC), less often by a more immature B cell neoplasm (2). FLC amyloid deposition can occur in any organ except the central nervous system, underscoring the variable and often complex clinical presentation. A high index of clinical suspicion is crucial to rapidly pursue diagnostic studies and definitive tissue diagnosis in an effort to preserve organ function and maximize likelihood of short-term survival. AL amyloidosis treatment relies on cytoreductive, PC-directed chemotherapy and/or immune-therapy with the goal of achieving rapid and deep hematologic remission to halt progression of end-organ damage. Drugs that are active in the PC cancer multiple myeloma (MM) are typically efficacious in AL amyloidosis, albeit the therapeutic index may substantially differ. For decades a neglected disease with significant limitations in clinical trial execution and accrual, it was not until early 2021 that the U.S. Food and Drug

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ABBREVIATIONS AND ACRONYMS

AL = immunoglobulin light chain

ASCT = autologous stem cell transplant

FLC = free light chains

Ig = immunoglobulin

MM = multiple myeloma

PC = plasma cell

Administration (FDA) approved the first treatment for newly diagnosed AL amyloidosis: a combination of cyclophosphamide, bortezomib, and dexamethasone with the monoclonal antibody (MoAb) daratumumab hyaluronidase (Dara-CyBorD). Dara-CyBorD is the only FDA-approved treatment for AL amyloidosis, with the remainder of PC-directed therapies being used off-label.

The clinical use of proteasome inhibitors (PIs), the scrupulous selection of patients eligible for high-dose chemotherapy followed by autologous stem cell transplant (ASCT) rescue, and most recently, the introduction of CD38-targeting MoAbs have profoundly impacted the outcomes of AL amyloidosis patients. Intensification of upfront treatment with a combination of targeted drugs, immunotherapy, and alkylating agents has resulted in rapid and deep responses even in patients with advanced cardiac involvement, allowing for increased consideration of solid organ transplantation.

In this state-of-the-art review, we briefly discuss the pathogenesis, epidemiology, clinical presentation, and diagnostic criteria of AL amyloidosis as the foundation, and then detail the current therapeutic approaches, with an eye toward promising therapeutic agents.

AL PATHOGENESIS

AL amyloidosis pathogenesis is invariably related to deposition of FLC amyloid fibrils, a distinctive feature from other PC disorders, including MM (**Table 1**). Unorganized amyloidogenic FLCs are directly cytotoxic while deposited FLC fibrils, as they amass, cause distortion of histological architecture, resulting in progressive organ failure and, eventually, death. Amyloidogenic FLC are skewed toward λ Ig light chain (about 75% of cases), and specific Ig light chain genotypes are associated with particular organ tropism (3). It is thought that beyond the intrinsic instability of certain Ig light chain sequences, somatic hypermutation of the variable region and dysfunction of extracellular proteostasis mechanisms both contribute to amyloid formation (4,5). Although AL amyloidosis has been generally regarded as a particularly ominous MM variant or, alternatively, a monoclonal gammopathy of undetermined significance (MGUS) with a mischievous protein, a recently surfaced genetic and functional observation suggests that AL amyloidosis cells and their surrounding bone marrow microenvironment are intrinsically distinct from both these entities (6).

HIGHLIGHTS

- Cardiac involvement in AL amyloidosis is common and represents the single most adverse prognostic factor.
- Chemo-immunotherapies and autologous stem cell transplant lead to prolonged remission and survival in low-stage patients.
- Early diagnosis is critical in AL amyloidosis to avoid irreversible organ damage.
- Rapid and deep FLC reduction is necessary to ensure long-term survival and functional recovery of affected organs.

EPIDEMIOLOGIC CONSIDERATIONS

Historically considered a rare disorder, modern epidemiologic studies suggest that AL amyloidosis is rather underdiagnosed because of the vague nature of early symptoms and variable, often multisystemic clinical presentation. The median age of AL amyloidosis patients at diagnosis is 63 years, and there is a slight male predominance (55%) (7). A preexisting diagnosis of MGUS or smoldering MM is a risk factor for AL amyloidosis (8,9). Further, 15% of newly diagnosed MM patients are concurrently diagnosed with AL, and an extra 1% will be diagnosed with AL amyloidosis throughout the course of their care. The current prevalence of AL amyloidosis is estimated at about 12,000 patients in the United States, and although data regarding impact of race on AL are lacking, the increased incidence of MGUS in Black American individuals suggests that AL amyloidosis may also be more frequent in this patient population (10).

DIAGNOSIS, STAGING, AND PROGNOSTIC FACTORS. A high index of suspicion and prompt diagnostic workup is imperative to diagnose AL amyloidosis at early stages, before extensive and irreversible and cardiac damage occurs. Heart and/or kidneys are frequently affected, with three-quarters of patients presenting with involvement of both. As AL PC are immunophenotypically indistinguishable from MGUS or MM PC, clinicians should carefully evaluate for the presence of signs/symptoms concerning for AL amyloidosis in patients with an underlying PC dyscrasia (**Table 2**). Consideration should be given to screen these patients with N-terminal pro-B-type natriuretic peptide and albuminuria, as biomarkers that raise suspicion for cardiac and renal involvement by AL amyloidosis, respectively. Although N-terminal pro-

TABLE 1 Comparison of Diagnostic Criteria for Common PC Disorders

	FLC	M protein		BM PC		Presence of Disease-Related Organ Damage
AL amyloidosis	Abnormal FLC ratio[a]	Absent/present in SPEP/UPEP with IFE	AND	Typically present, at highly variable %	AND	Yes. Always caused by deposition of FLC organized in amyloid fibrils.
MGUS[e]	Abnormal/normal FLC ratio[b]	<3 g/dL (serum)	AND	<10%	AND	No[c]
SMM[e]	Abnormal/normal FLC ratio[b]	≥3 g/dL (serum) or ≥500 min/24 h (urine)	OR	10%-60%	AND	No[c]
MM[e]	Abnormal/normal FLC ratio	Absent/present in SPEP/UPEP with IFE	AND	≥10% or plasmacytoma	AND	Yes. Generally secondary to expansion of PC clone.[d] • MM-defining event (hypercalcemia, renal insufficiency, anemia, bone disease [CRAB criteria]) OR • Biomarkers of malignancy (clonal BM PC ≥60%, involved to uninvolved FLC ratio ≥100; >1 focal lesions on CMR studies.

The table outlines the diagnostic criteria and distinctive feature for the most common PC disorders. [a]Ratio may be spuriously normal in patients with λ FLC AL amyloidosis and advanced renal failure caused by disproportionate elevation of κ FLC compared with λ FLC. [b]FLC ratio must be <100 based on most recent diagnostic criteria. [c]Occasionally, MGUS/SMM may present clinical manifestations directly related to FLC/Ig pathogenicity, such as in monoclonal gammopathy of renal significance (MGRS). The term monoclonal gammopathy of clinical significance (MGCS) has been proposed to classify these conditions. [d]Occasionally caused by direct FLC/M protein pathogenicity (cast nephropathy, hyperviscosity, and so on). At least 1 MM-defining event or 1 biomarker of malignancy must be present to fulfill MM diagnostic criteria, according to Rajkumar et al (13). [e]Congo red staining must be negative to exclude amyloidosis.

BM = bone marrow invasion by monoclonal malignant plasma cells; CMR = cardiac magnetic resonance; FLC = serum free light chains; M = monoclonal; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; PC = plasma cells; SMM = smoldering multiple myeloma; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

B-type natriuretic peptide is not a biomarker specific for AL amyloidosis, its elevation in a patient with unexplained heart failure and biopsy-proven AL amyloidosis in an organ other than the heart is highly suggestive of cardiac amyloidosis. Excitingly, the use of genomic, FLC proteomics and high-throughput competition assay are being investigated for use in early diagnosis of AL in MGUS/SMM patients (11,12). According to the International Myeloma Working Group, 4 criteria must be fulfilled to render a definitive diagnosis of AL amyloidosis: 1) clinical presentation compatible with AL pattern of injury; 2) evidence of a PC (or less often lymphoproliferative) disorder based on bone marrow aspirate/biopsy and serologic parameters; 3) histopathological identification of amyloidosis deposition in periumbilical fat or affected organ; and 4) amyloidosis typing for identification of Ig light chain precursor protein via LC-MS or immunoelectronmicroscopy (13). In a small minority of patients, an underlying lymphoproliferative disorder may not be identified. It is important to note that histopathological evidence of amyloidosis in a patient with a PC dyscrasia does not automatically equal AL amyloidosis, because other amyloidoses, particularly transthyretin, can coexist with MGUS (14).

Table 3 outlines the diagnostic and staging studies recommended for patients with suspected/confirmed AL amyloidosis. Because cardiac involvement has a major prognostic impact by driving early mortality, current staging systems incorporate the extent of cardiac involvement as measured by serum markers (**Table 4**) (15-17). A staging system for renal involvement predicting renal survival has also been validated (**Table 5**) (18). An overlapping diagnosis of MM based on the presence of CRAB criteria, or a bone marrow clonal plasmacytosis exceeding 10% both represent adverse prognostic factors in AL amyloidosis (19). Translocation t(11;14) resulting in the juxtaposition of the cyclin D1 gene locus to the Ig heavy chain locus is the most common cytogenetic abnormality in AL, present in 40%-60% of patients, and portends a worsened prognosis (**Table 6**). This is in contrast to MM where t(11;14) is a standard-risk cytogenetic abnormality. Furthermore, t(11;14) is a predictive factor of poor response to bortezomib (20). The molecular basis for the biological impact of t(11;14) on prognosis and response to therapy remain obscure.

