Perspective

Approach to a patient with cardiac amyloidosis

Christopher Strouse1, Alexandros Briasoulis2, Rafael Fonseca3, Yogesh Jethava1,#

1Department of Internal Medicine, Division of Hematology, Oncology, and Blood and Marrow Transplantation, University of Iowa, Iowa City, IA, USA
2Cardiomyopathy Section, Cardiology Division, University of Iowa, Iowa City, Iowa, USA
3Bone Marrow Transplant Program, Mayo Clinic, Phoenix, Arizona, USA

J Geriatr Cardiol 2019; 16: 567–574. doi:10.11909/j.issn.1671-5411.2019.07.010

Keywords: Cardiac amyloidosis; Heart failure; The elderly

1 Introduction

Cardiac amyloid (CA) is characterized by inexorably progressive heart failure making early diagnosis and treatment imperative. This article will review the pathophysiology, clinical presentation, diagnosis, prognostication and treatment of patients with CA.

2 Pathophysiology

Cardiac amyloidosis (CA) is the result of extracellular deposition of a misfolded protein into cardiac tissue, forming insoluble aggregations of rigid, nonbranching 10 nm wide fibrils. This causes impaired cardiac function by disrupting cardiac architecture, direct myotoxicity and ischemic injury secondary to infiltration of intramyocardial vessels.[1–3] Amyloid deposits demonstrate a pathognomonic affinity for Congo red, with apple green birefringence under polarization.[1] Nearly all cases of clinically significant CA are caused by one of six proteins: immunoglobulin light chain, immunoglobulin heavy chain, serum amyloid A, transthyretin (TTR), apoliprotein A1, or atrial naturitic factor.[1] Of these, immunoglobulin light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR) account for > 90% of cases in the United States (US).[4]

2.1 Immunoglobulin light chain cardiac amyloidosis (AL-CA)

In AL amyloidosis, amyloid deposits are formed by kappa or lambda light chain proteins which are produced by a clonal population of malignant plasma cells. The myocardium is involved in around 50% of cases.[5] In addition to mechanical damage mediated by cardiac fibril deposition, the soluble AL protein has directly toxic effects on myocardial tissues, mediated via p38α mitogen-activated protein kinases (MAPK) signaling.[6] Brain natriuretic peptide (BNP) is also upregulated by p38 MAPK signaling, and thus serum BNP reflects both the amyloid disease activity and cardiac injury.[7]

2.2 Transthyretin cardiac amyloidosis (ATTR-CA)

Transthyretin, a transporter of thyroxine and retinol, can form amyloid deposits in both its wild type and mutant forms.[8] Wild type transthyretin amyloid (ATTRwt) affects elderly patients and predominantly affects the heart and peripheral nerves. In mutant transthyretin amyloidosis (ATTRm), the tropism and age of clinical onset can be affected by mutations of the TTR gene, of which over 90 mutations have been identified. The Val122Ile mutation is present in 4% of African Americans in the US, and causes predominately CA. The Val30Met mutation causes familial amyloid polyneuropathy. The Thr60Ala is found in Northern Ireland, and may be seen in younger CA patients (Table 1).[9]

2.3 Clinical features

Clinically, CA is characterized by features of restrictive cardiomyopathy such as dyspnea (92%) and syncope. Characteristic physical signs include jugular venous distension (52%), rales (54%), prominent edema (81%), and hepatomegaly.[10] Systolic blood pressure < 100 mmHg, and impaired 6 min-walk test are both indicative of a high degree of cardiac impairment, and each have prognostic significance.[11,12]

3 Diagnosis and prognostication

The diagnosis of CA requires demonstration of amyloid infiltration in an affected tissue, though not necessarily cardiac tissue. Upon demonstration of amyloid deposits, the causative protein must be identified for appropriate therapy. The following points are general principles for amyloidosis diagnosis.

