AL Amyloidosis: Unfolding a Complex Disease

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Abstract

Light chain (AL) amyloidosis is a rare plasma cell dyscrasia. An estimated 12,000 people live with the disease in the United States. AL amyloidosis occurs from the misfolding of proteins that deposit in organs (heart, kidneys, digestive tract, tongue, lungs, and nervous system), leading to progressive organ damage and impairment of quality of life. The treatment of AL amyloidosis has improved greatly over the past several years, with new treatments currently in development. This article will focus on the pathophysiology, diagnosis, and treatment of AL amyloidosis.

Amyloidosis is a disease in which misfolded proteins deposit within the organs and tissues, leading to progressive organ failure and ultimately death (Gillmore & Hawkins, 2013). There are many different subtypes of amyloidosis, including amyloid protein immunoglobulin light chain (AL) amyloidosis, serum amyloid A protein (AA) amyloidosis, dialysis-related amyloidosis, and transthyretin (TTR) amyloidosis (Blancas-Mejía & Ramirez-Alvarado, 2013). While there are many types of amyloidosis, this article will focus on AL amyloidosis, which involves the misfolding of immunoglobulin light chains produced by monoclonal plasma cells. Currently, there are approximately 12,000 patients living with AL amyloidosis (Quock, Yan, Chang, Guthrie, & Broder, 2018). Due to the small number of patients diagnosed, the National Institutes of Health has designated amyloidosis an orphan disease. Significant strides have contributed to the further understanding of the pathophysiology of AL amyloidosis and continued advancements have elucidated more effective treatment regimens in combating this potentially deadly disease.

PATHOPHYSIOLOGY

In a study by Kyle and colleagues (2019), investigators reviewed records of individuals living in Olmstead County in Minnesota and found an incidence of 1.2 per 100,000 persons, which suggests an estimated 3,852 new cases of amyloidosis yearly. AL amyloidosis is generally diagnosed in the later decades of life and afflicts patients

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at a median age of 67, with most patients older than 45. The median survival of patients first diagnosed with this disease is predicted to be approximately 12 to 40 months (Blancas-Mejía & Ramirez-Alvarado, 2013).

Defective plasma cells produce monoclonal proteins, which are found in plasma cell dyscrasias such as multiple myeloma (MM) and Waldenström macroglobulinemia (WM), and in large quantities can produce devastating effects (Wechalekar, Gillmore, & Hawkins, 2016). Specifically in AL amyloidosis, the monoclonal protein causes an increase of serum light chains that forms insoluble amyloid fibrils that then self-assemble into identical, highly structured, abnormal cross β-sheet formations (Wechalekar et al., 2016). Usually, the isotype of the light chain produced is the λ light chain occurring in approximately 80% of cases (Merlini, 2017). However, AL amyloidosis is not solely limited to the unnatural production of light chains and can sometimes, albeit infrequently, involve an overproduction of heavy chains or fragments (Gertz & Zeldenrust, 2014). The light chain isotype may affect certain tissues more than others due to the variability in light chain sequencing, which may result in structural and biophysical differences. This may affect the level and severity of organ involvement and may somewhat explain why amyloid deposition may tend to occur more commonly in certain organs such as the heart, kidneys, gastrointestinal (GI) tract, peripheral nerves, and liver (Blancas-Mejía & Ramirez-Alvarado, 2013).

In general, patients with AL amyloidosis have a relatively low level of clonal plasma cells in the bone marrow, with the median plasma cell percentage at about 7% to 10% (Kourelis et al., 2013). Higher amounts of clonal plasma cells correlates with poorer prognosis. Patients with extensive plasma cell infiltration of greater than 30% do not usually present with typical myeloma symptoms (hypercalcemia, renal dysfunction, anemia, lytic lesions), but rather present with symptoms of organ damage, such as cardiac symptoms, nephrotic range proteinuria, dysphagia, peripheral neuropathy, fatigue, or GI symptoms (Kastritis & Dimopoulos, 2015). Patients who do not have an initial concurrent diagnosis of MM will have a less than 1% likelihood of progressing to overt myeloma (Gertz & Zeldenrust, 2014).

While it is unclear what causes amyloidosis and why these proteins reorder in a disorderly fashion, this disease is likely associated with advancing age and the presence of genetic mutations. Using interphase fluorescence in situ hybridization (iFISH), translocation (11;14) was found to be the most prevalent genetic abnormality and is associated with poorer prognosis (Merlini, 2017).