TREATMENT CONSIDERATIONS

AL amyloidosis patients often present with complex syndromes and multisystemic disease that require a multidisciplinary treatment approach to optimize supportive care. Although the goal of therapy in AL amyloidosis is rapid and deep reduction of circulating FLC through PC-directed therapy, intensive supportive care and treatment of underlying organ dysfunction is of paramount importance to improve not only quality but also quantity of life. Although MM patients generally die from complications of widespread, relapsed/refractory cancer, patients with AL die as a consequence of irreversible, progressive

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TABLE 2 System-Based, Clinical Presentation of AL Amyloidosis Patients and Key Diagnostic Findings

Organ	Frequency of Involvement	Common Presenting Signs/Symptoms	Diagnostic Findings	Consensus Criteria for Involvement[a]
Heart	60%-75%	• Dyspnea on exertion • Orthopnea • Paroxysmal nocturnal dyspnea • Lower extremity edema • Pleural effusions • Jugular venous distension • Arrhythmia • Syncope • Angina[b]	ECG • Low QRS voltage • Conduction system disease • Atrial fibrillation • Poor R-wave progression in precordial leads TTE • Increased wall thickness • Diastolic dysfunction with preserved LVEF • Reduced GLS • CMR • Late gadolinium enhancement • RHC • Restrictive physiology	NT-proBNP > 332 ng/L[c] OR Mean IVSd >12 mm
Kidney	50%-70%	• Lower extremity edema • Anasarca • Uremia	• Glomerular proteinuria (albuminuria) • Acute kidney injury • Hypercholesterolemia • Hypercoagulability	Proteinuria ≥0.5 g/24 h (mostly glomerular proteinuria, thus albumin)
Liver	20%	• Right upper quadrant tenderness • Early satiety • Weight loss	• Hepatomegaly • Isolated increase in alkaline phosphatase • Coagulopathy caused by coagulation factor deficiency[d]	Liver span >15 cm[e] OR Alkaline phosphatase elevation >1.5 times upper limit of normal
Gastrointestinal tract	10%-20%	• Diarrhea • Weight loss • Malabsorption • Hematochezia or melena		Direct biopsy verification
Lung[f]	30%-90%[f]	• Shortness of breath • Dry cough • Recurrent pleural effusions	• Pleural effusions • Interstitial pulmonary nodules	Direct biopsy verification
Peripheral nervous system	10%-20%	• Distal sensorimotor PN	• EMG: symmetric, axonal sensorimotor polyneuropathy	Clinical diagnosis
Autonomic nervous system	10%-20%	• Orthostatic hypotension • Early satiety • High (pseudo-obstruction, vomiting), or low (constipation alternating with diarrhea) intestinal dysmotility • Erectile dysfunction • Voiding dysfunction	• Delayed gastric emptying • Positive tilt test	Clinical diagnosis
Soft tissue	10%-20%	• Periorbital (or upper body) purpura • Macroglossia • Arthropathy • Myopathy • Ecchymotic bullae • Jaw or buttock claudication[g] • Carpal tunnel (often bilateral)		Clinical diagnosis

The table outlines incidence of organ involvement and frequent signs/symptoms and diagnostic findings in patients with AL amyloidosis based on pattern of organ involvement (125,126). Consensus criteria for diagnosis also reported. [a]Alternative etiologies must be excluded. [b]Typical of patients with amyloid deposition in the smaller vessels within the heart wall, mimicking coronary artery disease in the absence of large-vessel disease. [c]In the absence of renal failure or atrial fibrillation. [d]Factor X deficiency can occur independently of liver involvement caused by direct absorption of factor X by amyloid fibrils. [e]In the absence of congestive hepatopathy secondary to heart failure. [f]Depending on single institution series, often asymptomatic and detected postmortem. [g]Presumed related to vascular deposition of amyloid.

CMR = cardiac magnetic resonance; ECG = electrocardiogram; EMG = electromyography. GLS = global longitudinal strain; IVSd = interventricular septal wall thickness at end diastole; LV = left ventricular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PN = peripheral neuropathy; RHC = right heart catheterization; TTE = transthoracic echocardiogram.

organ failure, most commonly cardiac failure, caused by ongoing amyloid deposition. Thus, time is truly of the essence in AL amyloidosis. Although PC-directed therapy does not directly affect the amyloid deposits, when successful, it stops, or significantly reduces, FLC secretion, thus indirectly halting amyloid deposition and progressive organ dysfunction. A major branching point when a clinician is faced with a newly diagnosed AL amyloidosis patient is deciding whether ASCT is an appropriate treatment strategy. Historically, ASCT has been the only therapy resulting in sustained remission and, thus, long-term survival in selected AL amyloidosis patients. The availability of highly effective chemo-immunotherapies has radically changed this paradigm, and clinicians should take into consideration not just whether a

patient fulfills criteria for ASCT candidacy (**Table 7**), but also what the personal preferences of each individual are. The lack of randomized data regarding the impact of ASCT in the era of modern chemo-immunotherapy limits our counselling, but also offers patients more flexibility regarding treatment options. Extrapolating from MM, it is likely that achievement of minimal residual disease negative hematologic response has the most impact on progression free survival (PFS), regardless of the treatment strategy pursued to achieve it (21).

RESPONSE CRITERIA

Although not sufficient, a deep and sustained hematologic remission is necessary for organ response to occur. The exact molecular mechanisms underlying organ response remain largely obscure. Because achievement of a deep hematologic remission translates into higher chances of organ response, it is reasonable to speculate that a significant removal of circulating FLC is necessary for organ response. Further, reabsorption of amyloid fibrils over time has been observed in patients who achieve a hematologic remission, although it remains unknown what extent of amyloid reabsorption is needed to elicit organ response. Importantly, as the removal of deposited amyloidosis by intrinsic mechanisms is rather inefficient, organ response typically follows a hematologic response by months, sometimes years, although significant interpatient variability in the extent and kinetics of amyloid reabsorption exists (22). The causes underlying inefficient amyloid clearance remain poorly understood, and MoAbs directly targeting amyloid fibrils are currently being evaluated in clinical trials (23,24). **Tables 8 and 9** summarize the validated hematologic and organ response criteria, respectively, in AL. Emerging data support the notion that the deeper the hematologic response, the better the outcome in terms of major organ improvement and/or PFS (25). In recent retrospective studies, deep suppression of AL-PC clone as reflected in suppression of involved FLC (≤10 mg/L) and difference between involved and uninvolved FLC ≤10 mg/L was shown to associate with improved PFS, organ remission and overall survival (OS) (26,27). Similarly, minimal residual disease negativity as measured by next generation flow cytometry was shown to associate with PFS prolongation and increased organ response in several studies (25,28,29). The definition of progressive disease in AL amyloidosis is evolving. Under the premises that even low levels of circulating FLC may be sufficient to precipitate progressive organ dysfunction over time, a recent paper examined a high-risk difference between involved and uninvolved FLC progression criteria and showed its impact on OS, supporting its use as a trigger for treatment in patients who previously achieved a hematologic remission (30). Although both hematologic and organ remission affect long-term survival, advanced cardiac involvement is the single most important factor in driving early mortality, highlighting the necessity to raise awareness about AL to improve early diagnosis (31).

TABLE 3 Diagnostic Work-Up in Patients With Suspected AL Amyloidosis

	Test/Procedure
Blood/serum tests[a]	CBC with manual differential
	Basic metabolic panel
	Liver function tests
	SPEP+IFE
	FLC
	LDH
	β2 microglobulin
	Albumin
	High-sensitivity troponin
	NT-proBNP
	TSH and free T4
	Cholesterol panel
	PT and PTT[b]
Urine tests	Albumin/creatinine ratio
	UPEP+IFE
Imaging studies and diagnostic procedures	Bone survey inclusive of long bones and skull and/or PET/CT
	ECG
	TTE
	CMR[c]
	Right heart catheterization (with endomyocardial biopsy if indicated)[c]
	Chest x-ray/CT chest[c]
	Abdominal imaging[c]
	EMG[c]
	GI transit[c]
	Upper and lower endoscopies[c]
Pathology specimens	Unilateral bone marrow aspirate and biopsy for IHC, Congo red stain, flow cytometry, and CD138-selected cytogenetics and FISH
	Biopsy of plasmacytoma, if present
	Target organ or fat pad, minor salivary gland or rectum aspirate, for Congo red stain, immunofluorescence and, if available, EM. Typing of amyloid needs to be performed for accurate precursor protein identification.

[a]Transthyretin (TTR) gene sequencing should be performed in patients where familial transthyretin amyloidosis is in the differential diagnosis and/or if transthyretin amyloidosis is diagnosed. [b]Factor X absorption onto amyloidosis can lead to PTT prolongation and bleeding diathesis. [c]As needed depending on clinical presentation.

