Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Future Perspectives

Angela Dispenzieri, MD[a,*], Giampaolo Merlini, MD[b]

KEYWORDS

• Systemic amyloidosis • Pathogenesis • Early diagnosis • Outcome measures
• Trial design

KEY POINTS

- Further research is necessary to improve our understanding of the structure and biophysics of immunoglobulin light chains and amyloid tropism, formation, and equilibrium.
- Late diagnosis in systemic AL amyloidosis is the biggest impediment to improve patient outcome. Increased awareness, appropriate use of biomarkers and imaging technologies are necessary to overcome this obstacle.
- Innovative trial designs, combined with updated measures of outcome, may accelerate the development of novel drugs and reduce the costs of trials, thus facilitating the access to more effective medicines.

Opportunities and challenges in the field of systemic amyloidosis can be grouped into 4 categories (**Table 1**). First, a deeper understanding of the pathogenesis of the disease is required. Second, a greater awareness of the disease, which will lead to an earlier diagnosis, is imperative. Third, end points for interventional trials are required to convey us to our fourth aspiration, novel therapies for patients with light chain (AL) amyloidosis.

DISEASE PATHOGENESIS

As described in articles elsewhere in this issue, AL amyloidosis is a condition in which clonal light chains both form nonbranching fibrils that deposit in tissues and directly are toxic to organs. The formation of amyloid is a complex process involving the immunoglobulin light chain, protein homeostasis network, extracellular chaperones and matrix components, metal ions, shear forces, and cells.[1] Although there has been considerable progress in the understanding of the disease, there is much to learn about the structure and biophysics of immunoglobulin light chains and about amyloid tropism, formation, and equilibrium.[2,3]

[a] Division of Hematology, Mayo Clinic, 200 First Street SW Rochester, MN 55905, USA; [b] Amyloidosis Center, Foundation IRCCS Policlinico San Matteo, University of Pavia, Viale Golgi 19, Pavia 27100, Italy
* Corresponding author.
E-mail address: dispenzieri.angela@mayo.edu

Hematol Oncol Clin N Am 34 (2020) 1205–1214
https://doi.org/10.1016/j.hoc.2020.08.009
hemonc.theclinics.com

Table 1
Opportunities for better outcomes for amyloidosis

More science to understand pathogenesis	1. Biophysics of light chains and amyloid fibrils 2. Tissue tropism and damage 3. Amyloid proteome 4. Tissue microenvironment 5. Animal models
Earlier diagnosis	1. Awareness by cardiologists and internists via amyloid transthyretin awareness 2. Glycosylation by MASS-FIX 3. Light chain stability assays 4. *C elegans* toxicity assay 5. Imaging with small molecules 6. Use of biomarkers of organ involvement
Trial design	1. Improve hematologic response end points 2. Improve organ response end points 3. Novel trial designs including remote monitoring
Novel therapies directed at plasma cells	1. Daratumumab 2. Venetoclax 3. BiTE, chimeric antigen receptor T cells, drug–antibody conjugates
Novel therapies directed at light chains and amyloid fibrils	1. Silencers 2. Stabilizers 3. Doxycycline 4. Anti-amyloid antibodies (eg, Cael-001)

Destabilizing somatic mutations in the variable genes of light chains increase the propensity for light chains to aggregate.[4] A greater understanding (and a high-throughput mechanism for screening for) these biophysical properties could lead to earlier diagnosis and potential treatment strategies.[5,6] Akin to the beneficial effect of tafamadis in stabilizing transthyretin tetramers, thereby improving a composite end point of hospitalizations and death,[7] an immunoglobulin stabilizer might help patients with AL amyloidosis.[8]

The mechanisms leading to tissue tropism are not understood in AL amyloidosis. Although there are tendencies for certain immunoglobulin light chains to deposit in a particular organ like IGVL6-57 in the kidney, IGVL1-44 in the heart, and IGKV1-33 in the liver, these associations are imperfect.[9–11] If and whether other parts of the proteome direct the amyloidogenic light chain to a given organ is unknown.[12] The specific interactions between amyloid proteins and the tissue resident cells, and the ensuing proteotoxicity, may play a role in organ targeting and damage.