(1) Endocardial biopsy is the gold standard for diagnosis
Table 1. Characteristics of patients with amyloidosis.

|                  | AL\textsuperscript{[4]} | ATTR wild type (senile systemic amyloidosis)\textsuperscript{[9]} | ATTR mutant\textsuperscript{[9]} |
|------------------|--------------------------|-------------------------------------------------|-----------------------------|
| Incidence        | 8.9 per million person years\textsuperscript{[2]} | Present in 1% of northwestern Irish population,\textsuperscript{[92]} | 1.3 million US African American patients carry Ile 122 allele, 13,000 homozygous patients,\textsuperscript{[63]} |
| Gender M: F      | 2: 1                     | 20: 1                                           | 2: 1 3: 1                   |
| Age, yrs         | 60–70                    | 70–80                                           | 45 70                       |
| Organs involved  | Cardiac in 33%– 50% of patients, CNS∥ | Cardiac, nerves Cardiac, autonomic neuropathy, peripheral neuropathy | Primarily heart            |

AL: light chain amyloidosis; Ala: alanine; ATTR: transthyretin amyloidosis; CNS: central nervous system; Ile: isoleucine; Thr: threonine; US: United States; Val: valine.

of CA, but is associated with about 1% risk of severe complication (right atrial perforation and cardiac tamponade).\textsuperscript{[13]} It is thus not routinely performed if amyloid deposits can be demonstrated in other tissues.

(2) Fat pad biopsy is approximately 79%–100% sensitive in cases of AL amyloidosis. Samples greater than > 700 mm\textsuperscript{2} are reported to have sensitivity is 100%. Fat pad sampling is only 12% sensitive for diagnosis of ATTR.\textsuperscript{[14,15]} Salivary gland biopsy is 58% sensitive in patients with negative fat pad sampling, and rectal biopsy is 85% sensitive overall.\textsuperscript{[16]}

(3) Upon diagnosis of CA, it is essential to verify the amyloidogenic protein. Protein identification can be accomplished with high specificity via mass spectrometry of the biopsy tissue. Alternatively, immunohistochemistry can identify the amyloidogenic protein if mass spectrometry is not available.\textsuperscript{[17]}

(4) Serum or urine paraprotein by serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), immunofixation or free light chain assay can identify monoclonal gammopathy related AL amyloidosis (Table 2).

(5) Coexistent multiple myeloma is present in 20% of patients with AL amyloidosis at the time of diagnosis, and is associated with inferior survival at 1 year (39% vs. 81%). Thus, patients diagnosed with AL amyloidosis should be evaluated for multiple myeloma, using positron emission tomography (PT) or magnetic resonance imaging (MRI) to evaluate for skeletal lesions, and bone marrow biopsy to evaluate for bone marrow infiltration.\textsuperscript{[18]}

(6) AL only: bone marrow examination should be performed to evaluate for clonal plasma cells, and to obtain
Table 2. Prognostic markers in AL amyloidosis.

| Markers associated with poor prognosis | Prognostic significance (HRs for OS) |
|---------------------------------------|-------------------------------------|
| Serum markers                          |                                     |
| N-terminal pro-BNP                    | ≥ 1,800 pg/mL (HR 1.4) [69] (AL only) |
| Free light chain difference (Involved - Uninvolved Light Chains) | ≥ 18 mg/dL (HR 1.4) [69] (AL only) |
| Troponin T                            | ≥ 0.03 ng/mL (HR 2.4) [69] (AL only) |
| Soluble suppression of tumorigenicity 2 | ≥ 30 ng/mL (HR 2.7) [69] (AL only) |
| Osteopontin                           | ≥ 426.8 ng/mL [69] (AL only)         |
| Growth Differentiation Factor -15     | ≥ 7575 pg/mL [69] (AL only)          |
| Cytogenetic Abnormalities             |                                     |
| t(11;14), trisomy karyotype, -17p     |                                     |
| Echocardiogram                        |                                     |
| Left ventricular ejection fraction    | < 45% [69]                         |
| Left ventricular diastolic deceleration time | < 150 ms [69]                |
| Cardiac MRI findings                 |                                     |
| Late gadolinium enhancement           | Transmural pattern (HR 4.9) [21]  |
| Increased myocardial T2               | Reflective of myocardial edema (HR 1.32) [19] |

AL: light chain amyloidosis; BNP: brain natriuretic peptide; HR: hazard ratio; MRI: magnetic resonance imaging; OS: overall survival.