CBC = cell blood count; EM = electron microscopy; FISH = fluorescent in situ hybridization; FLC = serum free light chain; IFE = immunofixation; IHC = immunohistochemistry; LC-MS = liquid chromatography mass spectrometry; LDH = lactate dehydrogenase; MM = multiple myeloma; PET/CT = positron emission tomography/computed tomography; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; other abbreviations as in **Table 2**.

TABLE 4 Prognostic Impact of AL Amyloidosis Staging Systems

Mayo Clinic (2004) Integrating European Collaborative Study 3B Staging					Mayo Clinic (2012)				
Risk Factors	Risk Factors Present (n)	Stage	Patients (%)	Median OS (months)	Risk Factors	Risk Factors Present (n)	Stage	Patients (%)	Median OS (Months)
cTnT >0.035 ng/mL NT-proBNP >332 pg/mL	0	1	33	86	cTnT >0.025 ng/mL NT-proBNP >1,800 pg/mL dFLC >180 mg/L	0	1	25	94.1
	1	2	30	43		1	2	27	40.4
	2	3A	18	17		2	3	25	14
	NT-proBNP ≥8,500 pg/mL	3B	19	4.6		3	4	23	5.8

The table compares the Mayo 2004 integrating the European Collaborative Study vs Mayo 2012 staging systems for AL amyloidosis (15-17).
cTnT = cardiac troponin T; NT-proBNP = N-terminal pro–B-type natriuretic peptide; OS = overall survival.

THERAPEUTIC AGENTS

Historically, AL amyloidosis therapy has followed in the footsteps of anti-MM therapies, and patients have been treated with anti-PC drugs off label. For decades, oral melphalan in combination with steroids constituted the mainstay treatment for AL. It was not until the late 1990s that high-dose melphalan with ASCT was pioneered. Molecularly targeted agents such as immunomodulatory drugs (IMiDs) and PIs were evaluated in AL in the late 2000s (**Figure 1**). The past 5 years have seen an acceleration in novel therapies for AL, including the investigational use of antifibrillary antibodies. In January 2021, the FDA approved Dara-CyBorD for the treatment of newly diagnosed AL (excluding stage IIIB patients) based on the results of the Andromeda study, a randomized, open-label, active-controlled trial in 388 newly diagnosed AL amyloidosis patients. Although Dara-CyBorD is the first and only FDA-approved therapy for AL amyloidosis, several chemo-immunotherapy, multidrug regimens as well as ASCT in selected patients are effective in AL amyloidosis (32,33). We will review the most commonly used agents in AL amyloidosis starting from preclinical data of mechanism of function and resistance and then outlining clinical evidence (prospective studies are reported in **Table 10**). The lack of reliable, preclinical models of AL amyloidosis limits basic-translational research on the molecular bases of effectiveness of distinct drugs. For the purpose of this review, data obtained in MM systems will be cited instead.

ALKYLATING AGENTS. Melphalan, cyclophosphamide, and bendamustine are nitrogen mustard alkylating agents with antineoplastic activity secondary to the alkylation of guanines and formation of interstrand crosslinks (ICL), leading to DNA damage with consequent interference with DNA replication and DNA-to-RNA transcription. Recently, these agents have been shown to induce an immunogenic cell death and skew the cytokine milieu from a cancer-tolerant to a cancer-surveilling microenvironment (34). As alkylating agents are cell-cycle nonspecific agents, cytopenia and gastrointestinal toxicities are frequently observed.

Oral melphalan. Based on the detection of Ig fragments in deposited amyloid and extrapolating from MM, the combination of melphalan and prednisone was applied to the treatment of AL patients in the late 1970s (35). This regimen was shown to be superior to colchicine, a drug that was preliminarily reported effective in AL amyloidosis, and became a de facto standard of care treatment for AL amyloidosis patients for decades (36). Combination of melphalan with dexamethasone (MelDex) remains a highly effective treatment in AL amyloidosis and has been shown to abrogate the adverse prognostic impact of t(11;14) (37). Triplet combinations subsequently incorporating lenalidomide or bortezomib into MelDex backbone demonstrated good efficacy and a tolerable safety profile (38,39).

Autologous stem cell transplant. High-dose (200 mg/m^2), intravenous melphalan followed by ASCT remains a mainstay of AL amyloidosis treatment in many centers since its pioneer use in the late 1990s (40). In a randomized, phase 3 study in newly diagnosed AL amyloidosis, MelDex resulted in superior OS compared with high-dose melphalan followed by ASCT (57 months vs 22 months; $P = 0.04$) (41). A prohibitive treatment-related mortality (TRM) of 24% in the ASCT arm as well as trend toward harm in the 6-month landmark analysis suggest that careful patient selection, intensive supportive care, and risk-adapted approaches are critical when deciding eligibility of AL amyloidosis patients for ASCT. Recently, an outcome analysis of the Center for International Blood and Marrow Transplant Research database

TABLE 5 Renal Staging in AL Amyloidosis and Impact on Renal Survival (18)

Risk Factors	Risk Factors Present (n)	Stage	Patients (%)	% of Patients on Renal Replacement Therapy at 3 y
Proteinuria >5 g/24 h eGFR <50 ml/min/1.73 m^2	0	1	23	4
	1	2	60	30
	2	3	17	85

eGFR = estimated glomerular filtration rate.

showed a progressive improvement in 100-day transplant related mortality over time, reaching 5% across all centers and 3% in high-volume centers from 2007-2012 (42). Because patient staging was comparable over time, the improved outcome was attributed to increased expertise in caring for this complex patient population and enhanced supportive care rather than mere patient selection. A retrospective study from a large transplant center showed ASCT-TRM to be 8% in patients with stage 3 AL amyloidosis compared with 4% for the entire cohort, consistent with cardiac involvement driving TRM in ASCT (43). Risk-adapted strategies with dose reduction of melphalan to 140 or 100 mg/m^2 based on extent of cardiac and/or renal involvement, number of organs involved, and age have resulted in improved outcome for high-risk patients (33).

Given the availability of highly effective, well-tolerated, combinatorial chemo-immunotherapies, the amyloidosis community is now faced with the task to understand the most appropriate sequencing of agents and role of ASCT in the treatment course of AL amyloidosis patients. Several studies have supported the use of ASCT as a tool to deepen the hematologic remission in patients with suboptimal response to induction chemotherapy (44,45). However, whether this approach is superior to chemo-immunotherapy-based treatment intensification remains unknown. Randomized clinical trials would be of utmost importance, and until high-quality modern data are available, ASCT remains a valuable therapeutic option to intensify therapy (**Figure 2**). Of note, although t(11;14) is a biomarker of suboptimal response to bortezomib, it is a favorable prognostic marker for hematologic response and PFS in patients undergoing ASCT (46). The opposite is true for t(4;14), t(14;16), and del(17p13), well-established high-risk cytogenetics in MM, that portend worse outcome in the setting of ASCT, but not bortezomib-containing regimens, in AL amyloidosis. These data outline the urgent need for a deeper understanding of AL amyloidosis biology and development of biomarkers to improve our patient stratification capabilities.

Cyclophosphamide. Differently from melphalan, cyclophosphamide is a prodrug and requires P450-mediated activation. Cyclophosphamide active metabolites are phosphoramide mustard and acrolein, the latter being responsible for the development of hemorrhagic cystitis. In AL amyloidosis, cyclophosphamide is administered by mouth or intravenously at low dose in combination with PIs, IMiDs, or MoAbs. Although high-dose, intravenous cyclophosphamide is routinely used for stem cell mobilization ahead of ASCT in MM, its use in AL amyloidosis is generally contraindicated because of added cardiac toxicity and increased risk of morbidity and mortality (47,48).

The combination of cyclophosphamide with bortezomib and dexamethasone (CyBorD) became the de facto standard of care regimen based on extensive retrospective data in newly diagnosed AL amyloidosis patients showing efficacy and good tolerability (32,49). Depth and length of response were superior with CyBorD compared with a combination of cyclophosphamide with thalidomide and dexamethasone (CTD), also an effective regimen in AL amyloidosis (50). In a phase 2, single arm, prospective study, in combination with lenalidomide and dexamethasone, cyclophosphamide was shown to elicit deep hematologic and organ responses (51).

Bendamustine. Bendamustine is administered intravenously and is metabolized via the cytochrome P450 liver system to its active metabolites. A multicenter, prospective, phase 2 study of bendamustine plus dexamethasone and a large, retrospective analysis of patients treated with bendamustine plus prednisone showed these combinations to be effective in inducing hematologic and organ responses with a tolerable pattern of side effects (52,53).