Ideally, a mammalian model, like a mouse model, would provide insight into amyloid formation and deposition, but such attempts have been without major success. There is a transgenic mouse model in which amyloid like substance can be found in the stomach,[13] but this is far from a true amyloid model. Subcutaneous injection of amyloid fibrils into mice has provided some insight into antibodies that facilitate amyloid removal.[14] Ex vivo systems using explanted human tissue have been informative, but are complex.[15,16] The *Caenorhabditis elegans*[2] and the zebrafish AL amyloidosis models[17,18] may prove to be helpful understand light chain toxicity and to test drugs that stabilize light chains and decrease cellular injury, but may fall short in terms of understanding fibril formation and deposition. Tissue culture models may also prove useful for similar hypotheses.[19–22] Such models may facilitate an understanding of light chain processing, organelle damage, apoptotic pathways, and cellular interactions.

EARLY RECOGNITION OF LIGHT CHAIN AMYLOIDOSIS

Late diagnosis in systemic AL amyloidosis is the biggest risk factor for poor outcomes. The majority of patients with AL amyloidosis present with chemosensitive clonal plasma cells. With modern therapy, a very good partial response or better is expected in nearly two-thirds of patients, assuming they live long enough to achieve it.[23,24] Over the years, patient and physician advocacy groups have tried to educate medical communities about the diagnosis with limited success. As recently as the early 2010s, the median time from symptoms to diagnosis was in the range of 9 to 12 months, and only 20% of diagnoses of amyloidosis were made by cardiologists despite the fact that 80% of AL patients have cardiac involvement (**Fig. 1**).[25]

AL amyloidosis patients will benefit from the increasing numbers of recognized cases of wild-type transthyretin amyloidosis, which is primarily a cardiac disease. Because wild-type transthyretin is found in approximately 3% of patients aged 75 years or older,[26] all cardiologists and internists will have patients with recognized amyloidosis in their practices. As long as a physician has amyloidosis as part of his or her differential diagnosis and the tools to distinguish AL from amyloid transthyretin, we predict that the time from symptoms to a diagnosis of AL amyloidosis will shorten and with that prognosis will improve dramatically. Rates of patients with Mayo 2012 stage IV disease and Mayo 2004 stage IIIb disease will be lower, and early mortality will decrease.[23,27]

Once the diagnosis of AL is considered, making the diagnosis of AL amyloidosis is typically not difficult. Congo red staining of a fat aspirate and a bone marrow biopsy

