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Future Perspectives

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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.\textsuperscript{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.\textsuperscript{2,3}
Destabilizing somatic mutations in the variable genes of light chains increase the propensity for light chains to aggregate. A greater understanding (and a high-throughput mechanism for screening for) these biophysical properties could lead to earlier diagnosis and potential treatment strategies. Akin to the beneficial effect of tafamadis in stabilizing transthyretin tetramers, thereby improving a composite end point of hospitalizations and death, an immunoglobulin stabilizer might help patients with AL amyloidosis.

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. If and whether other parts of the proteome direct the amyloidogenic light chain to a given organ is unknown. 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, 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. Ex vivo systems using explanted human tissue have been informative, but are complex. The Caenorhabditis elegans models 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. Such models may facilitate an understanding of light chain processing, organelle damage, apoptotic pathways, and cellular interactions.

| 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) |
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.\textsuperscript{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\textsuperscript{5} and fibril recruitment.\textsuperscript{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.\textsuperscript{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 gammapathy 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.\textsuperscript{31} Amyloid imaging using small molecules like florbetapir, florbeta-ben\textsuperscript{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.\textsuperscript{35}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{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.)}
\end{figure}

\textbf{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. 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 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. One would think that hematologic response would be straightforward 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. 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. More granular organ response criteria and composite response end points are also works in progress. 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.

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.

**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). 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. The Andromeda Trial is an important phase III randomized such trial testing cyclophosphamide, bortezomib, and dexamethasone with or without daratumumab (NCT03201965). Venetoclax has already been shown to be effective therapy in myeloma patients with up regulated BCL2 and or translocation t(11;14). Case reports have demonstrated similar efficacy among patients with AL. Venetoclax is especially appealing in patients with AL because nearly 50% of them harbor t(11;14).

Silencing RNAs have been a stunning addition to the treatment armamentarium for amyloid transthyretin amyloidosis. Zhou and colleagues 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.

Finally, amyloid-directed therapy is an appealing opportunity. The antibiotic doxycycline has been shown to interfere with amyloid fibril formation and in 2 uncontrolled studies demonstrated improved survival. Two prospective studies are on-going (NCT02207556; NCT03474458) to assess the value of this intervention. The NEOD001 compound seemed to be quite promising, 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. 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, the same should be achievable for patients with AL amyloidosis.

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