PROTEASOME INHIBITORS. Initially employed as research tools to investigate molecular mechanisms of proteolysis, PIs have completely revolutionized the treatment paradigm of PC disorders (54). In total, 3 PIs are FDA approved in MM: peptide boronic acids bortezomib and ixazomib, the former for parenteral, the latter for enteral use; and epoxyketone-derived carfilzomib (55). All 3 PIs mainly target the chymotryptic-like (CT-L, β5) catalytic activity of the

TABLE 6 Frequency and Clinical Impact of Common Genetic Abnormalities in AL Amyloidosis

	Incidence, %	Clinical Impact
t(11;14)	40-60	Adverse prognostic factor Predictive factor of poor response to bortezomib-based therapy Melphalan may abrogate unfavorable prognosis
Del(13)/(13q)	30-40	-
Trisomy of a single chromosome	25-30	Shorter OS in patients treated with melphalan
Gain(1q21)	15-20	Standard risk in patients treated with bortezomib
Hyperdiploid	12	Standard risk
t(14;16) and t(4;14)	3-4 each	Standard risk in patients treated with bortezomib Associated with adverse outcome after high dose melphalan and ASCT
Del(17p)/17	2-6	Associated with higher BM plasmacytosis Cardiac involvement almost universally present Circa 45% with stage III cardiac involvement Associated with adverse outcome after high dose melphalan and ASCT

ASCT = autologous stem cell transplantation; BM = bone marrow; OS = overall survival.

proteasome, a large, barrel-shaped multicatalytic protease responsible for the degradation of most misfolded proteins tagged via polyubiquitin chains (54). Extensive research on the molecular mechanisms underlying PI activity in MM has shown that exacerbation of proteotoxicity, induction of immunogenic cell death, and modulation of the bone marrow microenvironment contribute to PI effectiveness (56). Inhibition of canonical NF-κB signaling caused by stabilization of IκB was initially thought to be the prime mechanism of action of PIs (57). Subsequently, exacerbation of baseline proteotoxicity and impairment in proteostasis emerged as the main drivers of PI-induced cytotoxicity, with the ratio between load on the proteasome and proteasome activity itself serving as a biomarker of PI sensitivity (58,59). Sensitivity of AL amyloidosis cells to PIs was subsequently shown to be caused by altered proteostasis in the setting of impaired autophagy (60). A reduction in proteasome load, an increase in proteasome capacity, or up-regulation of alternative proteolytic mechanisms, such as aggresome or autophagy, have been suggested as potential molecular mechanisms mediating PI resistance (55,61).

Although the research community was initially concerned that systemic administration of PIs would be too toxic for humans because of the ubiquitous expression and critical function of the proteasome, PIs are generally well tolerated, with distinct toxicities across different chemically-derived compounds (56).

Bortezomib. The first-in-class PI bortezomib is a peptide boronic acid that reversibly blocks the β5 proteasome subunit. It is approved for administration via intravenous or subcutaneous injection in MM (62). Its characteristic side effect is sensory peripheral neuropathy with a poorly defined etiology. Generally, dose reduction and treatment discontinuation lead to resolution or improvement in symptoms in the majority of patients (63).

Bortezomib radically changed the treatment landscape in AL amyloidosis. Since its use in combination with dexamethasone, bortezomib has shown improved outcome when added to any other chemo/immunotherapeutic agent as a multidrug regimen. Since its initial use in 2009, CyBorD has been commonly used as frontline treatment in AL amyloidosis because of its efficacy and safety, including in patients with end-stage renal disease (49). Cardiac toxicity is not a significant adverse event in AL amyloidosis, including in patients with advanced heart failure and systolic dysfunction. Recent data suggest that within this triplet, bortezomib and low-dose dexamethasone are the main drivers of efficacy (64). Translocation t(11;14) has emerged as a predictive factor of suboptimal response to bortezomib-containing regimens in AL amyloidosis, whereas cytogenetics considered high-risk in MM, such as t(4;14), t(14;16), del(17p), and/or gain of 1q21, had no impact on outcome (20). Interestingly, overexpression of cyclin D1 associates with increased expression of genes involved in endoplasmic reticulum quality control and protein homeostasis, suggesting lower baseline proteotoxicity as a mechanism of bortezomib resistance (59,60,65). In a multicenter, randomized phase 3 study of 109 patients, the combination of bortezomib, melphalan, and dexamethasone (VelMelDex) was superior to MelDex for frequency and depth of response. Importantly, the triplet treatment led to an improvement in overall survival by decreasing mortality 2-fold (38). The combination of bortezomib

TABLE 7 Criteria for Autologous Stem Cell Transplant Eligibility in AL Amyloidosis in Our Centers

	Transplant Eligible (All Criteria Must Be Met)	Transplant Ineligible[a] (Any Criteria)
Age, y	≤70	>70
ECOG PS	0-2	>2
Staging (revised Mayo 2004)	I-II	III
LVEF, %	>45	≤45
NYHA functional class	I-II	III-IV
eGFR	≥30 ml/min/1.73 m^2	<30 ml/min/1.73 m^2
SBP	≥90 mm Hg without orthostatic hypotension	<90 mm Hg or untreated orthostatic hypotension
DLCO, %	>50	<50

The table outlines criteria implemented to determine transplant eligibility in AL amyloidosis in our centers. [a]Consideration can be given to risk-stratified, dose-reduced melphalan conditioning and ASCT for selected patients, including patients with end-stage renal disease if all other eligibility criteria are satisfied.

DLCO = diffusing capacity for carbon monoxide; ECOG PS = Eastern Cooperative Oncology Group Performance Status; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SBP = systolic blood pressure.

with lenalidomide and dexamethasone is also effective in inducing hematologic remission in the frontline setting; however, side effects and treatment discontinuation were more common compared with CyBorD (66).

Carfilzomib. Carfilzomib is an epoxyketone PI that irreversibly inhibits the β5 subunit. This critically distinct pharmacodynamic feature is likely at the base of the increased potency, but also broader toxicity of carfilzomib. In fact, cardiovascular side effects, including tachyarrhythmia, hypertension, systolic heart failure, and renal failure, have been reported in patients treated with carfilzomib (67). This pattern of toxicity makes the use of carfilzomib problematic in AL amyloidosis patients in whom cardiac and/or renal involvement is frequently present. However, in selected patients and with careful monitoring, carfilzomib monotherapy at low dosage was shown to elicit responses in 63% of patients, including bortezomib-refractory individuals. In patients with pre-existing peripheral neuropathy, carfilzomib represents an effective therapeutic alternative to bortezomib (68).

Ixazomib. Ixazomib is an orally bioavailable boronic acid PI. Similar to bortezomib, peripheral neuropathy can occur with ixazomib, and GI toxicities, including nausea and diarrhea, and rash are common adverse events (69). Ixazomib was effective at inducing both hematologic and organ responses in relapsed/refractory AL amyloidosis as a single agent and in combination with lenalidomide and dexamethasone (70). In the TOURMALINE-AL1 study, a randomized, phase 3 clinical trial of ixazomib plus dexamethasone vs clinician choice, the investigational arm did not meet the primary endpoint of overall hematologic response rate. However, vital organ response (36% vs 11%; $P = 0.0001$), median vital organ PFS (18 months vs 11 months; $P = 0.019$), and median time to vital organ deterioration or death (34.8 months vs 26.1 months; $P = 0.0116$) all favored ixazomib plus dexamethasone, suggesting that this doublet may more effectively mitigate AL amyloidosis-related organ damage compared with other regimens with similar hematologic activity (71).

IMMUNOMODULATORY DRUGS. Thalidomide and its derivatives, lenalidomide and pomalidomide, are FDA-approved oral agents for the treatment of MM. Their clinical effectiveness is based both on direct anti-MM cytotoxicity and modulation of cancer microenvironment, including antiangiogeneic and immunostimulatory properties (72). Cereblon (CRBN) has been recently identified as the molecular target mediating lenalidomide effectiveness in MM. Together with DNA damage-binding protein 1, CRBN is the substrate receptor of the cullin 4 ring E3 ubiquitin ligase complex ($CRL4^{CRBN}$), which is responsible for proteasome-mediated degradation of IKZF1 (Ikaros) and IKZF3 (Aiolos). IKZF1 and IKZF3 are transcriptional repressors of interleukin (IL)-2, and their lenalidomide-mediated degradation results in increased IL-2 levels and T-cell immunostimulation (73-75).

All IMiDs are administered orally and are all considered class X drugs because of the infamously known teratogenic effect of thalidomide, whose administration in pregnant women as an effective antiemetic medication resulted in phocomelia. Other notable side effects include increased risk of venous thromboembolic events when administered as a combinatory regimen, thus warranting appropriate VTE prophylaxis; fatigue; rash; diarrhea; nausea; and cytopenia. In combination with melphalan, lenalidomide has been reported to increase the risk of secondary myeloid dyscrasias (76). IMiDs also carry a black box warning for arterial vascular events. Caution should be used in dosing lenalidomide in AL amyloidosis patients as the therapeutic index is

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TABLE 8 Hematologic Response Criteria

Hematologic Response Parameters	Complete Response (CR)[a]	Very Good Partial Response (VGPR)	Partial Response (PR)	Progression From CR	Progression From PR
FLC	Normal ratio	dFLC <40 mg/L	dFLC >50%	Abnormal FLC[b]	>50% increase in affected FLC AND >100 mg/L absolute value
SPEP+IFE	No M spike. Negative IFE	Not applicable	Not applicable	Positive	>50% increase in M spike AND >0.5 g/dL M spike
UPEP+IFE	No M spike. Negative IFE	Not applicable	Not applicable	Not applicable	>50% increase in urinary M spike AND >200 min/24 h M spike

The table synthesizes the most updated hematologic response criteria in AL amyloidosis (31). [a]All criteria must be met. [b]Affected serum free light chains must double in absolute value.
dFLC = difference between involved and uninvolved serum free light chains; IFE = immunofixation; M spike = monoclonal spike; SPEP = serum protein electrophoresis.

significantly different than in MM. A starting dose of 5 mg D1-21 is recommended, and careful monitoring for side effects, including cardiac deterioration, is warranted.