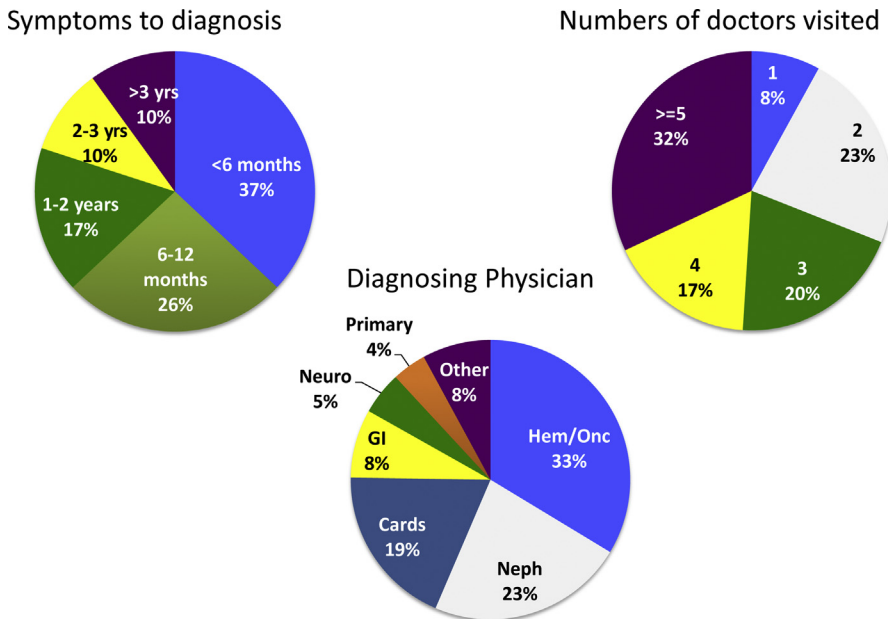

Fig. 1. Road to a diagnosis of amyloidosis. Five hundred fifteen patients were surveyed, 72% of whom had AL amyloidosis; the remainder had hereditary and wild-type transthyretin. Cards, cardiologist; GI, gastroenterologist; Hem/Onc, hematologist/oncologist; Neph, nephrologist; Neuro, neurologist. (*Data from* Lousada I, Comenzo RL, Landau H, Guthrie S, Merlini G. Light Chain Amyloidosis: Patient Experience Survey from the Amyloidosis Research Consortium. Adv Ther. 2015 Oct;32(10):920-8.)

will detect approximately 90% of cases.[28] The typing of the amyloid fibrils by mass spectrometry, immunogold, or immunohistochemistry is straightforward when done by experts to exclude other types of amyloid. For those other 10% to 15% of patients who have a monoclonal protein and symptoms or signs consistent with amyloidosis, a biopsy of the affected organ will typically be required to make the diagnosis.

Why some patients with small monoclonal proteins go on to develop amyloid and others do not has been a major puzzle. Currently, there are no readily available blood assays to diagnose AL amyloidosis. There are, however, some interesting assays that may be available in the not too distant future that measure light chain stability[5] and fibril recruitment.[6] These assays indicate a propensity to form amyloid; however, the diagnosis of amyloidosis requires evidence of organ involvement. This holds true also for the presence of glycosylated light chains on routine MASS-FIX that has been shown to be a potent risk factor for developing AL amyloidosis.[29,30] This finding is more notable for clonal kappa light chains than lambda light chains, and it can serve as a clue for a subset of patients otherwise thought to have monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma (SMM), or multiple myeloma with unusual symptoms. Furthermore, the restricted repertoire of Ig light chain variable region germline gene use, particularly in those with AL lambda type, may enable identification of AL-related genes expressed by the clones of patients with MGUS, SMM, or multiple myeloma, providing opportunities for early diagnosis of AL or risk of AL.[31] Amyloid imaging using small molecules like florbetapir, florbetaben[32–34] may also someday be able to differentiate an MGUS or SMM case from an early AL amyloidosis case. More research will be required to better understand the sensitivity and specificity of such imaging techniques. The use of sensitive biomarkers of organ involvement, NT-proBNP for heart and proteinuria for kidney, during the follow-up of MGUS and SMM, may allow early diagnosis of AL amyloidosis and trigger timely and optimal therapy.[35]

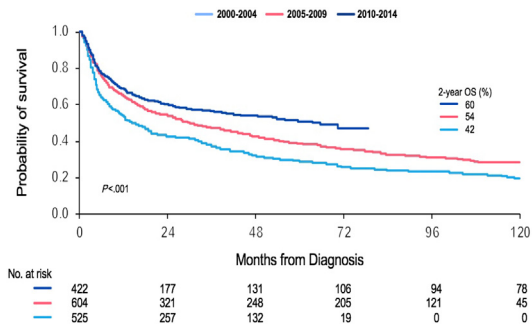

Fig. 2. Improved survival over time: overall survival (OS) for AL amyloidosis by period of diagnosis. (*From* Muchtar E, Gertz MA, Kumar SK, Lacy MQ, Dingli D, Buadi FK, et al. Improved outcomes for newly diagnosed AL amyloidosis between 2000 and 2014: cracking the glass ceiling of early death. Blood. 2017 Apr 13;129(15):2111-9.)