fluorescence in-situ hybridization (FISH) analysis of the clonal plasma cells. The most frequent cytogenetic abnormality in AL is t(11;14), occurring in approximately 40%–60% of patients. [19] The presence of trisomies, deletion 17p or t(11;14) are each associated with adverse outcome. [19,20]

(7) Cardiac MRI (CMR): Circumferential subendocardial late gadolinium enhancement by CMR is highly sensitive (76%–97%) and specific (86%–94%) for the diagnosis of CA. [21]

(8) Echocardiogram: the most characteristic structural findings on echocardiogram are septal and posterior wall thickening at least > 12 mm, and with mean thickness of 16 mm at the time of diagnosis. [10,22] Myocardial speckling has low sensitivity (26%) and modest specificity (71%–81%). [22]

(9) Nuclear imaging: Technetium-labeled phosphates (e.g., Technetium-99m 3, 3-diphospho-1,2-propanodicarboxylic acid (99mTc-DPD), technetium-99m pyrophosphate (99mTc-PYP), have been found to have strong affinity for ATTR deposits in the heart, and much weaker affinity for AL amyloid deposits. This makes technetium-labeled phosphate scintigraphy useful to non-invasively distinguish AL-CA from ATTR-CA (sensitivity 84%–97%, specificity 94%–100%). [23-26]

4 Management

4.1 Heart failure therapy

CA clinically presents as heart failure and arrhythmias, which are the most frequent cause of death. [27] Cardiac function is often tenuous, requiring intensive management by a heart failure specialty service to maintain optimal function and minimize treatment delays. [27] Loop diuretics and aldosterone antagonists are mainstays in maintaining euolemia. [28] Anecdotally, higher doses of diuretics are sometimes required if concurrent nephrotic range proteinuria and hypoalbuminemia are present. [27]

Contrary to patients with other kinds of cardiomyopathy, treatments with beta blockers have not been shown to have beneficial effect, and in fact are often unmanageably toxic. Similarly, renin angiotensin-aldosterone system inhibitors often cause marked hypotension even at low doses, possibly due to concurrent autonomic nervous system dysfunction from amyloidosis. [27] Non-dihydropyridine calcium channel blocking agents appear to have particularly high toxicity in these patients, due to selective concentration in the amyloidotic tissues, and should be avoided. [29]

The prognosis of patients with CA and cardiogenic shock is dismal. [30] Implantation of left ventricular assist devices (LVAD) in patients with CA is technically feasible, though is a class IIIB recommendation by International Society of Heart and Lung Transplant (ISHLT) guidelines. CA patients receiving LVADs have worse 2-year survival than patients receiving LVADs for other indications, but some patients have been successfully bridged to heart transplants. [31]

4.2 Role of heart transplantation

4.2.1 AL amyloidosis

Orthotopic heart transplantation may be considered for patients with AL-CA who achieve a good hematologic response but none-the-less continue to have severe heart failure. [32] It is a class IIa indication per the ISHLT guidelines and cardiac transplantation showed a 1 year survival of 50%, and 5 year survival of only 20%. [32] However, more recent
series have demonstrated significant improvements, with 1 and 5 year survivals of 89.5% and 65%, respectively.[33,34]

4.2.2 Transthyretin

Heart transplantation in patients with ATTRwt-CA offers the possibility of prolonged graft function because the rate of amyloid re-accumulation is very slow, however because ATTRwt-CA generally presents in elderly patients, this approach is rare.[33]

For patients with mutations associated with CA, such as Thr60Ala or Val122Ile, heart transplantation can be combined with liver transplantation to simultaneously address the source of amyloidogenic protein (liver) and the primary end-organ involved (heart).[35]

4.3 Treatment of conduction disorders

Symptomatic electrical conduction abnormalities, such as heart block, sick sinus syndrome, chronotropic incompetence are highly prevalent in CA and can be effectively managed with permanent pacemaker implantation.[36] Though sudden cardiac death is a common in patients with CA, the role of prophylactic implantable cardioverter defibrillators (ICD) remains controversial. Trials have not demonstrated a survival benefit to ICD implantation, possibly because cardiac death in these patients is most often the result of pulseless electrical activity, which is not amenable to defibrillation.[37] However, in one series of CA patients implanted with an ICD, 28% went on to receive appropriate shock, and 75% of patients who were shocked survived the arrhythmia event. Thus, implantation can be considered in patients with moderate cardiac involvement, particularly in patients with history of syncope or non-sustained ventricular tachycardia.[38]