Thalidomide. The use of thalidomide in the treatment of AL amyloidosis has been significantly limited by its narrow therapeutic index. In particular, peripheral neuropathy and symptomatic bradycardia emerged during a phase 2 clinical trial evaluating thalidomide in combination with dexamethasone (77). Although this doublet showed promising results in terms of both hematologic and organ response, toxicities were felt to be prohibitive. Thalidomide/dex was also evaluated as a fixed-duration treatment consolidation/maintenance for patients who failed to achieve a CR after risk-adapted ASCT with encouraging results, suggesting a potential value of IMiDs for long-term disease control (78).

Lenalidomide. Lenalidomide showed limited activity when used as single agent in AL amyloidosis, but hematologic and organ responses were observed in phase 3 studies of lenalidomide in combination with weekly dexamethasone. A very limited number of patients were able to tolerate the standard MM 25 mg daily D1-21 schedule caused by cytopenia, rash, and infections (79-81). Importantly, an increase in cardiac biomarkers of unclear etiology and not necessarily consistent with organ progression, as well as renal failure, were observed in patients enrolled in these studies, raising concerns for the routine use of lenalidomide in this patient population (82). Of note, lenalidomide is renally excreted, and thus requires dose adjustment based on renal function. Triplet combinations of PI, lenalidomide, and steroids, such as lenalidomide, bortezomib, and dexamethasone or ixazomib, lenalidomide, and dexamethasone, have significant activity in AL amyloidosis as measured by hematologic response; however, tolerability was limited with a high rate of treatment discontinuation despite low-dose lenalidomide administration (66,70). Lenalidomide proved to be effective also when used in combination with the alkylator agents cyclophosphamide or melphalan plus dexamethasone, although grade 3 cytopenias were common (51,83).

Pomalidomide. Pomalidomide is the most potent, FDA-approved IMiD and has shown activity in MM, including in patients with lenalidomide and/or bortezomib relapsed and/or refractory disease (84,85). In combination with dexamethasone, pomalidomide has been shown to be highly active in AL amyloidosis, inducing frequent hematologic remissions in highly refractory patients (86-88). Similar to lenalidomide, pomalidomide treatment was also linked to an increase in cardiac biomarkers without definitive evidence of cardiac progression (89). The significance and clinical impact of this finding remains unclear, and close monitoring of cardiac function is warranted. Based on its preclinical activity as an enhancer of immune response, the combination of pomalidomide with MoAbs targeting SLAMF7 or CD38 is currently being evaluated in clinical trials in AL amyloidosis (90-92).

MONOCLONAL ANTIBODIES TARGETING AL CELLS. Given its remarkable effectiveness in MM, MoAbs targeting PC markers have been evaluated in AL amyloidosis (93-95). In particular, daratumumab (DARA) proved highly effective in AL amyloidosis and has radically changed the natural history of this disease. DARA and isatuximab (ISA) are IgG1 MoAb targeting CD38, a universal marker of plasmablasts and PCs (96). Preclinical studies have demonstrated that DARA and ISA induce MM cell death through different mechanisms, including complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cell-mediated cytotoxicity (ADCC), direct apoptosis, and modulation of CD38 enzymatic activity with subsequent impact on the soluble bone marrow milieu (97). Elotuzumab (ELO) is a humanized IgG1κ MoAb targeting the signaling lymphocytic activation molecule family member F7 (SLAMF7), a glycoprotein that is expressed by PCs as well as cytolytic lymphocyte subsets such as NK cells, NKT cells, or CD8+ T cells.

TABLE 9 Validated Organ Response Criteria

	NT-proBNP Response	NYHA Functional Class Response		NT-proBNP Progression
CARDIAC RESPONSE	NT-proBNP decrease of >30% AND >300 pg/mL from baseline[a]	2 NYHA functional class improvement from baseline[b]	**CARDIAC PROGRESSION**	NT-proBNP increase of >30% AND >300 ng/L from baseline
	Proteinuria			**eGFR**
RENAL RESPONSE	Decrease in proteinuria by >30% or to <0.5 g/24 h[c]		**RENAL PROGRESSION**	>25% increase in eGFR

The table outlines the cardiac and renal response criteria that have been validated in AL amyloidosis (15-17). [a]From baseline NT-proBNP over 650 ng/L. [b]Must be NYHA functional class 3 or 4 at diagnosis. [c]In the absence of eGFR decline by 25% or more.

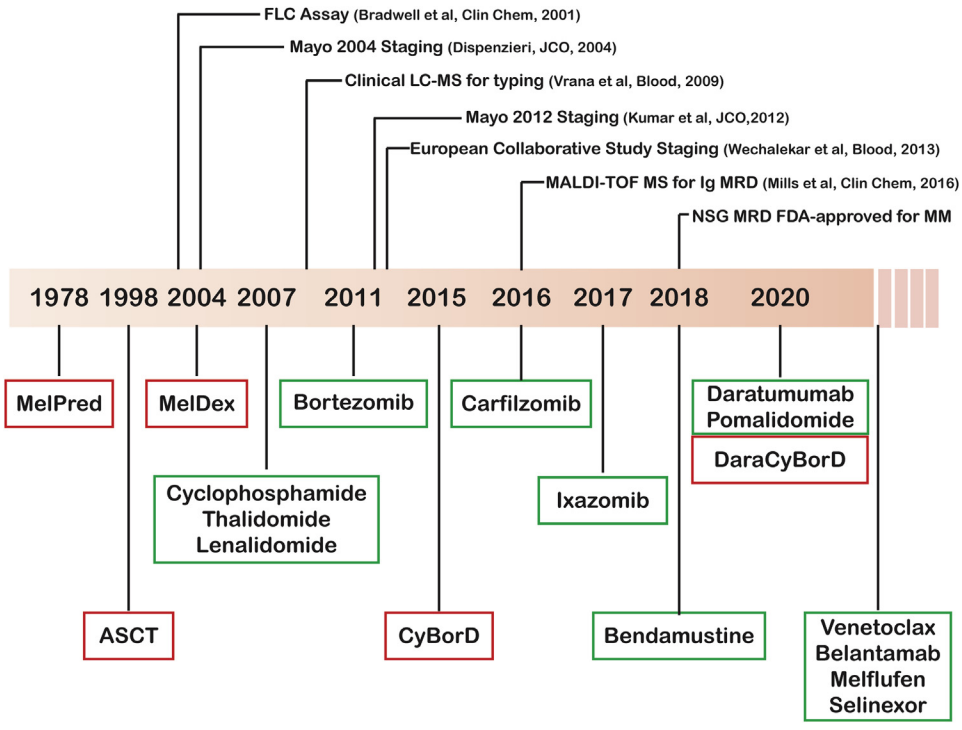
Abbreviations as in Table 7.

SLAMF7 is located on chromosome 1q23 that is often amplified in MM, making it an attractive target for therapy. Differently from DARA/ISA, ELO does not elicit ADCC or direct cytotoxicity.

Daratumumab. Initially available as an intravenous infusion, a subcutaneous formulation of DARA was approved in 2020 (98). DARA is generally well-tolerated, with main adverse events being infusion-related reactions, infections, and cytopenia (99). Aggressive premedication with steroids, H2 blockers, and leukotriene receptor antagonist montelukast effectively abated incidence of severe infusion reactions. In AL amyloidosis patients with advanced cardiac or renal disease, heart failure exacerbations or worsening anasarca have been observed with intravenous administration, and the subcutaneous formulation is strongly preferred (100). Daratumumab in combination with lenalidomide or bortezomib has shown impressive activity in MM, achieving deep and durable responses in the relapsed and/or refractory population (93,94). DARA is currently approved for use in the frontline and relapsed/refractory setting in MM. In a phase 3, non-inferiority, randomized clinical trial comparing intravenous vs subcutaneous DARA (daratumumab plus hyaluronidase), the latter showed decreased incidence of infusion reactions with preserved efficacy, resulting in its FDA approval (98). In AL amyloidosis, single-agent DARA proved highly effective in inducing deep and lasting hematologic and organ responses in heavily pretreated patients (100,101). Importantly, deep hematologic responses were observed after 1 single infusion of daratumumab (100,102). These remarkable results as monotherapy paved the way for upfront use of DARA in combination with standard of care CyBorD. ANDROMEDA is an ongoing, multicenter phase III study randomizing patients to CyBorD alone or in combination with subcutaneous DARA (Dara-CyBorD) (103). Addition of daratumumab results in significantly higher hematologic (92% vs 77%), cardiac (42% vs 22%), and renal (54% vs 27%) response rates compared with CyBorD alone. A complete hematologic response was observed in 53% of patients treated with DaraCyBorD compared with 18% of patients receiving CyBorD at a median follow-up of 11 months. Importantly, major organ deterioration progression-free survival (MOD-PFS) also favored the quadruple therapy with an HR of 0.58 (95% CI: 0.36-0.93; $P = 0.02$) and cardiac and renal responses were approximately doubled in the quadruplet arm (41% vs 22% and 53% vs 24%, respectively). Dara-CyBorD was well tolerated without unexpected safety concerns, and subcutaneous DARA formulation resulted in fewer infusion-related reactions compared with historic data with intravenous DARA. Based on these positive results, on January 15, 2021, the FDA granted accelerated approval to DARA-CyBorD, the first and only FDA-approved treatment in AL amyloidosis for newly diagnosed patients.