CLINICAL FEATURES

Symptoms of AL amyloidosis are often vague, nonspecific, and can be confounding, leading the clinician to diagnose an incorrect, but seemingly probable differential. Patients may complain of symptoms like fatigue and weight loss. An accurate diagnosis of amyloidosis is not usually made until after the appearance of symptoms related to organ damage (Palladini & Merlini, 2016). Amyloidosis can involve a wide range of organ groups which include, but are not limited to, cardiac, renal, gastrointestinal, soft tissue, and nervous systems.

Involvement of the soft tissue such as macroglossia (i.e., tongue enlargement) and periorbital purpura are more classical findings for amyloidosis. However, the incidence of these symptoms is quite low (Picken & Barton, 2015). Periorbital purpura occurs in approximately 15% of patients and appears as bruising around the eyes (Gertz & Zeldenrust, 2014). Macroglossia occurs even less commonly, in fewer than 10% of patients with amyloid. When evaluating macroglossia, the provider would look on the underside of the tongue for dental indentations. Other soft tissue findings include the "shoulder pad sign," arthropathy, claudication, skin thickening, dry mouth, and carpal tunnel syndrome (Kastritis & Dimopoulos, 2015). The "shoulder pad sign" is a rarely observed symptom and is caused by amyloid infiltration into the skeletal muscle, producing pseudohypertrophy (Gertz & Zeldenrust, 2014). Notably, these symptoms may resemble a variety of rheumatologic conditions. Skin thickening caused by amyloid deposits can lead to scleroderma, while amyloid deposition into the periarticular areas may cause symptoms of joint swelling and stiffness similar to symptoms found in rheumatoid arthritis. Xerostomia, or dry mouth, caused by amyloid deposits in the salivary gland, can be mistaken as a symptom of Sjögren syndrome (Prokaeva et al., 2007).

Peripheral neuropathy is considered a dominant presentation of AL amyloidosis and found in about 20% to 34% of patients, with 7% to 12% who may present with months to years of isolated neuropathy prior to developing systemic disease (Bilbao & Schmidt, 2015). Most patients experience length-dependent neuropathy, which may start in the feet and spread proximally over time. Patients may complain of numbness, burning, stabbing, or tingling sensations, or may report muscle weakness. On exam, these patients may experience sensory loss in the large fibers, which help to detect light touch and vibration, and also loss in the small fibers, which may detect pain and temperature. Any report of peripheral neuropathy should be evaluated by nerve conduction studies such as an electromyography (EMG), which will typically show an axonal pattern (Naddaf & Mauermann, 2018) as opposed to a demyelinating pattern, which is more commonly seen in IgM-associated monoclonal gammopathies, such as WM (Chaudhry, Mauermann, & Rajkumar, 2017).

Some patients with AL amyloidosis may develop factor X deficiency, which is estimated to occur in about 8.7% to 14% of patients (Thompson et al., 2010). Amyloid fibrils are believed to absorb factor X, thus resulting in deficiency that may invariably cause difficult-to-treat, life-threatening hemorrhage. Conventional treatment such as fresh frozen plasma, vitamin K, platelet infusion, plasma exchange, and even autologous stem cell transplant have been found to be minimally effective in treating this complication (Thompson et al., 2010). The risk of bleeding is further compounded by the fragility of blood vessels, and impaired vasoconstriction from amyloid angiopathy can also lead to hemorrhage (Sucker, Hetzel, Grabensee, Stockschlaeder, & Scharf, 2006).

While these symptoms are specific to amyloid, they appear in a very small subset of patients and can often mislead the provider to an inaccurate diagnosis due to their nonspecificity. Thus, it is imperative for the clinician to consider the different amyloid syndromes that can occur. These include heart failure, nephrotic range proteinuria, hepatomegaly, peripheral neuropathy, and atypical multiple myeloma (Gertz & Zeldenrust, 2014). At diagnosis, 46% of patients may experience 3 or more organ involvement (Bayliss, McCausland, Guthrie, & White, 2017). The two most commonly affected organs are the heart (75%–80%) and kidneys (62%; Milani, Merlini, & Palladini, 2018; Muchtar et al., 2019).

Cardiac amyloidosis is the most common, affecting approximately 75% to 80% of patients at diagnosis, and usually confers poor prognosis (Milani, Merlini, & Palladini, 2018; Muchtar et al., 2019). Patients typically present with symptoms of restrictive cardiomyopathy and may complain of dyspnea on exertion and fatigue. These patients may have diastolic dysfunction, where left ventricular filling during diastole is impaired due to a rapid rise in the left ventricular end diastolic pressure (Gertz & Zeldenrust, 2014). Patients may also have symptoms of peripheral edema, arrhythmias, orthostatic hypotension, or any other symptoms commonly found with heart failure (Gillmore et al., 2015). In severe cases, patients may have sudden cardiac death, which has been seen in about 10% of individuals (Gertz & Zeldenrust, 2014).

