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# Novel Therapies in Light Chain Amyloidosis

Paolo Milani[1], Giampaolo Merlini[1] and Giovanni Palladini[1]

[1]Amyloidosis Research and Treatment Center, Foundation "Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo," and Department of Molecular Medicine, University of Pavia, Pavia, Italy

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

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

The clinical features of AL amyloidosis with renal involvement have been recently reviewed.[13] This disease is caused by the deposition of monoclonal light chains produced by a plasma cell clone that, in 50% of patients, infiltrates the bone marrow by less than 10%,[14] and is the most common disorder among monoclonal gammopathies of renal significance.[15,16]

**Correspondence:** Giovanni Palladini, Amyloidosis Research and Treatment Center, Foundation "IRCCS Policlinico San Matteo," Viale Golgi, 19 – 27100 Pavia, Italy. E-mail: giovanni.palladini@unipv.it

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**Table 1.** Systemic amyloidosis involving the kidney

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

ANS, autonomous nervous system; PNS, peripheral nervous system.
The amyloid types are identified by acronyms, where the letter "A" for amyloidosis is followed by the abbreviation of the protein forming the amyloid fibrils.

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

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

## Risk Stratification and Response Assessment

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

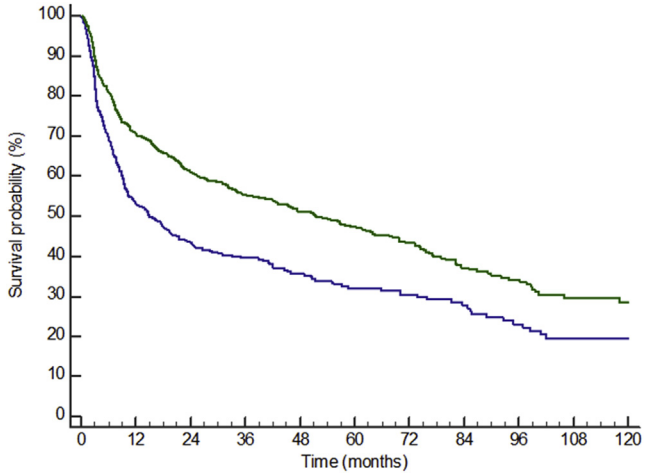


**Figure 1.** Survival of 1065 patients with light chain amyloidosis according to the presence of renal involvement ($P < 0.001$). Green line: 702 patients with kidney involvement, median survival 51 months; the heart was involved in 70% of cases. Blue line: 363 patients without kidney involvement, median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