Isatuximab. ISA is a chimeric, IgG1 MoAb that binds with high affinity to a specific epitope on CD38 that is distinct from the daratumumab-binding site (104). ISA is approved as a third-line therapy in combination with pomalidomide and dexamethasone and a second-line therapy in combination with carfilzomib and dexamethasone based on the positive results of the ICARIA and IKEMA phase 3 studies, respectively (105,106). The preliminary result of a multicenter phase 2 study of isatuximab for patients with previously treated AL amyloidosis proved to be safe with encouraging efficacy based on 3% hematologic complete response, 54% very good partial response, and 1-year estimated PFS of 85% (107). A trial investigating isatuximab for the treatment of high-risk, newly diagnosed AL is currently ongoing, and results are eagerly awaited (NCT04754945).

FIGURE 1 Evolution of Treatment in AL Amyloidosis



The timeline outlines in chronological order the clinical use of distinct treatments in immunoglobulin light chain (AL) amyloidosis. Commonly used agents/regimens are in **red boxes**, less commonly used agents/regimens are in **green boxes**. The **top of the figure** outlines some of the most impactful technological/clinical advances in AL amyloidosis. ASCT = autologous stem cell transplant; CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara = daratumumab; Dex = dexamethasone; FLC = free light chain; LC-MS = liquid chromatography-mass spectrometry; MALDI-TOF = matrix-assisted laser desorption ionization time-of-flight; Mel = melphalan; MM = multiple myeloma; MRD = minimal residual disease; NSG = next generation sequencing; Pred = prednisone.

Elotuzumab. ELO was shown to lyse SLAMF7-expressing MM cells via ADCC. Importantly, ELO has no clinical efficacy as monotherapy, but has been shown to increase activity of IMiDs in randomized clinical trials, leading to its approval in combination with lenalidomide-dexamethasone and pomalidomide-dexamethasone (92,95). The potential activity of ELO in AL amyloidosis stems from a single case report of a woman with heavily pretreated, overlapping MM/AL amyloidosis who achieved hematologic and organ response upon treatment with ELO-lenalidomide-dexamethasone (EloRD) (108). An ongoing phase 2 trial is evaluating EloRD with or without cyclophosphamide followed by EloRD maintenance as second line in AL amyloidosis.

AGENTS TARGETING AMYLOID FIBRILS. Early mortality is a major hurdle in AL amyloidosis, with a mortality risk of 35%-60% within the first 12 months from diagnosis, depending on the extent of cardiac involvement. Even highly effective, combinatorial chemo-immunotherapy such as Dara-CyBorD appears not to affect early mortality in AL amyloidosis because it lacks a direct effect on amyloid reabsorption. There has been great interest in the development of agents specifically targeting amyloid fibrils, with hope that preventing fibril deposition and/or removing deposited fibrils could improve the outcome of amyloidosis patients. However, data from randomized clinical trials of antifibrillary antibodies either have been negative or are not yet mature, perhaps reflecting the complexity of the deposition process and microenvironmental responses to it in different organs even in the same patient.

ANTI-SERUM AMYLOID P COMPONENT. Human serum amyloid P component (SAP) is an abundant plasma protein that binds to amyloid fibril regardless of its precursor protein, being an invariably present component of amyloid deposits. Given its function in stabilizing and shielding fibrils from degradation, SAP was postulated to be an ideal therapeutic target for antiamyloid therapy (109). Dezamizumab, a fully

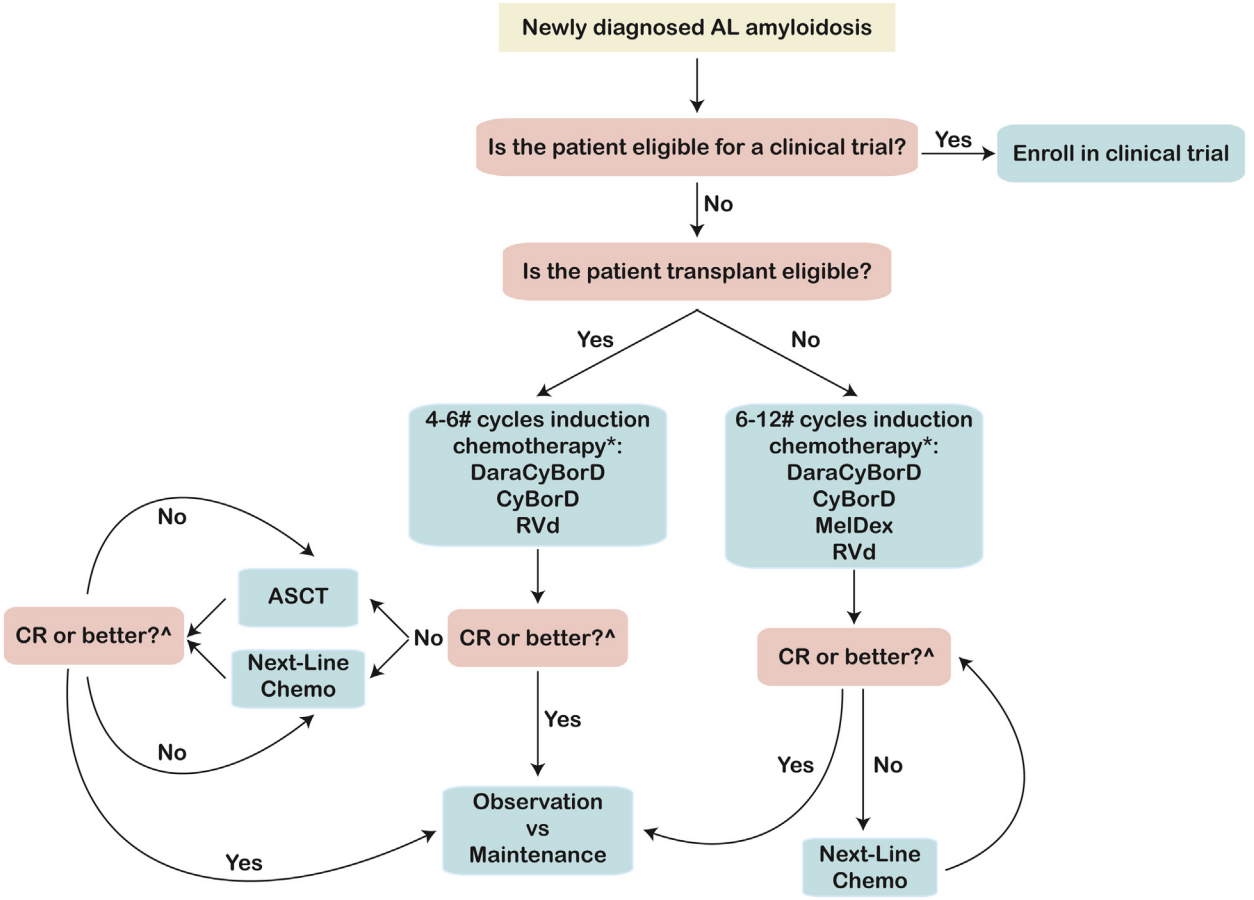
TABLE 10 Prospective Studies Evaluating Current Treatment Approaches In AL Amyloidosis

