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REVIEW

Novel Therapies in Light Chain Amyloidosis

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Light chain (AL) amyloidosis is the most common form of amyloidosis involving the kidney. It is characterized by albuminuria, progressing to overt nephrotic syndrome and eventually end-stage renal failure if diagnosed late or ineffectively treated, and in most cases by concomitant heart involvement. Cardiac amyloidosis is the main determinant of survival, whereas the risk of dialysis is predicted by baseline proteinuria and glomerular filtration rate, and by response to therapy. The backbone of treatment is chemotherapy targeting the underlying plasma cell clone, that needs to be risk-adapted due to the frailty of patients with AL amyloidosis who have cardiac and/or multiorgan involvement. Low-risk patients (~20%) can be considered for autologous stem cell transplantation that can be preceded by induction and/or followed by consolidation with bortezomib-based regimens. Bortezomib combined with alkylators, such as melphalan, preferred in patients harboring t(11;14), or cyclophosphamide, is used in most intermediate-risk patients, and with cautious dose escalation in high-risk subjects. Novel, powerful anti–plasma cell agents, such as pomalidomide, ixazomib, and daratumumab, prove effective in the relapsed/refractory setting, and are being moved to upfront therapy in clinical trials. Novel approaches based on small molecules interfering with the amyloidogenic process and on antibodies targeting the amyloid deposits gave promising results in preliminary uncontrolled studies, are being tested in controlled trials, and will likely prove powerful complements to chemotherapy. Finally, improvements in the understanding of the molecular mechanisms of organ damage are unveiling novel potential treatment targets, moving toward a cure for this dreadful disease.

Kidney Int Rep (2018) **3,** 530–541; https://doi.org/10.1016/j.ekir.2017.11.017
KEYWORDS: amyloidosis; prognosis; treatment

Systemic amyloidoses are caused by misfolding and aggregation of autologous proteins that deposit in tissues in the form of amyloid fibrils.[1] This process causes progressive organ dysfunction, eventually leading to organ failure and death if it is not arrested by effective therapy before advanced, irreversible organ damage has ensued.[2] To date, 36 different proteins have been recognized to form amyloid fibrils *in vivo*.[3] Involvement of the kidney can occur in several types of systemic amyloidosis (Table 1); however, Ig light chain (AL) amyloidosis is by far the most common form, accounting for 87% of all patients diagnosed with renal amyloidosis at the Pavia Amyloidosis Research and Treatment Center in the past 30 years. The second most common form (9%) is amyloid A amyloidosis, reactive to chronic inflammation; however, its incidence is declining because of improvements in the treatment of chronic inflammatory diseases.[4] Other rarer types include the amyloidosis caused by Leukocyte Chemotactic Factor-2 (ALECT2), described in patients of Hispanic, Native-American, and Middle East origin,[5] and hereditary forms. Although some clinical features, such as the association of a monoclonal component, heart or soft tissue involvement, and albuminuria, can in some instances strongly suggest AL amyloidosis, there is often substantial overlap in the clinical presentation of different types of renal amyloidosis.[6] Thus, unequivocal typing of the amyloid deposits is mandatory before starting specific treatment.[7] Immunofluorescence on kidney biopsy has poor specificity,[8] and reliable techniques, such as immunohistochemistry with custom-made antibodies,[9] immuno-electron microscopy,[10] or mass spectrometry,[11,12] should be used in referring patients to specialized centers. DNA analysis is required to confirm hereditary forms.

The clinical features of AL amyloidosis with renal involvement have been recently reviewed.[13] This disease is caused by the deposition of monoclonal light chains produced by a plasma cell clone that, in 50% of patients, infiltrates the bone marrow by less than 10%,[14] and is the most common disorder among

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Received 28 August 2017; revised 28 October 2017; accepted 21 November 2017; published online 28 November 2017

Table 1. Systemic amyloidosis involving the kidney

Acquired		
Fibril protein	**Precursor protein**	**Other organs**
AL	Ig light chain	All organs (except the brain)
AH	Ig heavy chain	All organs (except the brain)
AA	Serum amyloid A	Heart, liver, lung
AApoAIV	Uncertain	Medulla and systemic
ALECT2	Leukocyte chemotactic factor-2	Liver
Aβ2-M	β2-microglobulin, wild type	Musculoskeletal system
Hereditary		
Fibril protein	**Precursor protein**	**Other organs**
AApoAI	Apolipoprotein AI	Liver, testis, heart, PNS
AApoAII	Apolipoprotein AII	—
AApoCIII	Apolipoprotein ApoCIII	—
AFib	Fibrinogen α	—
ALys	Lysozyme	—
AGel	Gelsolin	Cranial nerves, cornea, skin
ATTR	Transthyretin	PNS, ANS, heart, eye, leptomeningeal
Aβ2-M	β2-microglobulin, variant	ANS, heart

ANS, autonomous nervous system; PNS, peripheral nervous system.
The amyloid types are identified by acronyms, where the letter "A" for amyloidosis is followed by the abbreviation of the protein forming the amyloid fibrils. Dashes indicate that no other major organ other than the kidney is involved.