The kidneys are the next organ most commonly affected by light chain amyloidosis. Renal involvement of amyloidosis may manifest with nephrotic syndrome, leading to lower extremity swelling, fatigue, pleural effusions, and even orthostatic hypotension (Gillmore et al., 2015). Peripheral edema is multifactorial and can lead to plasma leakage into the extravascular space due to hypoalbuminemia. The low albumin levels can lower the plasma oncotic pressure, resulting in peripheral edema or anasarca (Gertz & Zeldenrust, 2014). Furthermore, if the patient has concomitant cardiac involvement, symptoms will mimic heart failure with associated peripheral edema.

Other commonly involved organs include the GI tract and the liver. Patients with amyloid involvement of the GI tract may have gastroparesis, diarrhea, constipation, aphagia, hemorrhage, or malabsorption syndrome (Kastritis & Dimopoulos, 2015). Hepatomegaly is seen in about 25% of patients who have liver involvement. These patients may present with ascites and, in severe cases, jaundice. (Gertz & Zeldenrust, 2014). In patients with involvement of more than one organ, symptoms may overlap and/or lead to more severe symptoms.

DIAGNOSIS

The diverse symptoms of AL amyloidosis include cardiomyopathy, nephrotic range proteinuria, fatigue, peripheral neuropathy, and GI symptoms. Due to these diverse symptoms, the diagnosis of amyloidosis can be difficult. Therefore, it is important to perform a thorough workup, including laboratory values, urine protein electrophoresis, histology, and cardiac evaluation. Nephrotic range proteinuria, a common diagnostic feature apparent in amyloidosis, always warrants further workup. Elevated protein levels in the urine can occur in excess of 10 g/day, with a subsequent decline in serum albumin levels of less than 1 g/dL. Albuminuria of greater than 1 g is more common, occurring in about half of patients (Gertz & Zeldenrust, 2014). Immunohistochemistry should be collected to verify the diagnosis of AL amyloidosis and also to determine the light chain isotype (Kastritis & Dimopoulos, 2015). The assays needed in workup include the free light chain levels, urine protein electrophoresis, serum protein electrophoresis, and serum and urine immunofixation. While these assays have been found to appear in 98% of all AL amyloidosis cases, they are not confirmatory, although may be useful in assessing response (Kapoor, Thenappan, Singh, Kumar, & Greipp, 2011). Of note, the monoclonal protein spike (M spike) is only visible in about 40% of patients, with 35% revealing M spikes less than 0.5 (Gertz & Zeldenrust, 2014).

Histology examination such as the abdominal fat aspiration and biopsy is considered a quick, easy, and safe method to obtain an accurate diagnosis of amyloidosis, as it has a sensitivity of about 70% to 80% (Kastritis & Dimopoulos, 2015). The biopsy is stained with Congo red, which binds with the highly ordered amyloid fibrils. When viewed under cross-polarized light, this reveals apple-green birefringence, a characteristic that is the histologic gold standard for detecting amyloid (Wechalekar et al., 2015; see Figure 1). Additionally, the patient should undergo a bone marrow biopsy with Congo red staining. This is also necessary in part to concurrently rule out a diagnosis of multiple myeloma (Gertz & Zeldenrust, 2014). If this fails to yield a positive diagnosis, the clinician may consider obtaining a biopsy of the affected organ (Kastritis & Dimopoulos, 2015).

While these techniques have a high sensitivity and specificity in diagnosing amyloidosis, the gold standard for diagnosis and typing is mass spectrometry of amyloid deposits. However, this diagnostic technique is more expensive than fat aspiration and may only be available at a limited number of medical centers. This diagnostic tool uses laser capture microdissection to remove the amyloid deposit for analyses and mass spectroscopic sequencing (Gertz & Zeldenrust, 2014). This is beneficial because not only can a diagnosis of amyloidosis be made accurately, the amyloid type can also be determined as well.

Cardiac involvement is the most common amyloid syndrome and may exhibit as a restrictive cardiomyopathy or heart failure with a normal systolic function (Gertz & Zeldenrust, 2014). Unfortunately, 25% of patients with delayed diagnosis and irreversible cardiac damage are estimated to die within a year of diagnosis (Merlini, 2017). Thus, the degree of cardiac dysfunction is important as a prognostic indicator, and assessment should occur at diagnosis. Diagnostic indicators for determining cardiac involvement include cardiac biomarkers such as the N-terminal of the prohormone brain natriuretic peptide (NTproBNP), which has a diagnostic sensitivity of 100% in determining cardiac AL amyloidosis. The NTproBNP, along with cardiac troponin levels, are useful in assessing risk and evaluating treatment response (Merlini, 2017).