Therapy Regimens (Ref. #)	Study Phase[a]	N	Disease Setting	Hematologic Response	Organ Response	Median PFS/OS
Autologous transplant						
ASCT (127)	R	421	–	–	43%	2.6 y/6.3 y
ASCT (128)	R	434	–	76%	53%	–/OS not reached
Risk-adapted ASCT (45)	2	40	NDAL	79%	47%	At 2 y: PFS: 69% OS: 82%
MelDex vs ASCT (41)	3	50 vs 50	NDAL	68% vs 67%	39% vs 45%	2.7 y/4.7 y vs 2.7 y/1.8 y
Alkylators						
MelDex (129)	2	46	–	67%	48%	3.8/5.1 y
BendaPred (52)	R	122	NDAL: 12 RRAL: 110	35%	C: 12% R: 31%	9 mo/21 mo
BendaDex (53)	2	31	RRAL	57%	C: 13% R: 46%	11.3 mo/18.2 mo
IMiD-based therapy						
CTD (130)	R	75	NDAL: 31 RRAL: 44	74%	27%	1.7 y/3.4 y
RD (79)	2	23	NDAL: 10 RRAL: 13	41%	23%	1.6 y/–
CRD (51)	2	35	NDAL: 24 RRAL: 11	60%	31%	2.4 y/3.1 y
MelRD (83)	1/2	26	NDAL	42%	50%	At 2 y: PFS: 54% OS: 81%
PD (87)	R	33	RRAL	48%	15%	1.2 y/2.3 y
Proteasome inhibitor-based therapy						
Bortezomib (131)	2	70	RRAL	67%-69%	C: 10% R: 27%-44%[b]	At 1 y: PFS: 72%-75% OS: 84%-93%[b]
VDex (132)	R	94	NDAL: 18 RRAL: 76	72%	30%	At 1 y: 76% OS
CyBorD (49)	R	230	NDAL	60%	C: 17% R: 25%	At 5 y: OS: 55%
RVd (66)	R	34	NDAL	89%	35%	At 1 y: OS: 73%
MelDex vs VelMelDex (133)	3	56 vs 53	NDAL	52% vs 7%	C: 28% vs 38% R: 43% vs 44%	At 2Y: PFS: 21% vs 47% OS: 45% vs 68%
K+/-D (134)	1/2	28	RRAL	63%	21%	Not applicable
IxaDex (69)	1/2	27	RRAL	52%	56%	At 2 y: 60%/85%
IRd (70)	R	40	RRAL	66%	C: 6% R: 13%	1.4 y/2.4 y
CD38-targeting MoAb-based therapy						
Daratumumab (135)	2	72	RRAL	77%	C: 55% R:52%	At 2 y: 62%/97%
Dara-CyBorD vs CyBorD (103)	3	195 vs 193	NDAL	92% vs 77%	C: 42% vs 22% R: 54% vs 27%	Not applicable
Agents targeting amyloid fibrils						
Doxycycline (113)	2	25	NDAL	100%[c]	36%	At 1 y: 100% OS
NEOD001 (136)	1/2	27	RRAL	–	C: 57% R:60%	Not applicable
11-1F4 (23)	1a/b	27	RRAL	–	67%	Not applicable

The table summarizes prospective studies evaluating therapeutic approaches to AL amyloidosis. [a]R: retrospective. [b]Depending on once weekly 1.6 mg/m^2 vs twice weekly 1.3 mg/m^2 schedule. [c]In patients surviving 1 year or longer.

ASCT = autologous stem cell transplant; C = cardiac response; CRD = cyclophosphamide, lenalidomide, dexamethasone; CTD = cyclophosphamide, thalidomide, dexamethasone; CyBorD = cyclophosphamide-bortezomib-dexamethasone; D = dexamethasone; Dex = dexamethasone; IRd = ixazomib, lenalidomide, and dexamethasone; K = carfilzomib; MelDex = melphalan-dexamethasone; MelRD = melphalan-lenalidomide-dexamethasone; MTD, maximum tolerated dose; NDAL, newly diagnosed AL amyloidosis; OHR = overall hematologic response; OS = overall survival; OW = once weekly; PD = pomalidomide-dexamethasone; PDex = pomalidomide, dexamethasone; PFS = progression-free survival; R = renal response; RD = lenalidomide-dexamethasone; RRAL = relapsed or refractory AL amyloidosis; RVd = lenalidomide, bortezomib, and dexamethasone; T = thalidomide; TW = twice weekly; VD = bortezomib-dexamethasone; VelMelDex = melphalan-bortezomib-dexamethasone.

FIGURE 2 Algorithm for Treatment Approach to Newly Diagnosed AL Amyloidosis Patients

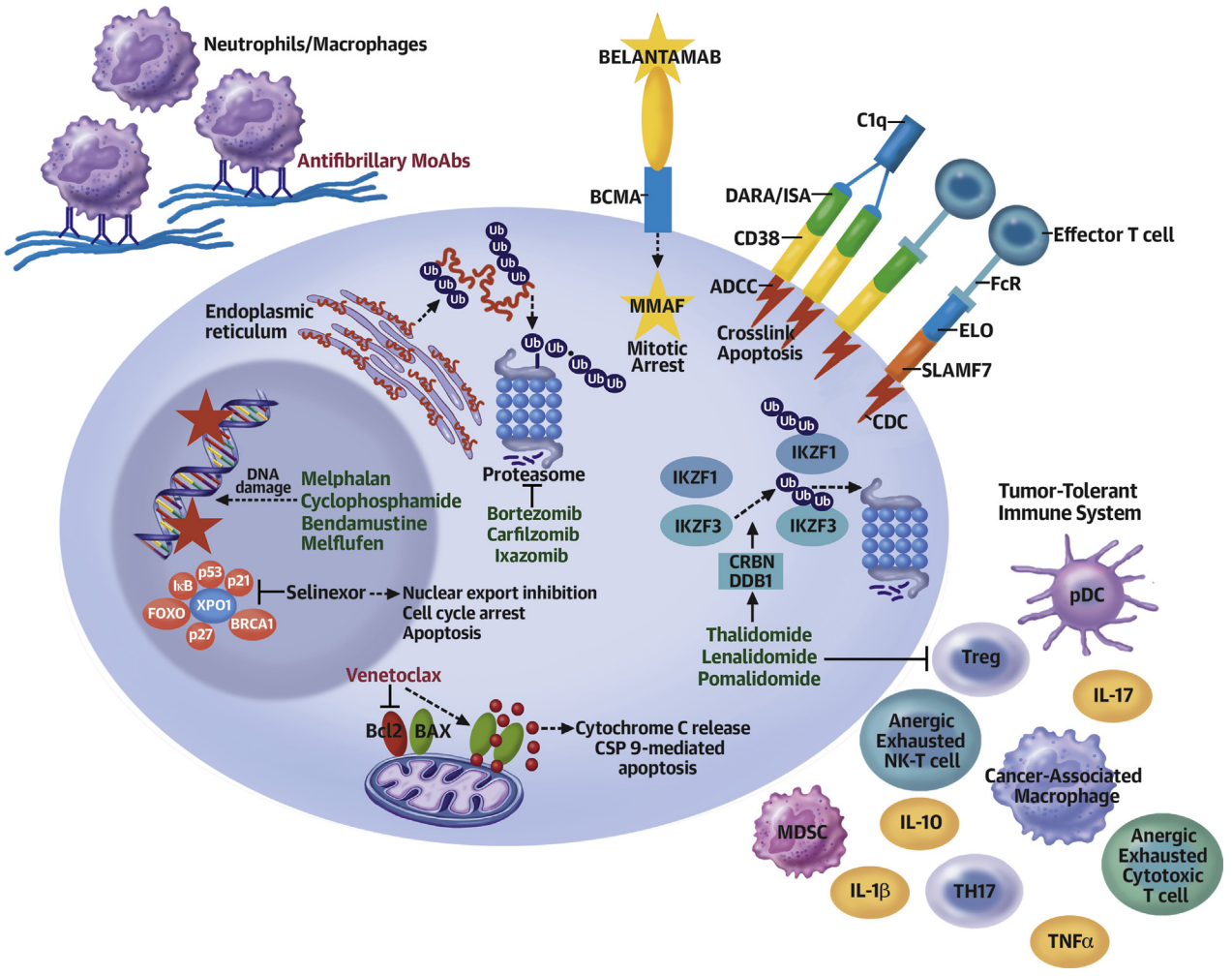


The schema outlines an algorithm for therapeutic decisions in newly diagnosed AL amyloidosis patients with the goal of achieving a deep hematologic response. An early branching point is eligibility for high dose chemotherapy and ASCT. We recommend induction chemotherapy for all patients for 4-6 cycles with monthly assessment of disease response and change of therapy after 2 months if an optimal response is not achieved. ASCT and/or distinct chemotherapy regimens can be used to intensify treatment to achieve a hematologic CR. #Number of cycles is arbitrary and dependent on kinetic of response, tolerability, and indication for ASCT. *Monthly monitoring of hematologic and organ response is mandatory. If a VGPR is not achieved after 2 cycles, we recommend changing chemotherapy. ^Stem cells should be harvested even if ASCT is deferred to second remission. MRD assessment may be useful to aid in discussion regarding intensification of treatment. CR = complete response; other abbreviations as in Figure 1.

humanized IgG1 anti-SAP MoAb, was shown to successfully bind and eliminate amyloid-bound SAP after serum SAP was cleared via Miridesap, a small-molecule drug. Excitingly, in a phase 1 study, miridesap followed by dezamizumab resulted in significant reductions in hepatic amyloid load and liver responses in patients with amyloidosis, including AL amyloidosis (110). Based on these results, a phase 2 trial was initiated, but was then closed because of the emergence of previously unknown side effects and changes in the risk/benefit ratio.

Doxycycline. Preclinical studies in vitro and in animal models have shown antiamyloidogenic activity of doxycycline across the spectrum of amyloidoses with most data in transthyretin amyloidosis (111). The molecular mechanisms underlying the antifibrillary activity of doxycycline remain largely obscure, but inhibition of matrix metalloproteinase has been suggested as a potential mechanism (112). Retrospective studies in AL amyloidosis patients treated with chemotherapy or ASCT showed improved OS in patients receiving doxycycline, prompting interest in prospective studies focused on cardiac protection. The DUAL (Doxycycline to Upgrade response in AL) study is a phase 2 prospective clinical trial that evaluated the safety and activity of doxycycline for 1 year in combination with standard of care chemotherapy in newly diagnosed AL amyloidosis (113). The 1-year OS was

CENTRAL ILLUSTRATION **Therapeutic Strategies in Immunoglobulin Light Chain Amyloidosis: Current Use and Clinical Development**



Bianchi, G. et al. J Am Coll Cardiol CardioOnc. 2021;3(4):467–487.