TOOLS FOR BETTER TRIAL DESIGN

Currently, there are no therapies approved by the US Food and Drug Administration (or the European Medicines Agency or other equivalents) for AL amyloidosis. Potential disincentives for pharmaceutical companies not choosing to engage heavily in this field are (1) the frailty of a large percentage of patients; (2) off-label adaption of drugs

approved for multiple myeloma; (3) the complexity of the disease; and (4) the small market share.

AL amyloidosis investigators have dealt effectively with the frailty issue by using cardiac biomarkers to identify those patients likely to die in the first 6 months of therapy.[36,37] In most instances, these patients—about 15% to 20% of newly diagnosed patients—are excluded from interventional trials. The second disincentive is a mixed blessing. Investigators are gratified to have myeloma drugs available for patients with AL amyloidosis, but also realize that the absence of controlled trials in this space can lead to late recognition of unexpected toxicities[38–40] in this cohort as well as patchy access to these drugs for their patients.

The third disincentive, that is, the complexity of the disease, is multifaceted and complex in its own right. Both hematologic and organ response (and progression) are relevant in this disease.[41–44] One would think that hematologic response would be straight forward given the experience in multiple myeloma trials with this measure, but hematologic response in AL amyloidosis is more difficult in part due to the fact that one-half of patients—even at diagnosis—have a very low clonal plasma cell burden. Patients need to have sufficient levels of a given hematologic marker to allow for reproducible measurement of improvement. In addition, because the light chain is what drives the disease, clinicians are wary about allowing them to increase for fear of having organ progression driven by small amounts of monoclonal protein.[45,46] The immunoglobulin free light chain ratio is an unstable measure, yet it is part of the complete hematologic response criteria. This situation leaves us with problems along multiple fronts for trial management: trial eligibility (measurable) hematologic (and organ disease); measurement of hematologic (and organ) response; and perhaps, most important, measurement of hematologic (and organ) progression. Minimal residual disease measurement has not made its way into response criteria for patients with AL amyloidosis, but limited data would suggest that it is a good surrogate for progression, although less valuable for overall survival.[47–50] More granular organ response criteria and composite response end points are also works in progress.[44,51] These are among the issues that the amyloidosis community is working on in association with pharmaceutical companies, academia, patient associations, and the US Food and Drug Administration.[52]

The fourth disincentive, the fact that AL amyloidosis is a rare disease, makes accrual challenging owing to long distances to travel to treatment centers. Pharmaceutical companies help by paying for transportation and lodging, but even with these opportunities, travel can be physically difficult for frail patients and increased time away from work for those still employed is also a major challenge. Innovative adaptations for clinical trial patients during the coronavirus disease-19 pandemic may pave the way for future opportunities for patients with rare disease who would like to participate on clinical trials, like video follow-up visits and home infusions.[53,54]

NOVEL THERAPIES FOR LIGHT CHAIN AMYLOIDOSIS

There are 2 potential treatment pathways for patients with AL amyloidosis. The first exploits treatments that are highly effective against the plasma cells that produce the amyloidogenic light chains, the mainstay of AL amyloidosis therapy for nearly 50 years. As described elsewhere, corticosteroids, alkylators, proteasome inhibitors, and immune modulatory drugs have more than tripled the overall survival of patients with AL amyloidosis (**Fig. 2**).[23,24,55–57] Daratumumab has been an important addition to the armamentarium to treat plasma cell disorders in general, and AL amyloidosis specifically. Trials are ongoing to explore the best use of daratumumab in patients

with AL amyloidosis.[58,59] The Andromeda Trial is an important phase III randomized such trial testing cyclophosphamide, bortezomib, and dexamethasone with or without daratumumab (NCT03201965).[60] Venetoclax has already been shown to be effective therapy in myeloma patients with up regulated BCL2 and or translocation t(11;14).[61] Case reports have demonstrated similar efficacy among patients with AL.[62] Venetoclax is especially appealing in patients with AL because nearly 50% of them harbor t(11;14).[63,64] Silencing RNAs have been a stunning addition to the treatment armamentarium for amyloid transthyretin amyloidosis.[65,66] Zhou and colleagues[67] have developed a siRNA that reduces lambda light chain production and causes terminal endoplasmic reticulum stress. Light chain stabilizers are also being explored in vitro. In addition, other immunotherapies that are showing promise in multiple myeloma clinical trials will hopefully be offered to patients with AL amyloidosis, including chimeric antigen receptor T cells, bispecific T-cell engager antibodies, and antibody–drug conjugates.[68]