Echocardiography is considered the noninvasive diagnostic test of choice and may show a "sparkling appearance" of the myocardium, increased ventricular wall thickness, enlarged atria, diastolic dysfunction with a restrictive pattern, as well as left ventricular strain pattern with apex preservation, and pericardial effusion (Grogan, Dispenzieri, & Gertz, 2017; Kapoor et al., 2011). Additionally, there may be right ventricular dysfunction early in the course of the disease. Furthermore, while most patients with cardiac involvement will have increased wall thickness of the left ventricle, there are patients who will have normal wall thickness and preserved left ventricular ejection fraction (Kapoor et al., 2011). Other findings on echocardiography include valve thickening and thickened endocardium (Grogan et al., 2017; Kapoor et al., 2011). Extensive echocar-

diography technique, including the use of a two-dimensional or three-dimensional speckle tracking, can help the clinician distinguish between cardiac amyloidosis from hypertrophic cardiomyopathy by evaluating speckle and strain patterns (Baccouche et al., 2012).

Cardiac MRI can be valuable particularly in patients whose echocardiography is inconclusive (Grogan et al., 2017). Typical findings on cardiac MRI include abnormal T1 signal and delayed enhancement within the myocardium. It may offer information similar to that found by an echocardiogram, but the use of echocardiography is superior in the evaluation of diastolic abnormalities. However, cardiac MRIs are helpful in characterizing myocardial tissue and can thus help differentiate between left ventricular hypertrophy from amyloid and hypertension (Gillmore & Hawkins, 2013; Grogan et al., 2017). While cardiac MRIs are useful in diagnosing cardiac involvement, there are limitations to this imaging modality. Cardiac MRI is not useful for distinguishing between the types of amyloid that are being deposited. Additionally, it is contraindicated in patients with a glomerular filtration rate of less than 30 mL/min and patients with pacemakers or those who have implantable devices (Grogan et al., 2017). The gold standard for diagnosing cardiac amyloidosis is the endomyocardial biopsy with a 100% sensitivity rate. However, this test is not routinely performed, as fat pad biopsy or bone marrow biopsy may be performed and is less invasive, with a sensitivity of 80% (Grogan et al., 2017; Kapoor et al., 2011).

Since renal involvement of amyloid is common (occurring in up to 53%–68% of patients), evaluation of renal dysfunction is important in improving outcomes (Merlini, 2017; Muchtar et al., 2018). This includes determining the degree of proteinuria, estimating glomerular filtration rate, and imaging studies such as ultrasound, CT, and MRI (Kastritis & Dimopoulos, 2015). The clinician should consider obtaining a renal biopsy in patients with a monoclonal gammopathy and long-standing diabetes, despite a positive fat pad biopsy for confirmation of organ involvement (Kastritis & Dimopoulos, 2015).

Risk assessment should be performed at diagnosis to predict the prognosis and overall survival of the patient, which can ultimately guide treatment. Current staging systems evaluate cardiac