monoclonal gammopathies of renal significance.[15,16] Herrera and coworkers showed that kidney involvement starts with the formation of the amyloid deposits in the mesangium.[17] The light chain is internalized in the mesangial cell and delivered to the mature lysosomal compartment in which the fibrils are formed.[18] The amyloid deposits are then externalized and replace the mesangial matrix. Different independent studies found associations between light chain germline gene usage and organ involvement.[19–23] More recently, the Mayo Clinic investigators reported that LV6–57 gene usage is more common in AL amyloidosis than in normal B cells, and is associated with renal involvement.[24] This observation suggests that patients with LV6–57 monoclonal gammopathy should be screened for the onset of amyloid renal involvement.

In recent years, our understanding of the pathogenesis of AL amyloidosis and of the mechanisms of organ involvement in this disease has greatly improved, and major advances have been made in biomarker-based risk stratification and disease monitoring, and novel powerful drugs are expanding the therapeutic options.[25] Overall, these advances are resulting in improved outcomes.[26] Current treatment of AL amyloidosis is based on chemotherapy targeting the underlying plasma cell clone[25]; however, novel approaches directly targeting the amyloid deposits are being developed.[27] In this review, we discuss the current approach to the treatment of AL amyloidosis and possible future developments.

Risk Stratification and Response Assessment

Amyloid kidney involvement is defined as a urinary protein excretion >0.5 g per 24 hours.[28] The urine protein should be predominantly albumin, to avoid confusion with patients who are excreting large amounts of Ig light chains but do not have glomerular involvement with amyloid.[28] Approximately 70% of patients with AL amyloidosis present with renal involvement.[29] Two-thirds to three-fourths of them have overt nephrotic syndrome at diagnosis, and one-half have some degree of renal failure, which is end-stage in 5% to 15% of cases.[29,30] Overall, the presence of kidney involvement is associated with longer survival, mainly because of a lower proportion of patients with cardiac amyloidosis (Figure 1). Indeed, among patients with renal amyloidosis, those who also have involvement of the heart have a significantly poorer outcome, whereas almost 60% of patients without heart involvement are projected to survive more than 10 years (Figure 2). The severity of heart dysfunction is best assessed by the cardiac biomarkers N-terminal pronatriuretic peptide type-B (NT-proBNP) and troponin.[31,32] A simple staging system based on these biomarkers can accurately stratify patients with AL amyloidosis and is applicable to subjects with renal involvement (Figure 3).[33,34] In patients with renal failure, BNP should be preferred over NT-proBNP due to greater interference of reduced glomerular filtration rate in the metabolism of this marker.[35] Parameters of clonal disease also predict survival in AL amyloidosis.[36] The difference between involved (amyloidogenic) and uninvolved free light chains can be incorporated in the staging system based on cardiac biomarkers.[37,38]

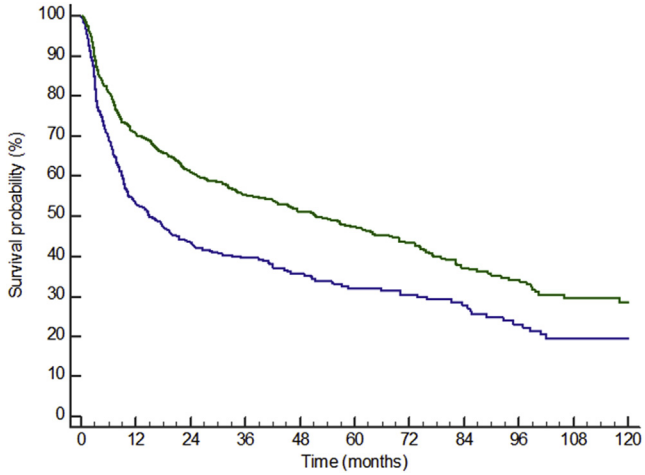

Figure 1. Survival of 1065 patients with light chain amyloidosis according to the presence of renal involvement ($P < 0.001$). Green line: 702 patients with kidney involvement, median survival 51 months; the heart was involved in 70% of cases. Blue line: 363 patients without kidney involvement, median survival 15 months; the heart was involved in 90% of cases.

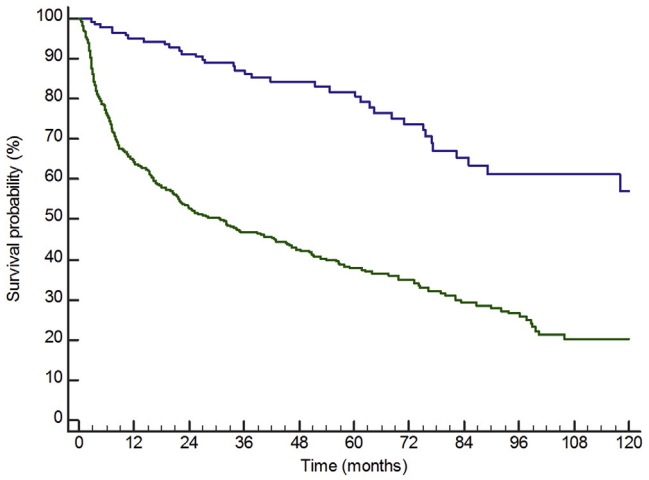

Figure 2. Survival of 702 patients with renal light chain amyloidosis according to the presence of heart involvement ($P < 0.001$). Blue line: 146 patients with kidney involvement without heart involvement, median survival not reached. Green line: 556 patients with kidney and heart involvement, median survival 31 months.