Atrial fibrillation is common in this population, putting patients with atrial fibrillation and CA at high risk for stroke. The decision to anticoagulate these patients must be carefully considered as they are also at high risk for bleeding, whether from gastrointestinal involvement of amyloidosis (present in 3%–7% of cases), or from acquired clotting factor deficiencies.[39,40] Achieving adequate rate control in this population can be a significant challenge, as anti-chronotropic agents such as beta blockers and calcium channel blockers are poorly tolerated, as described above. Additionally, digoxin should be avoided as amyloid fibrils can bind digoxin, resulting in an elevated risk of digoxin toxicity.[41]

4.4 Plasma cell directed therapy in AL amyloidosis

4.4.1 Goals of therapy

The goal of anti-plasma cell therapies in AL amyloidosis is to reduce the plasma cell clone, achieve minimum residual disease (MRD) negativity and thus reduce production of the amyloidogenic light chain proteins. The classes of drugs available for treatment are proteasome inhibitors, immunomodulatory agents (IMiDs), monoclonal antibodies and conventional chemotherapy. Based on performance status, AL amyloid patients are divided into two categories: those who are eligible for autologous stem cell transplant (ASCT) and those who are ineligible for ASCT.

4.4.2 Initial therapy

The depth and rapidity of response to therapy is highly correlated to survival in these patients, as patients responding within 30 days survive longer than those with later or no response.[42] The routinely used initial therapy is a combination of cyclophosphamide, bortezomib and dexamethasone (CyBorD), which achieves a response in 94% of patients, with complete hematologic response in 71%.[43] CyBorD is also the first line therapy for transplant ineligible patients, if they are robust enough to tolerate it. Evidence is accumulating to suggest that earlier incorporation of the IMiD class of medications (thalidomide, lenalidomide, pomalidomide) may result in improved survival, and these agents may be included in first line treatments in the future.[44] However, drugs like lenalidomide and thalidomide are typically less well-tolerated in patients with AL amyloidosis, so an induction regimen without one of these agents is often preferred. Induction therapy can also slow amyloid production and limit further organ damage while awaiting ASCT. Following ASCT, further therapies are considered based on the degree of response achieved.

4.4.3 Novel agents

Daratumumab is a monoclonal antibody directed against CD38. Its use in 129 patients with relapsed/refractory AL resulted in deep hematologic responses without significant toxicity. It is among the most promising new therapies for AL amyloidosis.[45] Venetoclax is a BCL-2 inhibitor which has recently garnered attention for its activity in multiple myeloma, particularly in the case of multiple myeloma with t(11;14). Venetoclax is thus an attractive option in AL amyloidosis, which frequently has t(11;14). To date, one case has been reported of refractory AL amyloidosis, in which a complete response was achieved with single agent venetoclax.[46]

4.4.4 Autologous stem cell transplant

The role of early transplantation has debated due to the development of highly active non-transplant regimens. Additionally, ASCT carries risk of mortality up to 5%. In the
presence of cardiac involvement, the transplant related mortality could increase up to 10%. Patients with severe cardiac involvement have a high risk of transplant related mortality, and may not be appropriate candidates. Elevations of troponin T (TnT > 0.06 μg/mL) or elevated N-terminal pro-BNP (NT-proBNP > 5000 pg/mL) are associated with marked excess risk of mortality and is a relative contraindication to transplant.[47,48]

4.4.5 Prognosis

Among patients with AL-CA who achieved normalization of the free light chain ratio, 64% of patients subsequently had an organ response, defined as NT-proBNP reduction of > 30% and > 300 pg/mL with a baseline NT-proBNP of ≥ 650 pg/mL. The majority of patients who went on to have an organ response (75%) did so within one year of starting treatment, however some patients do not achieve the maximum cardiac response until 2–3 years after induction therapy.[49,50] Patients who achieve a complete cardiac response (nadir NT-proBNP < 450 pg/mL) had a 5-year survival of 96%, compared to 74% in patients who achieved a very good partial cardiac response (> 60% reduction in NT-proBNP) and just 43% in patients who achieved a partial cardiac response (30%–59% reduction in NT-proBNP).[50]

4.5 Transthyretin directed therapies in transthyretin amyloidosis

Transthyretin is produced in the liver and hence, orthotopic liver transplantation has been established treatment for mutant ATTR for over 20 years, with overall survival greater than 50% at 20 years.[51,52] However, liver transplant is not widely utilized for this indication, due to the scarcity of organs and the cost and morbidity attendant to the procedure.