Finally, amyloid-directed therapy is an appealing opportunity. The antibiotic doxycycline has been shown to interfere with amyloid fibril formation[13] and in 2 uncontrolled studies demonstrated improved survival.[69,70] Two prospective studies are on-going (NCT02207556; NCT03474458) to assess the value of this intervention. The NEOD001 compound seemed to be quite promising,[71] but a phase III trial failed to meet its end points (NCT03474458). There is controversy as to whether this failure was related to the compound itself or to the trial design. The GSK drug proved to be too toxic. Another amyloid directed monoclonal antibody is CAEL-101.[72] Phase III trials are to begin in 2020.

The future of AL amyloidosis is bright. If 3 drugs to treat amyloid transthyretin amyloidosis could be approved by the US Food and Drug Administration in 2018 and 2019,[7,65,66] the same should be achievable for patients with AL amyloidosis.

DISCLOSURE

A. Dispenzieri - Trial support: Takeda, Celgene, Pfizer, Alnylam, Caelum. Consultancy: Akcea, Janssen, Prothena. G. Merlini has nothing to disclosure.

FUNDING

G. Merlini is supported by grants from the Italian Ministry of Health (Ricerca Finalizzata, grant RF-2013-02355259 and GR-2018-12368387), the CARIPLO Foundation (grant 2013-0964 and 2018-0257), the Amyloidosis Foundation, the “Associazione Italiana per la Ricerca sul Cancro–Special Program Molecular Clinical Oncology 5 per mille” (grant 9965) and by an Accelerator Award from the Cancer Research UK, the Fundación Científica – Asociación Española Contra el Cáncer and the Associazione Italiana Ricerca sul Cancro.

REFERENCES

1. Merlini G. AL amyloidosis: from molecular mechanisms to targeted therapies. Hematology Am Soc Hematol Educ Program 2017;2017(1):1–12.
2. Diomede L, Rognoni P, Lavatelli F, et al. A Caenorhabditis elegans-based assay recognizes immunoglobulin light chains causing heart amyloidosis. Blood 2014; 123(23):3543–52.
3. Marin-Argany M, Lin Y, Misra P, et al. Cell damage in light chain amyloidosis: fibril internalization, toxicity and cell-mediated seeding. J Biol Chem 2016;291(38): 19813–25.