Recently, it has been shown that patients with low difference between involved (amyloidogenic) and uninvolved free light chain levels (<50 mg/l) have lower rates of heart involvement and higher rates of kidney involvement and a more favorable outcome.[39,40] Moreover, characteristics of the amyloidogenic plasma cell clone can predict different response to treatment and can be used in the design of the therapeutic strategy.[25] In particular, patients who harbor the cytogenetic abnormality gain 1q21 have a poorer outcome when treated with oral melphalan, whereas the translocation (11;14) is associated with lower response rates and survival in patients treated with bortezomib.[41–44]

Progression of renal dysfunction and risk of end-stage renal disease depend on levels of proteinuria and renal function at diagnosis. Patients who are diagnosed with renal AL amyloidosis at an early, asymptomatic stage, before nephrotic syndrome has ensued, have a significantly lower risk of requiring dialysis (Figure 4). We have validated a staging system based on 24-hour proteinuria and estimated glomerular filtration rate that can accurately discriminate 3 groups with increasing risk of dialysis (Figure 5).[45] Recently, Kastritis and coworkers[46] validated this staging system in an independent population and proposed the ratio of 24-hour proteinuria to estimated glomerular filtration rate as a sensitive marker of renal risk. Overall, these data indicate that renal AL amyloidosis can be diagnosed at an early reversible stage, when institution of specific treatment can prevent end-stage renal disease. Thus, we advocated screening with albuminuria of patients with monoclonal gammopathy of undetermined significance and abnormal circulating free light chain ratio, to allow presymptomatic identification of renal AL amyloidosis.[2,47]

Reducing the concentration of the circulating amyloidogenic light chain by targeting the plasma cell clone with chemotherapy consistently improves organ dysfunction and prolongs survival in AL amyloidosis,

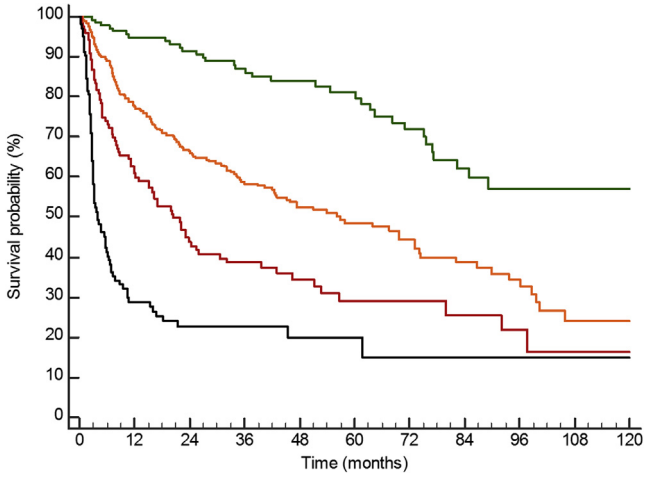

Figure 3. Prognostic stratification of 702 patients with renal light chain amyloidosis according to the concentration of cardiac biomarkers ($P < 0.001$). Green line: stage I, 146 patients, median survival not reached. Orange line: stage II, 307 patients, median survival 57 months. Red line: stage IIIa, 132 patients, median survival 20 months. Black line: stage IIIb, 117 patients, median survival 4 months. Staging is based on N-terminal pronatriuretic peptide type-B (NT-proBNP, cutoff 332 ng/l) and cardiac troponin I (cutoff 0.1 ng/ml). Stage I, II, and III patients have 0, 1, or 2 markers above the cutoff. In stage IIIb patients, NT-proBNP is >8500 ng/l.