Recently, tafamidis, a TTR binding agent, has emerged as an option for reducing or stopping ATTR amyloid aggregation. Tafamidis was assessed in 264 patients with ATTR-CA, and demonstrated a 30% reduction in all-cause mortality compared to placebo.[53] There was additionally a slower decline in 6-min walk test and slower decline in a measure of quality of life, indicating the progressive nature of ATTR-CA was significantly slowed by tafamidis.[53] Patisiran, a ribonucleic acid interference (RNAi), binds transthyretin messenger ribonucleic acid and prevents translation into transthyretin protein, thus dramatically reducing the serum level of transthyretin. Treatment with patisiran resulted in a 55% reduction in mean NT-proBNP, and improved measures of LV wall thickness and longitudinal strain.[54] Inotersen, a modified antisense oligonucleotide, which inhibits synthesis of transthyretin, has also demonstrated efficacy in improving neuropathy symptoms, however have failed to show efficacy in CA.[55]

4.6 Anti-amyloid deposit treatments

Effective treatments to address the amyloid deposits and end organ damage would represent an enormous improvement in the treatment of these patients. A phase 1a/b study of a fibril reactive monoclonal antibody (11–1F4), which opsonizes the fibrils and facilitating their removal, has demonstrated cardiac response in 8 of 12 treated patients.[56] Serum amyloid protein (SAP), which is universally present on amyloid deposits, is another attractive target. An antibody to SAP, dezamizumab, appeared safe and improved amyloid deposits in hepatic tissues, however there was no improvement in renal and cardiac amyloid deposits.[57] Doxycycline has inhibitory effects on matrix metalloproteases, and in a trial of 30 AL-CA patients, those receiving doxycycline had better outcomes as compared to matched control group.[58,59] Epigallocatechin-3-gallate, which is abundant in green tea, is also currently being studied in CA clinical trials.[60,61]

5 Conclusion

CA has historically been a disorder associated with marked morbidity and mortality, due to the severe heart failure it is associated with. Diagnosis, prognosis and management of these patients requires a multidisciplinary approach. The opportunity to reverse end-organ damage in both AL-CA and ATTR-CA may offer encouraging improvements in both quality and quantity of life for patients with these diseases.

References

1 Sipe JD, Benson MD, Buxbaum JN, et al. Amyloid fibril proteins and amyloidosis: chemical identification and clinical classification International Society of Amyloidosis 2016 Nomenclature Guidelines. Amyloid 2016; 23: 209–213.
2 Merlini G, Seldin DC, Gertz MA. Amyloidosis: pathogenesis and new therapeutic options. J Clin Oncol 2011; 29: 1924–1933.
3 Smith RR, Hutchins GM. Ischemic heart disease secondary to amyloidosis of intramyocardial arteries. Am J Cardiol 1979; 44: 413–417.
4 Magy-Bertrand N, Dupond JL, Mauny F, et al. Incidence of amyloidosis over 3 years: the AMYPRO study. Clin Exp Rheumatol 2008; 26: 1074–1078.
5 Palladini G, Kyle RA, Larson DR, et al. Multicentre versus
single centre approach to rare diseases: the model of systemic light chain amyloidosis. *Amyloid* 2005; 12: 120–126.

6 Shi J, Guan J, Jiang B, et al. Amyloidogenic light chains induce cardiomyocyte contractile dysfunction and apoptosis via a non-canonical p38alpha MAPK pathway. *Proc Natl Acad Sci U S A* 2010; 107: 4188–4193.

7 Ma KK, Ogawa T, de Bold AJ. Selective upregulation of cardiac brain natriuretic peptide at the transcriptional and translational levels by pro-inflammatory cytokines and by conditioned medium derived from mixed lymphocyte reactions via p38 MAP kinase. *J Mol Cell Cardiol* 2004; 36: 505–513.