4. Misra P, Blancas-Mejia LM, Ramirez-Alvarado M. Mechanistic insights into the early events in the aggregation of immunoglobulin light chains. Biochemistry 2019;58(29):3155–68.
5. Rennella E, Morgan GJ, Kelly JW, et al. Role of domain interactions in the aggregation of full-length immunoglobulin light chains. Proc Natl Acad Sci U S A 2019; 116(3):854–63.
6. Martin EB, Williams A, Wooliver C, et al. Differential recruitment efficacy of patient-derived amyloidogenic and myeloma light chain proteins by synthetic fibrils-A metric for predicting amyloid propensity. PLoS One 2017;12(3):e0174152.
7. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med 2018;379(11): 1007–16.
8. Morgan GJ, Yan NL, Mortenson DE, et al. Stabilization of amyloidogenic immunoglobulin light chains by small molecules. Proc Natl Acad Sci U S A 2019;116(17): 8360–9.
9. Kourelis TV, Dasari S, Theis JD, et al. Clarifying immunoglobulin gene usage in systemic and localized immunoglobulin light-chain amyloidosis by mass spectrometry. Blood 2017;129(3):299–306.
10. Perfetti V, Palladini G, Casarini S, et al. The repertoire of lambda light chains causing predominant amyloid heart involvement and identification of a preferentially involved germline gene, IGLV1-44. Blood 2012;119(1):144–50.
11. Comenzo RL, Zhang Y, Martinez C, et al. The tropism of organ involvement in primary systemic amyloidosis: contributions of Ig V(L) germ line gene use and clonal plasma cell burden. Blood 2001;98(3):714–20.
12. Kourelis T, Dasari S, Fayyaz AU, et al. A Proteomic Atlas of Cardiac Amyloidosis. Blood 2019;134:1790.
13. Ward JE, Ren R, Toraldo G, et al. Doxycycline reduces fibril formation in a transgenic mouse model of AL amyloidosis. Blood 2011;118(25):6610–7.
14. Wall JS, Kennel SJ, Paulus M, et al. Radioimaging of light chain amyloid with a fibril-reactive monoclonal antibody. J Nucl Med 2006;47(12):2016–24.
15. Vora M, Kevil CG, Herrera GA. Contribution of human smooth muscle cells to amyloid angiopathy in AL (light-chain) amyloidosis. Ultrastruct Pathol 2017;41(5): 358–68.
16. Teng J, Turbat-Herrera EA, Herrera GA. Extrusion of amyloid fibrils to the extracellular space in experimental mesangial AL-amyloidosis: transmission and scanning electron microscopy studies and correlation with renal biopsy observations. Ultrastruct Pathol 2014;38(2):104–15.
17. Mishra S, Guan J, Plovie E, et al. Human amyloidogenic light chain proteins result in cardiac dysfunction, cell death, and early mortality in zebrafish. Am J Physiol Heart Circ Physiol 2013;305(1):H95–103.
18. Mishra S, Joshi S, Ward JE, et al. Zebrafish model of amyloid light chain cardiotoxicity: regeneration versus degeneration. Am J Physiol Heart Circ Physiol 2019; 316(5):H1158–66.
19. Levinson RT, Olatoye OO, Randles EG, et al. Role of mutations in the cellular internalization of amyloidogenic light chains into cardiomyocytes. Sci Rep 2013;3: 1278.
20. Imperlini E, Gnecchi M, Rognoni P, et al. Proteotoxicity in cardiac amyloidosis: amyloidogenic light chains affect the levels of intracellular proteins in human heart cells. Sci Rep 2017;7(1):15661.