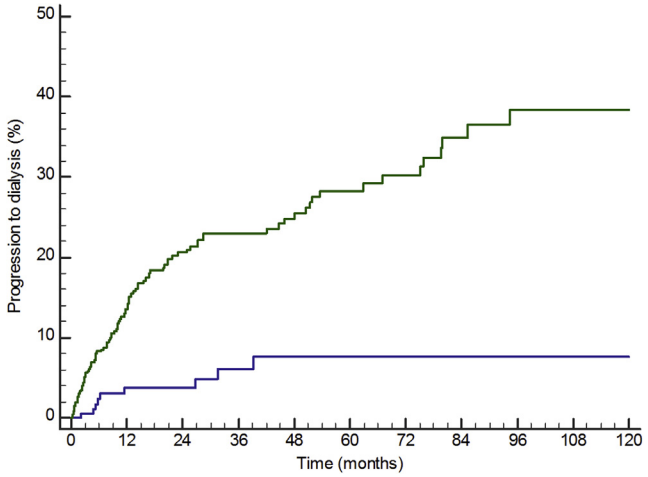

Figure 4. Progression to dialysis in 702 patients with renal involvement according to symptomatic state at presentation ($P < 0.001$). Green line: 480 symptomatic patients with nephrotic syndrome and/or end-stage renal disease defined as estimated glomerular filtration rate <15 ml/min per 1.73 m^2; dialysis rate at 1, 2, and 5 years of 14%, 21%, and 28%, respectively. Blue line: 222 asymptomatic patients; dialysis rate at 1, 2, and 5 years of 4%, 4%, and 8%, respectively.

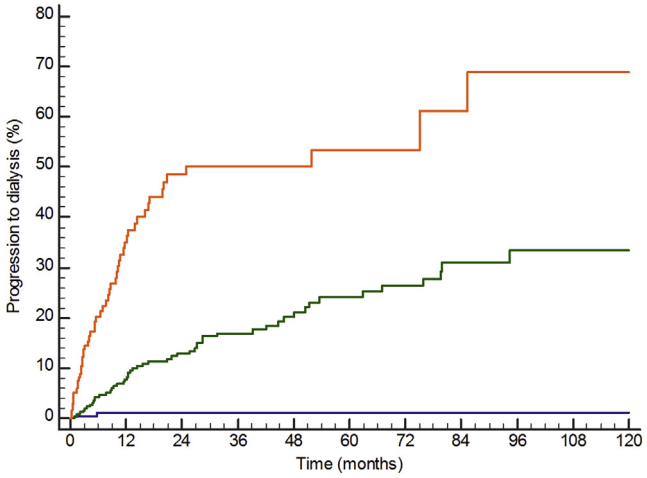

Figure 5. Progression to dialysis in 702 patients with renal involvement according to the renal staging system ($P < 0.001$). Blue line: stage I, 219 patients; dialysis rate at 1, 2, and 5 years of 1%, 1%, and 1%, respectively. Green line: stage II, 341 patients; dialysis rate at 1, 2, and 5 years of 8%, 13%, and 26%, respectively. Orange line: stage III, 142 patients; dialysis rate at 1, 2, and 5 years of 35%, 48%, and 53%, respectively.

Table 2. Validated criteria for response assessment in light chain amyloidosis

Response criteria	Definition
Hematologic response	
Complete response	Negative serum and urine immunofixation and normal FLC ratio
Very good partial response	dFLC <40 mg/L
Partial response	dFLC decrease >50% compared to baseline
No response	All other patients
Patients with dFLC <50 mg/l	
Complete response	Negative serum and urine immunofixation and normal FLC ratio
Low-dFLC-response	dFLC <10 mg/l
Cardiac response	Decrease of NT-proBNP by >30% and 300 ng/l (if baseline NT-proBNP >650 ng/l), or at least a 2-point decrease of NYHA class (if baseline NYHA class is III or IV)
Renal response	At least 30% decrease in proteinuria or drop below 0.5 g/24 h, in the absence of renal progression defined as a >25% decrease in eGFR

CR, complete response; dFLC, difference between involved and uninvolved light chain; eGFR, estimated glomerular filtration rate; FLC, free light chain; NT-proBNP, N-terminal pronatriuretic peptide type-B; NYHA, New York Heart Association.
Response criteria are validated in independent patient populations for use at 3 and 6 months after treatment initiation.

and major advances have been made in recent years. The criteria to assess hematologic response to treatment are based on the decrease of difference between involved (amyloidogenic) and uninvolved free light chain and disappearance of the monoclonal component at immunofixation of serum and urine, and can be used as early as 3 months after treatment initiation to identify patients with suboptimal response who should be shifted to second-line rescue therapy.[48] Clinical evidence exists that links cardiac dysfunction and NT-proBNP levels to the concentration of the circulating amyloidogenic light chain,[32,49,50] and changes in NT-proBNP concentration are used to assess cardiac response.[48] After chemotherapy, profound reductions in circulating amyloidogenic free light chains are also associated with better renal outcome,[30] whereas deep decreases in proteinuria predict prolonged patient survival.[51] We have validated a renal response criterion based on risk of progression to dialysis, defined as a decrease in proteinuria by at least 30% or drop below 0.5 g per 24 hours, in the absence of renal progression defined as a >25% decrease in estimated glomerular filtration rate.[45] Current validated hematologic and organ response criteria in AL amyloidosis are reported in Table 2.

Targeting the Amyloidogenic Plasma Cell Clone

The possibility of effectively reducing the production of the precursor protein with chemotherapy makes AL amyloidosis a treatable type of renal amyloidosis. The therapeutic approaches targeting the amyloidogenic plasma cell are usually borrowed from multiple myeloma; however, patients with AL amyloidosis not only have a hematologic malignancy, but their multiorgan involvement makes them particularly fragile and susceptible to treatment toxicity. Thus, the treatment of patients with AL amyloidosis should be risk-adapted.[25] To date, no randomized clinical trials of modern treatment approaches have been published, and there is little evidence in support of a standard treatment strategy in AL amyloidosis. Thus, whenever possible, patients should be referred to specialized centers for treatment and inclusion in clinical trials.