8 Fleming CE, Nunes AF, Sousa MM. Transthyretin: more than meets the eye. *Prog Neurobiol* 2009; 89: 266–276.

9 Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. *Blood* 2009; 114: 4957–4959.

10 Murtagh B, Hammill SC, Gertz MA, et al. Electrocardiographic findings in primary systemic amyloidosis and biopsy-proven cardiac involvement. *Am J Cardiol* 2005; 95: 535–537.

11 Wechalekar AD, Schonland SO, Kastritis E, et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. *Blood* 2013; 121: 3420–3427.

12 Pulido V, Doros G, Berk JL, et al. The six-minute walk test in patients with AL amyloidosis: a single centre case series. *Br J Haematol* 2017; 177: 388–394.

13 Leone O, Veinot JP, Angelini A, et al. 2011 consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. *Cardiovasc Pathol* 2012; 21: 245–274.

14 Fine NM, Arruda-Olson AM, Dispenzieri A, et al. Yield of noncardiac biopsy for the diagnosis of transthyretin cardiac amyloidosis. *Am J Cardiol* 2014; 113: 1723–1727.

15 Garcia Y, Collins AB, Stone JR. Abdominal fat pad excisional biopsy for the diagnosis and typing of systemic amyloidosis. *Hum Pathol* 2018; 72: 71–79.

16 Foli A, Palladini G, Caporati R, et al. The role of minor salivary gland biopsy in the diagnosis of systemic amyloidosis: results of a prospective study in 62 patients. *Amyloid* 2011; 18 (Suppl 1): S80–S82.

17 Vrana JA, Gamez JD, Madden BJ, et al. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens *Blood* 2009; 114: 4957–4959.

18 Dinner S, Witteles W, Witteles R, et al. The prognostic value of diagnosing concurrent multiple myeloma in immunoglobulin light chain amyloidosis. *Br J Haematol* 2013; 161: 367–372.

19 Warsame R, Kumar SK, Gertz MA, et al. Abnormal FISH in patients with immunoglobulin light chain amyloidosis is a risk factor for cardiac involvement and for death. *Blood Cancer J* 2015; 5: e310.

20 Wong SW, Hegenbart U, Palladini G, et al. Outcome of patients with newly diagnosed systemic light-chain amyloidosis associated with deletion of 17p. *Clin Lymphoma Myeloma Leuk* 2018; 18: e493–e499.

21 Austin BA, Tang WH, Rodriguez ER, et al. Delayed hyper-enhancement magnetic resonance imaging provides incremental diagnostic and prognostic utility in suspected cardiac amyloidosis. *JACC Cardiovasc Imaging* 2009; 2: 1369–1377.

22 Rahman JE, Helou EF, Gelzer-Bell R, et al. Noninvasive diagnosis of biopsy-proven cardiac amyloidosis. *J Am Coll Cardiol* 2004; 43: 410–415.

23 Bokhari S, Castano A, Pozniakoff T, et al. (99m) Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. *Circ Cardiovasc Imaging* 2013; 6: 195–201.

24 Maurer MS. Noninvasive Identification of ATTRwt Cardiac Amyloid: the re-emergence of nuclear cardiology. *Am J Med* 2015; 128: 1275–1280.

25 Falk RH, Lee VW, Rubinow A, et al. Sensitivity of technetium-99m-pyrophosphate scintigraphy in diagnosing cardiac amyloidosis. *Am J Cardiol* 1983; 51: 826–830.

26 Cappelli F, Gallini C, Di Mario C, et al. Accuracy of 99mTc-Hydroxymethylene diphosphonate scintigraphy for diagnosis of transthyretin cardiac amyloidosis. *J Nucl Cardiol* 2019; 26: 497–504.

27 Falk RH. Diagnosis and management of the cardiac amyloidoses. *Circulation* 2005; 112: 2047–2060.

28 Ritts AJ, Cornell RF, Swiger K, et al. Current concepts of cardiac amyloidosis: diagnosis, clinical management, and the need for collaboration. *Heart Fail Clin* 2017; 13: 409–416.

29 Pollak A, Falk RH. Left ventricular systolic dysfunction precipitated by verapamil in cardiac amyloidosis. *Chest* 1993; 104: 618–620.