21. Monis GF, Schultz C, Ren R, et al. Role of endocytic inhibitory drugs on internalization of amyloidogenic light chains by cardiac fibroblasts. Am J Pathol 2006;169(6):1939–52.
22. Lin Y, Marin-Argany M, Dick CJ, et al. Mesenchymal stromal cells protect human cardiomyocytes from amyloid fibril damage. Cytotherapy 2017;19(12):1426–37.
23. Muchtar E, Gertz MA, Kumar SK, et al. Improved outcomes for newly diagnosed AL amyloidosis between 2000 and 2014: cracking the glass ceiling of early death. Blood 2017;129(15):2111–9.
24. Manwani R, Cohen O, Sharpley F, et al. A prospective observational study of 915 patients with systemic AL amyloidosis treated with upfront bortezomib. Blood 2019;134(25):2271–80.
25. Lousada I, Comenzo RL, Landau H, et al. Light chain amyloidosis: patient experience survey from the amyloidosis research consortium. Adv Ther 2015;32(10):920–8.
26. Mohamed-Salem L, Santos-Mateo JJ, Sanchez-Serna J, et al. Prevalence of wild type ATTR assessed as myocardial uptake in bone scan in the elderly population. Int J Cardiol 2018;270:192–6.
27. 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(4):e165–8.
28. Gertz MA. Immunoglobulin light chain amyloidosis: 2020 update on diagnosis, prognosis, and treatment. Am J Hematol 2020;95(7):848–60.
29. Milani P, Murray DL, Barnidge DR, et al. The utility of MASS-FIX to detect and monitor monoclonal proteins in the clinic. Am J Hematol 2017;92(8):772–9.
30. Kumar S, Murray D, Dasari S, et al. Assay to rapidly screen for immunoglobulin light chain glycosylation: a potential path to earlier AL diagnosis for a subset of patients. Leukemia 2019;33(1):254–7.
31. Zhou P, Kugelmass A, Toskic D, et al. Seeking light-chain amyloidosis very early: the SAVE trial—identifying clonal lambda light chain genes in patients with MGUS or smoldering multiple myeloma. J Clin Oncol 2019;37(15_suppl):8010.
32. Ehman EC, El-Sady MS, Kijewski MF, et al. Early detection of multiorgan light chain (AL) Amyloidosis by Whole Body (18)F-florbetapir PET/CT. J Nucl Med 2019;60(9):1234–9.
33. Kircher M, Ihne S, Brumberg J, et al. Detection of cardiac amyloidosis with (18)F-Florbetaben-PET/CT in comparison to echocardiography, cardiac MRI and DPD-scintigraphy. Eur J Nucl Med Mol Imaging 2019;46(7):1407–16.
34. Wall JS, Martin EB, Richey T, et al. Preclinical validation of the heparin-reactive peptide p5+14 as a molecular imaging agent for visceral amyloidosis. Molecules 2015;20(5):7657–82.
35. Palladini G, Basset M, Milani P, et al. Biomarker-based screening of organ dysfunction in patients with MGUS allows early diagnosis of AL amyloidosis. Blood 2017;130:1670 [abstract].
36. Dispenzieri A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol 2004;22(18):3751–7.
37. 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(17):3420–7.
38. Dispenzieri A, Dingli D, Kumar SK, et al. Discordance between serum cardiac biomarker and immunoglobulin-free light-chain response in patients with

immunoglobulin light-chain amyloidosis treated with immune modulatory drugs. Am J Hematol 2010;85(10):757–9.
39. Batts ED, Sanchorawala V, Hegerfeldt Y, et al. Azotemia associated with use of lenalidomide in plasma cell dyscrasias. Leuk Lymphoma 2008;49(6):1108–15.
40. Palladini G, Perfetti V, Perlini S, et al. The combination of thalidomide and intermediate-dose dexamethasone is an effective but toxic treatment for patients with primary amyloidosis (AL). Blood 2005;105(7):2949–51.
41. Gertz MA, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. Am J Hematol 2005;79(4):319–28.
42. Palladini G, Dispenzieri A, Gertz MA, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. J Clin Oncol 2012;30(36):4541–9.
43. Comenzo RL, Reece D, Palladini G, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain (AL) amyloidosis. Leukemia 2012;26:2317–25.
44. Sidana S, Milani P, Binder M, et al. A validated composite organ and hematologic response model for early assessment of treatment outcomes in light chain amyloidosis. Blood Cancer J 2020;10(4):41.
45. Milani P, Gertz MA, Merlini G, et al. Attitudes about when and how to treat patients with AL amyloidosis: an international survey. Amyloid 2017;24(4):213–6.
46. Palladini G, Milani P, Foli A, et al. Presentation and outcome with second-line treatment in AL amyloidosis previously sensitive to nontransplant therapies. Blood 2018;131(5):525–32.
47. Staron A, Burks EJ, Lee JC, et al. Assessment of minimal residual disease using multiparametric flow cytometry in patients with AL amyloidosis. Blood Adv 2020;4(5):880–4.
48. Sidana S, Muchtar E, Sidiqi MH, et al. Impact of minimal residual negativity using next generation flow cytometry on outcomes in light chain amyloidosis. Am J Hematol 2020;95(5):497–502.
49. Palladini G, Massa M, Basset M, et al. Persistence of minimal residual disease by multiparameter flow cytometry can hinder recovery of organ damage in patients with AL amyloidosis otherwise in complete response. Blood 2016;128(22):3261.
50. Muchtar E, Dispenzieri A, Jevremovic D, et al. Survival impact of achieving minimal residual negativity by multi-parametric flow cytometry in AL amyloidosis. Amyloid 2020;27(1):13–6.
51. Muchtar E, Dispenzieri A, Leung N, et al. Depth of organ response in AL amyloidosis is associated with improved survival: grading the organ response criteria. Leukemia 2018;32(10):2240–9.
52. Panelists TiAF. The Amyloidosis Forum: a public private partnership to advance drug development in AL amyloidosis. Orphanet Journal of Rare Disease 2020. [Epub ahead of print].
53. Pollard VT, Ryan MW, Geetter FS, et al. FDA offers guidance on clinical trials during COVID-19 Pandemic. The National Law Review 2020;X(84).
54. Shah T. FAQs On FDA Guidance For Clinical Trials During The COVID-19 Pandemic. imarc research. 2020. Available at: https://www.imarcresearch.com/blog/fda-guidance-covid-19. Accessed April 8, 2020.