Treatment for Low-Risk Patients

Low-risk patients represent approximately 15% to 20% of all subjects with renal AL amyloidosis and are candidates for autologous stem cell transplantation (ASCT). This procedure is associated with a substantially higher risk of early mortality in AL amyloidosis compared with multiple myeloma. However, careful patient selection and a critical level of expertise reduce the risk to an acceptable level. The great majority of transplant-related mortality occurs in patients with elevated cardiac biomarkers, and subjects whose NT-proBNP is >5000 ng/l and/or cardiac troponin T is >0.06 ng/ml are not suitable candidates for ASCT.[52,53] Other criteria defining eligibility for ASCT are age <65 years, performance status (Eastern Cooperative Oncology Group) 0 to 2, estimated glomerular filtration rate >50 ml/min per 1.73 m^2 unless on dialysis, New York Heart Association class <III, cardiac ejection fraction >45%, systolic

blood pressure >90 mm Hg (standing), and lung CO diffusion capacity >50%.[25] Similar criteria are used at all major referral centers.[53,54] Refinement in selection criteria has reduced transplant-related mortality over time.[55] Accumulation of a critical level of experience in transplanting patients with AL amyloidosis also is crucial, the outcome being significantly poorer at centers where fewer than 4 transplants per year are performed in patients with this disease.[55] When adequate selection of transplant candidates is applied at referral centers, the outcome of patients with AL amyloidosis undergoing ASCT is excellent, with hematologic response in 71% of subjects and complete response (CR) in 35% to 37%.[55,56] This results in an overall median survival of 7.6 years, with 55% of patients in CR surviving more than 14 years.[56] Renal response rate to ASCT is 32%.[55] Patients who fail to reach CR after ASCT can receive "adjuvant" bortezomib-based treatment, increasing the CR rate to almost 60%.[57] Bortezomib can be used as induction therapy before ASCT, and this approach increases the response rate and quality of response, particularly in patients with a bone marrow plasma cell infiltrate >10%.[58] Acute kidney injury can frequently occur in patients with AL amyloidosis who have other features associated with engraftment syndrome in the setting of ASCT.[59] This syndrome is characterized by rash, fever, weight gain, diarrhea, and noncardiogenic pulmonary edema within days of leukocyte engraftment. Other causes of acute kidney injury around the time of engraftment, particularly infection, need to be excluded. In this setting, steroid therapy should be initiated as soon as possible.[59] Nevertheless, the recent HOVON 104 trial of induction with bortezomib/dexamethasone before ASCT, showed a CR rate of only 30% 6 months after ASCT, and a high proportion (24%, 8% due to bortezomib toxicity) of patients who could not proceed to ASCT.[60] However, in this study, a very intensive induction treatment (bortezomib 1.3 mg/m^2 twice weekly and dexamethasone 20 mg 4 times per week) was used that can at least in part account for the high dropout rate. At our center, we offer upfront treatment with cyclophosphamide, bortezomib, and dexamethasone (CyBorD) to all transplant candidates, unless they present contraindications to bortezomib, and we proceed to ASCT in case a CR is not reached with CyBorD alone. Overall, at our center, 8% of all patients with renal AL amyloidosis (corresponding to 50% of low-risk subjects) receive ASCT upfront or after induction.

Treatment for Intermediate-Risk Patients

Intermediate-risk patients account for approximately 65% of patients with renal AL amyloidosis. They receive nontransplant chemotherapy. Until recently, a standard treatment for these patients has been oral melphalan/dexamethasone (MDex).[61,62] This regimen is very well tolerated and yields a 76% overall hematologic response rate, with CR in 31% of cases and renal response in 24%.[38] One of the few randomized trials completed in AL amyloidosis compared MDex with ASCT and failed to demonstrate an advantage for ASCT in terms of response rate and survival.[63] This trial was performed before the availability of biomarker-based selection of transplant candidates, and the results were considered influenced by a very high transplant-related mortality. Nevertheless, a landmark analysis excluding early deaths confirmed these results. The availability of the proteasome inhibitor bortezomib was enthusiastically welcome, because the amyloidogenic plasma cell used the proteasome to cope with the toxicity generated by the plasma cells they produce.[64] Indeed, we have recently shown that amyloidogenic light chains are intrinsic stressors for plasma cells and increase their sensitivity to proteasome inhibition.[65] A large European retrospective study and a prospective trial showed promising efficacy of bortezomib in relapsed and refractory patients.[66–69] Subsequently, 2 small retrospective series showed unprecedented response rates with the CyBorD combination upfront.[70,71] In the largest study of frontline treatment with CyBorD of patients with AL amyloidosis, the overall hematologic response rate was 60%, with CR in 23% of cases and renal response in 25%.[72] Two retrospective case-control studies showed a higher response rate with bortezomib in combination with alkylating agents and dexamethasone compared with the previous standards of care with MDex and cyclophosphamide/thalidomide/dexamethasone, although without a survival benefit.[73,74] An international phase III study (NCT01277016) comparing MDex with bortezomib plus MDex has recently been completed, showing a significantly higher overall hematologic response rate with bortezomib plus MDex (81% vs. 57%, $P = 0.005$), with longer time to second-line therapy or death and comparable rates of CR (23% vs. 20%) and of renal response (44% with both regimens).[75] Based on these data, bortezomib should be offered to intermediate-risk patients, in the absence of contraindications such as peripheral neuropathy. The choice of the best combination should take into account clonal and patient characteristics. A recent study by Kastritis *et al.*[76] showed that addition of cyclophosphamide and higher doses of dexamethasone do not improve outcomes of patients with AL amyloidosis treated with bortezomib. Treatment with bortezomib plus MDex has the advantage of overcoming the effects of both gain 1q21 (poor outcome with oral melphalan)