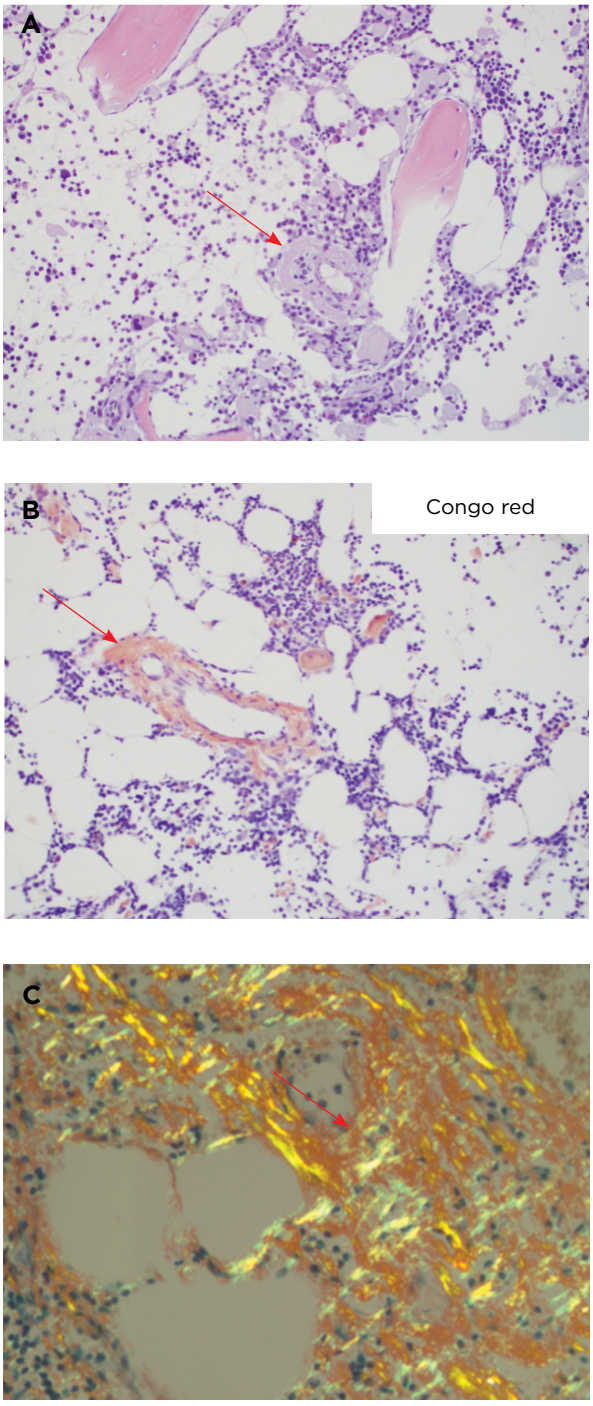

Figure 1. (A) H & E section showing eosinophilic amorphous materials in the wall of a vessel and some in the interstitium of a bone marrow trephine biopsy. (B) Congo red stains the vessel. (C) Apple green birefringent materials in the Congo red–stained soft tissue viewed under polarized light.

biomarkers as well as serum free light chains. Cardiac biomarkers such as the NTproBNP can help predict 1-year mortality and early outcomes, while evaluating serum free light chains can predict long-term outcomes, including organ involvement progression (see Table 1; Kumar et al., 2012a). Cardiac enzymes such as cardiac troponin I (cTnI) and cardiac troponin T (cTnT) detect myocardial injury due to its sensitivity and specificity. More recently, high-sensitivity troponin T assay (hs-cTnT), a fifth-generation cardiac troponin, has been found to be useful in staging, with a four- to five-fold increased sensitivity over fourth-generation cTnT assay with a strong correlation between the two (Muchtar et al., 2018). The use of hs-cTnT was found to be more predictive and thresholds of hs-cTNT at 40 ng/L were found to be comparable to cTnT levels of 0.025 µg/L based on the Mayo 2012 risk model (see Table 1; Muchtar et al., 2018). The use of cardiac biomarkers becomes even more significant when predicting outcomes for patients who undergo autologous stem cell transplant. Exclusion criteria for transplant include cTnT ≥ 0.06 µg/L or hs-cTnT 73 ng/L and an NTproBNP of > 5,000 ng/L, although the NTproBNP is not often used for exclusion criteria due to its weaker predictive power (Muchtar et al., 2018).

TREATMENT

Treatment modalities for AL amyloidosis have expanded in recent years, which have improved the overall survival and quality of life for patients. Deterring disease progression at early stages has helped to double the median survival rate over the past decade. It is estimated that 30% to 40% of patients are now surviving longer than 10 years (Merlini, 2017).

Since the underlying clonal plasma cell dyscrasia is often discrete, it may be difficult to monitor response quantitatively (Lachmann et al., 2003). Thus, the goal of therapy is to obtain reduction and normalization of serum free light chains and to obtain a deep response (Kaufman et al., 2015). Hematologic and organ response criteria have been formulated to gauge patient prognosis; the best responses are a complete response (CR) or a very good partial response (VGPR; Table 2). In order to measure hematologic response, a minimum difference in the involved free light chain and the uninvolved free light chain (dFLC) of 50 mg/L is required prior to starting therapy (Comenzo et al., 2012).

While there have not been many trials for treatment, advancements in novel agents in MM have translated to AL amyloidosis. Earlier treatment modalities for AL amyloidosis included chemotherapy with melphalan and prednisone, which neither produced remarkable response rates (RR) nor changes in overall survival (OS; Merlini, 2017). More recent studies with melphalan and dexamethasone (mDex) found a higher rate of hematologic response of 76% and a CR in 31% of cases. However, the rate of response was significantly lower in patients with advanced cardiac amyloidosis, with a 51% hematologic RR (Palladini et al., 2014).