55. Kyle RA, Gertz MA, Greipp PR, et al. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. N Engl J Med 1997;336(17):1202–7.
56. Skinner M, Anderson J, Simms R, et al. Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone, and colchicine versus colchicine only. Am J Med 1996;100(3):290–8.
57. Kumar SK, Gertz MA, Lacy MQ, et al. Recent improvements in survival in primary systemic amyloidosis and the importance of an early mortality risk score. Mayo Clin Proc 2011;86(1):12–8.
58. Sanchorawala V, Sarosiek S, Schulman A, et al. Safety, tolerability, and response rates of daratumumab in relapsed al amyloidosis: results of a phase II study. Blood 2020;135(18):1541–7.
59. Roussel M, Merlini G, Chevret S, et al. A prospective phase II of daratumumab in previously treated systemic light chain amyloidosis (AL) patients. Blood 2020; 135(18):1531–40.
60. Palladini G, Kastritis E, Maurer MS, et al. Daratumumab Plus CyBorD for patients with newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA. Blood 2020;136(1):71–80.
61. Moreau P, Chanan-Khan A, Roberts AW, et al. Promising efficacy and acceptable safety of venetoclax plus bortezomib and dexamethasone in relapsed/refractory MM. Blood 2017;130(22):2392–400.
62. Leung N, Thome 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(3):e135–7.
63. 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.
64. Bochtler T, Hegenbart U, Kunz C, et al. Translocation t(11;14) Is associated with adverse outcome in patients with newly diagnosed AL amyloidosis when treated with bortezomib-based regimens. J Clin Oncol 2015;33(12):1371–8.
65. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med 2018;379(1):11–21.
66. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. N Engl J Med 2018;379(1):22–31.
67. Zhou P, Ma X, Iyer L, et al. One siRNA pool targeting the lambda constant region stops lambda light-chain production and causes terminal endoplasmic reticulum stress. Blood 2014;123(22):3440–51.
68. Soekojo CY, Ooi M, de Mel S, et al. Immunotherapy in multiple myeloma. Cells 2020;9(3):292–8.
69. Kumar SK, Dispenzieri A, Lacy MQ, et al. Doxycycline used as post transplant antibacterial prophylaxis improves survival in patients with light chain amyloidosis undergoing autologous stem cell transplantation. ASH Annual Meeting Abstracts 2012;120(21):3138.
70. Wechalekar AD, Whelan C. Encouraging impact of doxycycline on early mortality in cardiac light chain (AL) amyloidosis. Blood Cancer J 2017;7(3):e546.
71. Gertz MA, Landau H, Comenzo RL, et al. First-in-human phase I/II Study of NEOD001 in patients with light chain amyloidosis and persistent organ dysfunction. J Clin Oncol 2016;34(10):1097–103.
72. Edwards CV, Bhutani D, Mapara M, et al. One year follow up analysis of the phase 1a/b study of chimeric fibril-reactive monoclonal antibody 11-1F4 in patients with AL amyloidosis. Amyloid 2019;26(sup1):115–6.