and t(11;14) (poor outcome with bortezomib).[41–44] Treatment with CyBorD or bortezomib/dexamethasone alone is preferred in patients with potentially reversible contraindication to ASCT, being stem cell sparing, as well as in subjects with renal failure.

Treatment for High-Risk Patients

The remaining 15% to 20% of patients with renal AL amyloidosis are high-risk, most frequently because of advanced cardiac stage (IIIb) or severe heart failure (New York Heart Association class III or IV). So far, no treatment approach, including those based on bortezomib, was able to overcome the poor prognosis of these patients, and median survival ranges from 3 to 7 months.[77] Nevertheless, the few patients who survive long enough (at least 3 months) to take advantage of response to chemotherapy survive significantly longer.[72] High-risk patients are treated with low-dose combinations, with weekly dose escalation based on tolerability under intensive monitoring.[25]

Treatment for Relapsed/Refractory Disease

Relapsed patients can be treated by repeating upfront therapy, if possible, although this is associated with shorter time to retreatment without reduction in overall survival.[78] Lenalidomide can be used in refractory patients, being able to overcome resistance to alkylating agents, proteasome inhibitors, and thalidomide.[79–84] However, use of lenalidomide is associated with worsening renal failure in patients with renal AL amyloidosis with nephrotic syndrome.[85] Lenalidomide combinations have been also used upfront with encouraging results.[82,83,86–89] Pomalidomide also is a very effective agent in refractory AL amyloidosis, being able to rescue patients exposed to other classes of drugs including alkylators, first- and second-generation proteasome inhibitors, and lenalidomide.[90–92] Hematologic response to pomalidomide is rapid (median 1 month) and is observed in up to two-thirds of patients in the refractory setting, with renal response in 17% of cases.[92] Newer agents have proven effective in relapsed/refractory patients, and are being considered for novel upfront combinations. The proteasome inhibitor carfilzomib has been tested in a trial in previously treated patients with AL amyloidosis. The hematologic response rate was 63% (CR 12%), and renal response was observed.[93] In this study, 39% of patients had NT-proBNP progression, which was clinically relevant in 18% of cases, and cardiac toxicity of carfilzomib will probably limit the role of this drug in AL amyloidosis. A trial of carfilzomib in combination with thalidomide and dexamethasone is ongoing (NCT02545907). The oral proteasome inhibitor ixazomib was particularly active in bortezomib-naïve patients,[94] and is currently being tested in a randomized phase III trial (NCT01659658). Two trials of this agent in combination with cyclophosphamide and dexamethasone (NCT03236792, NCT01864018) are ongoing in the upfront setting. Daratumumab is also a very promising drug in AL amyloidosis. A recently published series showed a 76% hematologic response rate with 36% CRs in a median time of 1 month.[95] Two phase II trials of daratumumab in relapsed/refractory patients are under way (NCT02841033, NCT02816476) and a phase III randomized trial of daratumumab in combination with CyBorD versus CyBorD alone in newly diagnosed patients is about to begin (NCT03201965). The list of ongoing clinical trial for AL amyloidosis is reported in Tables 3 and 4.

Targeting the Amyloid Deposits and Interfering With Amyloidogenesis and Organ Damage

New therapeutic approaches specifically targeting the amyloid deposits or interfering with amyloid formation and organ targeting are emerging as a possible complement of chemotherapy, given in combination with anti–plasma cell therapy or after achievement of hematologic response.