Autologous Stem Cell Transplant

The introduction of autologous stem cell transplant (ASCT) after successful treatment demonstrated outcomes that were superior to those in myeloma and produced greater durable responses (Wechalekar et al., 2016). Although a previous small randomized trial did not demonstrate that ASCT was superior to mDex, several uncontrolled stud-

Table 1. Amyloidosis Staging System (Mayo 2012 Model)

Stage	Troponin T (µg/L) or hs-cTnT (ng/L)	NTproBNP (ng/L)	Difference between involved and uninvolved (mg/dL)	Prognosis in patients not undergoing AuSCT (months)	Prognosis in patients undergoing AuSCT (months)
I	< 0.025 µg/L	< 1,800	< 18	55	NR
II	Any one factor elevated			19	62.8
III	Any two factors elevated			12	16.8
IV	> 0.025 µg/L OR ≥ 40 ng/L	> 1,800	> 18	5	5.8

Note. hs-cTnT = high-sensitive cardiac troponin T; NTproBNP = N-terminal of the prohormone brain natriuretic peptide; AuSCT = autologous stem cell transplant; OR = overall response. Adapted from Kumar et al. (2012a); Muchtar et al. (2018).

Table 2. Hematologic and Organ Response Criteria

Hematologic response			
	Serum IFE	**Urine IFE**	**dFLC**
CR	Negative	Negative	Normal
VGPR	–	–	< 40 mg/L
PR	–	–	> 50% reduction
Organ response			
Cardiac	Decrease in NTproBNP by 30% and 300 pg/mL (baseline should be greater than 650 ng/L or a > 2-point decrease in NYHA class if baseline III or IV)		
Renal	50% decrease of 24-hour urine protein (proteinuria must be greater than 500 mg/day prior to treatment), and creatinine clearance must not worsen by 25% over baseline		
Liver	50% decrease in abnormal alkaline phosphatase value; decrease in liver size by at least 2 cm		
Peripheral nervous system	Improvement in nerve conduction studies		

Note. CR = complete response; IFE = immunofixation; dFLC = difference between the involved and uninvolved light chains; VGPR = very good partial response; PR = partial response; NTproBNP = N-terminal of the prohormone brain natriuretic peptide; NYHA = New York Heart Association. Table adapted from Comenzo et al. (2012); Palladini et al. (2012).

ies did find that RR were superior in patients who received ASCT, with hematologic RR exceeding 70% and approximately 35% in CR (Merlini, 2017). However, caution should be taken in patients with cardiac dysfunction, and ASCT should only be performed if safe and in those with treatment-related mortality of < 10% (Wechalekar et al., 2016).

Proteasome Inhibitors

Bortezomib (Velcade) was the first proteasome inhibitor to be investigated in the treatment of amyloidosis with an impressive hematologic response (see Table 3). Bortezomib is a novel agent that is highly effective in the induction setting prior to ASCT, especially in patients with > 10% clonal plasma cells in the bone marrow. Furthermore, patients who have failed to achieve a CR post ASCT may increase the CR rate to 60% with consolidation with bortezomib (Merlini, 2017). This is considered the treatment of choice in the frontline setting for patients with intermediate risk disease (Wechalekar et al., 2016).

Ixazomib (Ninlaro) was given orphan drug designation in 2012 for its efficacy in the treatment of amyloidosis and then was later granted Breakthrough Therapy designation by the U.S. Food & Drug Administration (FDA) in 2014 (Shirley, 2016). It has been investigated in phase I/II trial in patients with relapsed/refractory AL amyloidosis (Sanchorawala et al., 2017; Table 3).

Immunomodulatory Agents

Other agents that have been found to have activity against amyloidosis include immunomodulatory agents such as lenalidomide (Revlimid) and pomalidomide (Pomalyst); however, combinations with these agents yield poorer outcomes for individuals with cardiac involvement (Kastritis & Dimopoulos, 2015; Table 4). This may be due to a rise in the NTproBNP previously reported in studies (Kastritis et al., 2017).