30 d’Humieres T, Fard D, Damy T, et al. Outcome of patients with cardiac amyloidosis admitted to an intensive care unit for acute heart failure. *Arch Cardiovasc Dis* 2018; 111: 582–590.

31 Grupper A, Park SJ, Pereira NL, et al. Role of ventricular assist therapy for patients with heart failure and restrictive physiology: Improving outcomes for a lethal disease. *J Heart Lung Transplant* 2015; 34: 1042–1049.

32 Sousa M, Monohan G, Rajagopalan N, et al. Heart transplantation in cardiac amyloidosis. *Heart Fail Rev* 2017; 22: 317–327.

33 Davis MK, Kale P, Liedtke M, et al. Outcomes after heart transplantation for amyloid cardiomyopathy in the modern era. *Am J Transplant* 2015; 15: 650–658.

34 Lacy MQ, Dispenzieri A, Hayman SR, et al. Autologous stem
cell transplant after heart transplant for light chain (AL) amyloid cardiomyopathy. J Heart Lung Transplant 2008; 27: 823–829.

35 Cannon RM, Hughes MG, Jones CM, et al. A review of the United States experience with combined heart-liver transplantation. Transpl Int 2012; 25: 1223–1228.

36 Mathew V, Olson LJ, Gertz MA, et al. Symptomatic conduct system disease in cardiac amyloidosis. Am J Cardiol 1997; 80: 1491–1492.

37 Kristen AV, Dengler TJ, Hegenbart U, et al. Prophylactic implantation of cardioverter-defibrillator in patients with severe cardiac amyloidosis and high risk for sudden cardiac death. Heart Rhythm 2008; 5: 235–240.

38 Rezk T, Whelan CJ, Lachmann HJ, et al. Role of implantable intracardiac defibrillators in patients with cardiac immunoglobulin light chain amyloidosis. Br J Haematol 2018; 182: 145–148.

39 Koop AH, Mousa OY, Wang MH. Clinical and endoscopic manifestations of gastrointestinal amyloidosis: a case series. Clujul Med 2018; 91: 469–473.

40 Cowan AJ, Skinner M, Seldin DC, et al. Amyloidosis of the gastrointestinal tract: a 13-year, single-center, referral experience. Haematologica 2013; 98: 141–146.

41 Muchtar E, Gertz MA, Kumar SK, et al. Digoxin use in systemic light-chain (AL) amyloidosis: contra-indicated or cautious use? Amyloid 2018; 25: 86–92.

42 Manwani R, Foard D, Mahmood S, et al. Rapid hematologic responses improve outcomes in patients with very advanced (stage IIIb) cardiac immunoglobulin light chain amyloidosis. Haematologica 2018; 103: e165–e168.

43 Mikhail JR, Schuster SR, Jimenez-Zepeda VH, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood 2012; 119: 4391–4394.

44 Afrough A, Saliba RM, Hamdi A, et al. Impact of Induction therapy on the outcome of immunoglobulin light chain amyloidosis after autologous hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2018; 24: 2197–2203.

45 Rahman MA, Khan AY, Ijaz A, et al. Efficacy and tolerability of daratumumab in heavily pretreated al amyloidosis: a systematic review. Blood 2018; 132 (Suppl 1): S2025–S2025.

46 Leung N, Thorne SD, Dispenzieri A. Venetoclax induced a complete response in a patient with immunoglobulin light chain amyloidosis plateaued on cyclophosphamide, bortezomib and dexamethasone. Haematologica 2018; 103: e135–e137.

47 Gertz MA, Lacy MQ, Dispenzieri A, et al. Refinement in patient selection to reduce treatment-related mortality from autologous stem cell transplantation in amyloidosis. Bone Marrow Transplant 2013; 48: 557–561.

48 Manwani R, Hegenbart U, Mahmood S, et al. Deferred autologous stem cell transplantation in systemic AL amyloidosis. Blood Cancer J 2018; 8: 101.

49 Kaufman GP, Dispenzieri A, Gertz MA, et al. Kinetics of organ response and survival following normalization of the serum free light chain ratio in AL amyloidosis. Am J Hematol 2015; 90: 181–186.