Treatments Interfering the Amyloid Formation

Our observation that the anthracycline 4′-iodo-4′-deoxy-doxorubicin inhibited amyloidogenesis *in vitro* and could induce clinical improvement in patients with AL amyloidosis, prompted the investigation of related noncytotoxic compounds.[96–100] Among them, the antibiotic doxycycline proved able to disrupt the amyloid fibrils in transgenic mouse models of transthyretin and AL amyloidosis.[101,102] Moreover, doxycycline can interfere with light chain–induced toxicity in a *Caenorhabditis elegans* model, in which exposure to amyloidogenic light chains from patients

Table 3. Ongoing clinical trials in light chain amyloidosis, chemotherapeutic approaches

Trial Number	Phase	Regimen
Newly diagnosed patients		
NCT03236792	I/II	Ixazomib, cyclophosphamide, and dexamethasone
NCT01864018	I/II	Ixazomib, cyclophosphamide, and dexamethasone
NCT01807286	I/II	Pomalidomide, melphalan, and dexamethasone
NCT03201965	III	Daratumumab with cyclophosphamide, bortezomib, and dexamethasone versus cyclophosphamide, bortezomib, and dexamethasone alone
Relapsed/refractory patients		
NCT01659658	III	Ixazomib plus dexamethasone versus physician's best choice
NCT02545907	Ib	Carfilzomib, thalidomide, and dexamethasone
NCT02841033	I/II	Daratumumab (single agent)
NCT02816476	II	Daratumumab (single agent)
NCT03000660	I	Venetoclax and dexamethasone

Table 4. Ongoing clinical trials in light chain amyloidosis, nonchemotherapeutic approaches

Trial Number	Phase	Regimen
Newly diagnosed patients		
NCT02312206	III	NEOD001/bortezomib-based regimen versus placebo/bortezomib-based regimen
Relapsed/refractory patients		
NCT03044353	II	GSK2398852 administered following and along with GSK2315698
NCT02245867	Ia/Ib	Chimeric fibril-reactive monoclonal antibody 11–1F4
NCT02632786	IIb	NEO001 (single agent) versus placebo (patients with heart involvement)
NCT03168906	IIb	NEO001 (single agent) versus placebo (patients with kidney involvement)

with cardiac AL amyloidosis results in the reduction of the pumping function of the nematode's pharynx, which resembles the vertebrate heart.[103] A recent retrospective case-control study showed that patients with cardiac AL amyloidosis who received doxycycline together with chemotherapy had a reduction in early mortality, translating into higher response rates and prolonged survival.[104] A prospective, international, randomized trial of chemotherapy with or without doxycycline is being designed. In the *C. elegans* model, the toxicity of amyloid light chains appeared to be dependent on metal ions and was prevented by metal chelators synergistically with doxycycline, paving the way to future clinical studies on this combination.[105]

Polyphenols are also being investigated as inhibitors of fibril formation by redirecting amyloidogenic polypeptides into unstructured, off-pathway oligomers.[106] Among them is epigallocatechin-3-gallate.[107] Case reports and retrospective series showed promising activity of epigallocatechin-3-gallate on cardiac AL amyloidosis.[108,109] In a phase II trial, epigallocatechin-3-gallate was well tolerated, and in some patients a decrease in albuminuria was observed.[110] Other trials of this compound in AL amyloidosis are under way (NCT01511263, NCT02015312).

Treatments Targeting the Amyloid Deposits

The London group developed a palindromic compound CPHPC that is a competitive inhibitor of the binding of serum amyloid P component (SAP) to amyloid fibrils, which protects them from degradation, and is able to remove SAP from the bloodstream.[111] Subsequently, they showed that administration of anti-human-SAP antibodies to mice with amyloid deposits containing human SAP triggers a complement-dependent, macrophage-derived giant cell reaction that removes visceral amyloid deposits,[112] and proposed a combination approach based on CPHPC and anti-SAP antibodies. A pilot clinical study of this approach showed encouraging results,[113] and a clinical trial in patients with AL amyloidosis who undergo or have completed chemotherapy is ongoing (NCT03044353). Future trials based on validated organ response criteria are eagerly awaited.

A different immunotherapy approach has been explored by Hrncic *et al.*,[114] who showed that infusion of an anti–light chain monoclonal antibody specific for an amyloid-related epitope led to the resolution of amyloidomas generated in mice by injection of amyloid proteins extracted from the spleens or livers of patients with AL amyloidosis. A phase I study of this antibody (11–1F4) is ongoing. An interim analysis presented at the last American Society of Hematology annual meeting (December 2016), showed organ response, including reduction of proteinuria, in 5 of 8 patients with measurable disease.[115] In the phase Ib study, 5 of 6 patients who completed the follow-up showed organ response. In addition, no grade 3 and 4 adverse events related to the drug were reported.

Currently, the immunotherapy targeting amyloid deposits in the most advanced stage of clinical development is based on NEOD001, a monoclonal antibody that binds to amyloid protofilaments and fibrils. The murine form of this antibody, 2A4, binds soluble and insoluble light chain aggregates from patients with AL amyloidosis and promotes clearance of amyloid deposits by phagocytosis.[116] In a phase I/II study on patients with AL amyloidosis who had completed chemotherapy and had persisting organ dysfunction, cardiac and renal response rates were 57% and 60%, respectively.[117] The results of this study were recently updated, showing that organ response to NEOD001 was independent of rate and depth of previous hematologic response.[118] A phase II randomized, placebo-controlled trial to evaluate renal response rate in patients with AL amyloidosis who have a maintained hematologic response to chemotherapy is under way (NCT03168906), and 2 phase III randomized, placebo-controlled trials of NEOD001 combined with bortezomib-based chemotherapy in newly diagnosed patients (NCT02312206), and as a single agent in subjects who completed chemotherapy (NCT02632786) have recently completed enrollment and results are eagerly awaited.