Monoclonal Antibodies

Daratumumab (Darzalex) is an anti-CD38 monoclonal antibody demonstrating single-agent activity in MM with a RR of 36% in patients who had relapsed/refractory multiple myeloma (Lokhorst et al., 2015). These results led to FDA approval in patients who had at least three prior lines of therapy and who were refractory to immunomodulatory agents and proteasome inhibitors. Subsequently, daratumumab was combined with other novel agents such as lenalidomide, bortezomib, and pomalidomide, with overall response rates of 60% to 92.2% (Chari, Nahi, Mateo, Lokhorst, & Kaufman, 2017; Dimopoulos et al., 2016; Palumbo et al., 2016). These combinations have been approved in patients with myeloma who have had at least one prior line of therapy. Similar to myeloma, the clonal plasma cells in AL amyloidosis express CD38, which led

Table 3. Proteasome Inhibitor Studies in AL Amyloidosis

Regimen	Bortezomib schedule	Hematologic RR	Hematologic CR	Organ response	PFS	OS (months)
Bortezomib (Reece et al., 2014)	Weekly dosing	68.8%	37.5%	Not reported	72.2% at 1 yr	62.1
	Twice weekly dosing	66.7%	24.2%	–	76.8% at 1 yr	NR
Bortezomib/ dexamethasone (Kastritis et al., 2010) All patients Untreated Previously treated	–	72% 81% 68%	25% 47% 20%	All: 30%; heart (29%), renal (19%), liver (22%)	NA	76% at 1 yr
Bortezomib/ cyclophosphamide/ dexamethasone (Mikhael et al., 2012)	Weekly	94%	71%	Renal (50%), heart (71%)	NA	
Bortezomib/ cyclophosphamide/ dexamethasone (Palladini et al., 2015)	–	All: 60% Stage 3b: 42%	23% 14%	Cardiac (17%), renal (25%)	NA	55% at 5 yr (projected)
Bortezomib/ cyclophosphamide/ dexamethasone (Venner et al., 2012)	Twice weekly	81.4%	39.5%	All: 46%; renal (40%), liver (40%), cardiac (11%)	NR for patients in CR; < CR: 17.5 mo	97.7% at 2 yr
Carfilzomib (Cohen et al., 2016)	–	63%	12%	All: 21%; renal (12%), GI (4%), liver (4%)	NA	NA
Ixazomib/dexamethasone (Sanchorawala et al., 2017)	–	All: 52% PI naive: 100% PI exposed: 38%	10% PI naive: 40% PI exposed: 0%	All: 56%; renal (45%); cardiac (45%) PI naive: 100%; renal (100%), cardiac (67%) PI exposed: 38%; cardiac (38%), renal (25%)	13.6 mo	80% at 1 yr

Note. RR = response rate; CR = complete response; PFS = progression-free survival; OS = overall survival; NR = not reached; NA = not applicable; GI = gastrointestinal; PI = proteasome inhibitor.

investigators to evaluate the effectiveness of daratumumab as single agent and in combination with other novel therapies in AL amyloidosis. A retrospective review of daratumumab showed that in 15 patients with AL amyloidosis who had received daratumumab as a single agent, the overall hematologic response was 82%, with 73% achieving a VGPR or better (Khouri et al., 2017). Additionally, 50% of the patients with cardiac involvement had a cardiac response and 60% of patients with renal involvement had a renal response. Patients tolerated treatment well, with the majority of adverse events being grade 1 and 2. The main grade 1/2 adverse events included infusion-related reactions (20%), infections, (20%) neutropenia (13%), increased diuretic use (7%), and fatigue (7%). The grade 3 adverse events included infusion-related reactions (13%) and fatigue (7%). In a phase II trial among 40 patients with previously treated disease, 63% achieved a hematologic response, with 29% achieving a VGPR or better (Roussel et al., 2017). The incidence of infusion-related reactions was 33% and were either grade 1 or 2.

Table 4. Immunomodulatory Agents

Regimen	Hematologic RR	Hematologic CR	Organ response	OS
Lenalidomide (Kastritis et al., 2017)	57%	5%	All: 10%; renal (11%), liver (8%)	29 mo
Lenalidomide +/-dexamethasone (Sanchorawala et al., 2007)	67% overall	29%	NA	NA
Lenalidomide +/- dexamethasone (Dispenzieri et al., 2007)	41%		23%	PFS 56% at 1 yr
Lenalidomide/cyclophosphamide/ dexamethasone (Kastritis et al., 2012)	55%	8%	22%	41% at 2 yr
Lenalidomide/cyclophosphamide/ dexamethasone (Kumar et al., 2012)	60%	11%	29%	PFS heme response: 28.3 mo Median OS: 37.8 mo Stage 1 OS: NR mo Stage 2 OS: 37.8 mo Stage 3 OS: 7 mo
Pomalidomide/dexamethasone (Sanchorawala et al., 2016)	50%	33%		NR
Pomalidomide/dexamethasone (Dispenzieri et al., 2012)	48%	3%	All: 15%; renal (17%), cardiac (15%)	PFS: 14.1 mo OS: 27.9 mo
Pomalidomide/dexamethasone (Palladini et al., 2017)	61%	4%	All: 17%; renal (17%)	PFS: 16 mo OS: 26 mo

Note. RR = response rate; CR = complete response; OS = overall survival; NR = not reached; NA = not applicable; PFS = progression-free survival.