The Figure outlines the target and/or mechanisms of action of the most frequently used drugs in immunoglobulin light chain amyloidosis and agents in advanced clinical development. Proteasome inhibitors block the function of the proteasome, inducing polyubiquitinated protein accumulation. IMiDs induce Ikaros and Aiolos (IKZF1 and IKZF2, respectively) proteasome-mediated degradation and enhance T-cell and NK-T-cell function. MoAbs DARA and ISA cause complement-dependent cytotoxicity (CDC), antibody-dependent cell cytotoxicity (ADCC), and direct cytotoxicity from crosslinking. ELO triggers ADCC, and the antibody drug conjugated (ADC) targeting BCMA, belantamab mafodotin, induces DNA damage via MMAF. Alkylating agents similarly induce DNA damage and selinexor blocks XPO1. Venetoclax binds BCL2, releasing BAX and triggering cytochrome C release and caspase 9-mediated apoptosis. Antifibrillary antibodies facilitating macrophage-mediated amyloid reabsorption are depicted in the **top left corner**. U.S. Food and Drug Administration–approved drugs in MM therapy are **green**, whereas investigational agents are in **red**. DARA = daratumumab; ELO = elotuzumab; IL = interleukin; ISA = isatuximab; MMAF = monomethyl auristatin F; TNFα = tumor necrosis factor alpha; MDSC = myeloid derived suppressor cell; pDC = plasmacytoid dendritic cell; TH17 = T helper 17; Treg = regulatory T cells; Ub = ubiquitin; XPO1 = exportin 1.

80% in the study population, with 60% of patients undergoing ASCT with 0% 100-day mortality. Importantly, organ responses were observed in 36% of patients in the absence of significant adverse events.

Birtamimab (NEOD001). Birtamimab is a humanized derivative of the murine MoAb 2A4 that recognizes a cryptic epitope on AL amyloid fibril thought to be exposed selectively by misfolded and aggregated FLC. In vitro, 2A4 specifically binds to both soluble and insoluble FLC aggregates and induces the clearance of insoluble aggregates by macrophage phagocytosis mediated by the Fc

receptor (114). NEOD001 showed promising activity in a phase 1/2 trial in 69 relapsed AL amyloidosis patients with high organ response rates. However, subsequent placebo-controlled studies failed to show clinical benefit, and a randomized, phase 3 study of NEOD001 vs placebo in combination with standard of care chemotherapy was halted because of futility at interim analysis (24). As a post hoc analysis showed a significant improvement in all-cause mortality in patients with stage IV AL amyloidosis, a randomized clinical trial of birtamimab in combination with standard of care chemotherapy in this high-risk patient population is currently ongoing (NCT04973137).

CAEL-101. 11-1F4 (CAEL-101) is an amyloid fibril-reactive murine MoAb that binds directly to an epitope present only on misfolded, human light-chain amyloid fibrils, but not properly folded FLC. CAEL-101 binds to AL amyloidosis fibrils and enhances their Fcγ receptor-mediated opsonization and proteolysis. A phase 1a/b study in relapsed or refractory AL amyloidosis showed CAEL-101 to be safe and effective with 67% renal and/or cardiac response and improvement in mean global longitudinal strain observed in 9 of 10 patients (23). A phase 2 trial with 13 patients demonstrated that CAEL-101 administered at doses of up to 1,000 mg/m^2, in combination with standard of care CyBorD, was well-tolerated, setting the stage for 2 phase 3 studies in patients with cardiac stage 3A and 3B AL amyloidosis that are currently recruiting (115).

PROMISING INVESTIGATIONAL AGENTS

Having discussed agents most advanced in clinical development, we now focus on the most promising investigational agents in AL amyloidosis. All of these drugs are FDA approved or in advanced clinical development in MM (**Central Illustration**).

VENETOCLAX. BCL2 is a mitochondrial, anti-apoptotic protein whose overexpression/overactivity has been shown to drive several hematologic malignancies, particularly B lymphoproliferative disorders (116). Although MM cells are generally dependent on a distinct antiapoptotic BCL2 family member, MCL1, t(11;14) is a biomarker for a BCL2 high state, translating into increased BCL2 dependency and predicting venetoclax efficacy (117). Consistent with MM data, t(11;14) AL amyloidosis patients showed high sensitivity to venetoclax with rapid and deep responses in heavily pretreated patients (118,119). Although clinical studies of venetoclax in AL amyloidosis were designed, the FDA put a hold on the BELLINI study, a phase 3 clinical trial comparing bortezomib/dexamethasone plus/minus venetoclax, because of excess mortality from infectious complications noted in the experimental arm (120). Because clinical benefit outweighed the risk for t(11;14) patients, the hold was lifted with a plan for increased surveillance of patients and prophylactic antimicrobials. Considering that t(11;14) is the most common cytogenetic abnormality in AL amyloidosis and portends poor prognosis, much-awaited clinical studies of these agents are finally at the horizon.

BCMA-TARGETING IMMUNO AND CELLULAR THERAPIES. The BCMA-targeting antibody drug conjugate belantamab mafodotin has shown activity in heavily pretreated MM and is FDA approved for triple class (PI, IMiD, and CD38-targeting MoAbs) relapsed/refractory MM patients. Belantamab mafodotin is an afucosylated IgG1 MoAb conjugated to the antitubular agent monomethyl auristin-F (MMAF). It targets BCMA, a surface receptor for BAFF/APRIL that is universally and rather specifically expressed in PCs and triggers anti-MM activity via direct cytotoxicity of intracellularly released MMAF, inhibition of pro-survival BAFF/APRIL signaling, and ADCC via enhanced Fc/FcγR binding (121). Belantamab mafodotin induces deep and sustained hematologic remissions in heavily pretreated MM patients with dose-limiting toxicity being reversible keratopathy and is FDA approved in relapsed and/or refractory MM. Clinical trials are eagerly awaited in AL amyloidosis (122). Trials exploring safety and efficacy of bispecific T-cell engagers (BiTEs) and chimeric T-cell receptor (CAR) T-cell therapy targeting BCMA in AL amyloidosis are being considered, carefully pondering risk/benefit ratio.

MELPHALAN FLUFENAMIDE. Melphalan flufenamide (melflufen) is a peptide-conjugated, melphalan derivative that has shown encouraging activity in MM, leading to its FDA approval in combination with dexamethasone in triple class relapsed/refractory MM. It leverages the increased expression of aminopeptidases in cancer cells, including MM, restricting the release of active alkylator payload in aminopeptidase-rich cancer cells and thereby reducing off-target and increasing on-target activity. The FDA put a partial clinical hold on all melflufen studies, including a phase 1/2 trial examining melflufen/dexamethasone in relapsed and/or refractory AL amyloidosis, in light of decreased OS in patients receiving melflufen/dexamethasone compared with pomalidomide/dexamethasone in the context of the OCEAN phase III noninferiority study (123).

SELINEXOR. Selinexor is a first-in-class inhibitor of the nuclear export protein, Exportin1 (XPO1). XPO1 is responsible for regulating export from the nucleus to

the cytoplasm of cargo proteins, including oncosuppressors p53, RB1, and p27; cell cycle regulators; and antiapoptotic proteins. By blocking their nuclear export, selinexor inhibits the function of these factors, resulting in potent antitumor activity across a wide range of hematologic and solid malignancies. Selinexor showed activity in heavily pretreated MM patients and is FDA approved in relapsed and/or refractory MM. Selinexor activity comes at the expense of tolerability with cytopenia, nausea, diarrhea, and electrolyte abnormalities being frequently observed and necessitating careful ancillary care and patient selection. Case reports are emerging of activity of selinexor in AL amyloidosis, and clinical trials are expected to commence soon in this patient population (124).

DISCUSSION

There has been tremendous progress over the last 3 decades in the treatment of AL amyloidosis, largely because of improved ancillary care, more effective PC-directed therapy, and improved patient stratification for ASCT. It is therefore an exciting time for the AL amyloidosis community. However, there are still obstacles to overcome in the care of AL amyloidosis patients. First, diagnostic delay leading to advanced cardiac involvement remains a major hurdle in the care of AL amyloidosis patients, negatively affecting outcome and driving early mortality. As a medical community, it is therefore of critical importance to raise awareness about AL amyloidosis, a great imitator and often overlooked systemic disease, and to invest in developing/validating tests and biomarkers for early diagnosis. Second, the lack of a deep understanding of AL amyloidosis biology and limited basic research efforts in this arena hampers the development of therapies targeting the intrinsic vulnerabilities of this disease. Mechanisms to better support scientists specifically studying AL amyloidosis biology are therefore welcome. Finally, AL amyloidosis patients and their families still face a significant financial burden during their treatment, largely caused by the off-label use of most therapies and frequent hospital admissions for disease-related complications. A stronger commitment from insurance companies, pharmaceutical companies, and regulatory bodies to support our patients as they embark on a long therapeutic journey is of outmost importance. We look forward to a time, not too far in the future, when AL amyloidosis patients will be rapidly diagnosed and effectively treated with innovative, molecularly-targeted drugs specifically tackling the Achilles' heel of this devastating illness.

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