Supportive Therapy

Supportive treatment is vital in patients with AL amyloidosis to sustain organ function while chemotherapy takes effect, and to improve quality of life. Patients with renal amyloidosis present nephrotic syndrome and volume overload that are frequently associated with severe hypotension, in particular if the

heart and/or autonomic nervous system are involved. Other consequences of the urinary protein loss include hyperlipidemia, increased risk of deep venous thrombosis, and malnutrition. We reported that nutritional status independently affects quality-of-life assessment in patients with AL amyloidosis.[119–121] The results of an interventional study run at our center documented that in outpatients with AL amyloidosis, nutritional counseling was helpful in preserving body weight, effective in improving mental quality of life, and associated with better survival.[122]

The combination of urinary protein loss and increased catabolic rate play a central role in the constitution of hypoalbuminemia.[123] The development of a significant peripheral edema requires diuretics associated with dietary sodium restriction. Patients should be frequently consulted on a low-salt diet and they should weigh themselves daily, and diuretic dosing should be titrated accordingly. Thiazide diuretics have less of a natriuretic effect than the loop diuretics, but are sometimes used in conjunction with them to increase natriuresis. Metolazone could be considered in patients with or without renal failure, with careful monitoring for possible hypotension.[124] Spironolactone may be useful for its action as a potassium-sparing diuretic and owing to its antiproteinuric affect. Patients with severe nephrotic syndrome may benefit from admission for i.v. diuretics, and albumin infusions could be considered. In some patients, asymptomatic involvement of the autonomic nervous system[125] could lead to overt, often severe hypotension when treatment with angiotensin-converting enzyme inhibitors is established. This therapy should be considered with caution and at the lowest effective dose. The presence of severe nephrotic syndrome can also increase the risk of venous thrombosis. This association has been attributed to an imbalance between prothrombotic and procoagulant factors, as well as antithrombotic and anticoagulant factors, that promotes thrombosis in deep veins. Anticoagulation should be considered in patients who have other procoagulant factors, most commonly treatment with immunomodulatory drugs. Patients who develop end-stage renal disease could initiate renal replacement therapy. However, patients with amyloidosis are prone to intradialytic hypotension due to cardiac and autonomic nervous system involvement, as well as the severe nephrotic syndrome that decreases capillary refill rates. Thus, ultrafiltration may be difficult to effectively perform. These patients may benefit from more frequent dialysis treatments to attenuate the ultrafiltration rate during each individual session. The median survival of patients with AL amyloidosis exceeds 3 years from dialysis initiation.[30,45] Renal transplantation can be offered to patients who achieve CR after chemotherapy, who are at lowest risk of recurrence of amyloidosis in the graft.[25]

In conclusion, chemotherapy reducing the supply of the toxic light chain is the backbone of treatment of AL amyloidosis. Regimens increasing the rate and depth of hematologic response significantly improved the outcome of patients with this disease in the past few years.[26,126] The development of newer, even more powerful anti–plasma cell agents, such as pomalidomide and daratumumab, which will soon be tested in clinical trials in combination with established regimens, will most likely further improve the outlook of patients with AL amyloidosis. However, many patients are still diagnosed when advanced organ damage has already established, and early diagnosis, at a presymptomatic stage, based on screening of patients at risk with sensitive biomarkers remains critical to improve survival in this disease. Several strategies are being developed to interfere with the amyloidogenic process and target the amyloid deposits in combination with chemotherapy or after hematologic response has been reached. If this approach succeeds, in the near future anti–plasma cell and antiamyloid drugs will be combined upfront, and the latter continued until a satisfactory organ response is achieved, potentially further improving survival and quality of life of patients with AL amyloidosis. Finally, the improvement in the understanding of the molecular mechanisms of amyloidogenesis and organ damage will unveil novel potential treatment targets, moving toward a cure for this dreadful disease.

DISCLOSURE

GP received honoraria from Jannsen-Cilag, honoraria and travel support from Prothena, and travel support from Celgene. GM is a consultant for Millennium Pharmaceuticals, Inc., Pfizer, Janssen, Prothena, and IONIS. The other author declared no competing interests.

ACKNOWLEDGMENTS

This study was supported in part by a grant from "Associazione Italiana per la Ricerca sul Cancro—Special Program Molecular Clinical Oncology 5 per mille n. 9965," from CARIPLO "Structure-function relation of amyloid: understanding the molecular bases of protein misfolding diseases to design new treatments n. 2013–0964," and from CARIPLO "Molecular mechanisms of Ig toxicity in age-related plasma cell dyscrasias n. 2015–0591." GP is supported in part by the Bart Barlogie Young Investigator Award from the International Myeloma Society.

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