50 Eckhart E, Wittlees R, Kaufman G, et al. Grading cardiac response in AL amyloidosis: implications for relapse and survival. Br J Haematol 2019; 186: 144–146.

51 Rela M, Muipesan P, Heaton ND, et al. Orthotopic liver transplantation for hepatic-based metabolic disorders. Transpl Int 1995; 8: 41–44.

52 Ericzon BG, Wilczek HE, Larsson M, et al. Liver transplantation for hereditary transthyretin amyloidosis: after 20 years still the best therapeutic alternative? Transplantation 2015; 99: 1847–1854.

53 Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med 2018; 379: 1007–1016.

54 Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med 2018; 379: 11–21.

55 Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. N Engl J Med 2018; 379: 22–31.

56 Edwards CV, Gould J, Langer AL, et al. Final Analysis of the Phase 1a/b study of chimeric fibril-reactive monoclonal antibody 11–14 in patients with relapsed or refractory AL Amyloidosis. Blood 2017; 130 (Suppl 1): S509.

57 Richards DB, Cookson LM, Barton SV, et al. Repeat doses of antibody to serum amyloid P component clear amyloid deposits in patients with systemic amyloidosis. Sci Transl Med 2018; 10: eaan3128.

58 Wechalekar AD, Whelan C. Encouraging impact of doxycycline on early mortality in cardiac light chain (AL) amyloidosis. Blood Cancer J 2017; 7: e546.

59 D’Souza A, Flynn K, Chhabra S, et al. Rationale and design of DUAL study: Doxycycline to Upgrade response in light chain (AL) amyloidosis (DUAL): A phase 2 pilot study of a two-pronged approach of prolonged doxycycline with plasma cell-directed therapy in the treatment of AL amyloidosis. Contemp Clin Trials Commun 2017; 8: 33–38.

60 Ehrnhoefer DE, Bieschke J, Boedrich A, et al. EGCG redirects amyloidogenic polypeptides into unstructured, off-pathway oligomers. Nat Struct Mol Biol 2008; 15: 558–566.

61 Meshitsuka S, Shingaki S, Hotta M, et al. Phase 2 trial of daily, oral epigallocatechin gallate in patients with light-chain amyloidosis Int J Hematol 2017; 105: 295–308.

62 Reilly MM, Staunton H, Harding AE. Familial amyloid polyneuropathy (TTR ala 60) in Northwest Ireland: a clinical, genetic, and epidemiological study. J Neurol Neurosurg Psychiatry 1995; 59: 45–49.

http://www.jgc301.com; jgc@jgc301.com | Journal of Geriatric Cardiology
63 Jacobson DR, Pastore RD, Yaghoubian R, et al. Variant-sequence transthyretin (isoleucine 122) in late-onset cardiac amyloidosis in black Americans. *N Engl J Med* 1997; 336: 466–473.

64 Kumar S, Dispenzieri A, Lacy MQ, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. *J Clin Oncol* 2012; 30: 989–995.

65 Dispenzieri A, Gertz MA, Saenger A, et al. Soluble suppression of tumorigenicity 2 (sST2), but not galectin-3, adds to prognostication in patients with systemic AL amyloidosis independent of NT-proBNP and troponin T. *Am J Hematol* 2015; 90: 524–528.

66 Kristen AV, Rosenberg M, Lindenmaier D, et al. Osteopontin: a novel predictor of survival in patients with systemic light-chain amyloidosis. *Amyloid* 2014; 21: 202–210.

67 Kastritis E, Papassotiriou I, Merlini G, et al. Growth differentiation factor-15 is a new biomarker for survival and renal outcomes in light chain amyloidosis. *Blood* 2018; 131: 1568–1575.

68 Kristen AV, Perz JB, Schonland SO, et al. Non-invasive predictors of survival in cardiac amyloidosis. *Eur J Heart Fail* 2007; 9: 617–624.

69 Klein AL, Hatle LK, Taliercio CP, et al. Prognostic significance of Doppler measures of diastolic function in cardiac amyloidosis: A Doppler echocardiography study. *Circulation* 1991; 83: 808–816.

70 Kotecha T, Martinez-Naharro A, Treibel TA, et al. Myocardial edema and prognosis in amyloidosis. *J Am Coll Cardiol* 2018; 71: 2919–2931.