A retrospective study found that patients who were heavily pretreated for AL amyloidosis produced deep and durable responses when treated with daratumumab, with an overall RR of 76%, 24% with VGPR, and 36% achieving a CR. The median time to response was 1 month. Infusion-related reactions occurred in 60% of patients and were grade 1 or 2. Additionally, patients with cardiac involvement tolerated therapy without the need for diuretics, and they did not experience decompensated heart failure. For these patients, daratumumab was not only effective but also well tolerated without any unexpected toxicities (Kaufman et al., 2017).

In an effort to improve the ease of administration, investigators conducted a phase Ib study of daratumumab administered subcutaneously in patients with myeloma (Chari et al., 2017). Of the patients in the 1,800-mg dose cohort, the overall RR was 42%, with 7% achieving CR or better. In this cohort, the infusion-related reaction rate was only 4%. The grade 3 and 4 adverse events included hypertension (8%), thrombocytopenia (8%), lymphopenia (8%), hyponatremia (4%), fatigue (4%), and neutropenia (4%; Chari et al., 2017).

Since investigators found subcutaneous daratumumab to have activity, they developed a study incorporating subcutaneous daratumumab with bortezomib/cyclophosphamide/dexamethasone in a phase II trial for patients with AL amyloidosis (Comenzo et al., 2018). Daratumumab was administered weekly for the first two cycles, then every 2 weeks for cycles 3 to 6, and then every 4 weeks thereafter. Cyclophosphamide was dosed at 300 mg/m^2 either orally or intravenously in combination with bortezomib at 1.3 mg/m^2 SQ on days 1, 8, 15, and 22 every 28 days. Dexamethasone was administered at 40 mg weekly. A total of 15 patients were treated with the main adverse events reported as nausea (47%), diarrhea (33%), fatigue (33%), injection-site erythema (20%), anemia (20%), rash (20%), dyspnea (7%), and peripheral edema (7%). Only 13.3% of patients experienced infusion-related reactions, which were all grade 1.

One of the main difficulties in the treatment of AL amyloidosis is the persistent organ dysfunction caused by the amyloid fibrils. In order to target the insoluble amyloid fibrils, a monoclonal antibody (Ch mAb 11-1F4) was investigated in 27 patients with relapsed or refractory amyloidosis (Edwards et al., 2017). Of the 26 patients evaluable for response, 63% of patients (5 of 8) had an organ response in the phase Ia portion of the study and 61% (11 of 18) in the phase Ib portion of the study. The median time to response was 2 weeks, and there were no grade 4 or 5 adverse events reported (Edwards et al., 2017).

Doxycycline

Based upon in vitro studies which showed doxycycline may inhibit the formation of amyloid fibrils, investigators performed a retrospective study of 455 patients with AL amyloidosis who underwent stem cell transplant (Kumar et al., 2012b). Two studies have been reported on the effect of doxycycline in patients with AL amyloidosis. One retrospective study evaluated the effect of doxycycline used as infection prophylaxis post SCT. Investigators did see a benefit in OS in those who received doxycycline. Another retrospective study involved the addition of doxycycline to standard-of-care regimens in patients with newly diagnosed cardiac amyloidosis (Wechalekar & Whelan, 2017). Investigators saw an improvement in those who received doxycycline compared to those who did not receive doxycycline. While these studies raise interesting data, randomized studies are currently ongoing to determine if incorporating doxycycline into standard-of-care therapy should occur.

CONCLUSION

The past decade has yielded greater understanding of AL amyloidosis and the meaningful role novel agents have in treating this fatal disease. However, this disease of misfolded proteins remains elusive and difficult to diagnose and treat. New treatments targeting the clonal plasma cell as well as the amyloid fibrils will hopefully lead to new treatments for this disease. Currently, studies show that chimeric antigen receptor (CAR) T-cell therapy has a positive effect in treating patients with relapsed and refractory MM, and one can hope that these promising results will translate for patients with amyloidosis since both diseases share similar targets, notably CS1 (Rosenzweig et al., 2017) As new discoveries and innovative treatments expand in MM, our knowledge and treatment of AL amyloidosis grow simultaneously. One can only wonder at what advances the next decade may unfold.

Disclosure

The authors have no conflicts of interest to disclose.

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