Renal involvement in AL amyloidosis: the facts, the promise and the hope*

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AL amyloidosis is a devastating, multisystem disorder that often affects the kidney, with proteinuria and elevated serum creatinine being detected in 55% and 45% of patients at presentation [1]. Many patients will develop end-stage renal failure (ESRF). However, there is little information on the predictors of ESRF and the outcome of dialysis, although it is generally considered that the quality of life under dialysis is poor with a high rate of mortality.

The paper by Gertz et al. from the Mayo Clinic examines the long-term outcomes of 145 patients with biopsy-proven AL amyloidosis [2]. Eighty-four had renal amyloidosis and 35 were ultimately dialysis dependent. This is the largest series of patients with renal AL amyloidosis, with an Italian collaborative study that included 198 patients with AL amyloidosis [3]. The Mayo Clinic study provides three pieces of information: (1) \(\lambda\) light chain predicts increased likelihood of renal involvement, (2) high serum creatinine and daily proteinuria are predictors for dialysis, (3) median survival for patients starting dialysis is \(<1\) year. These findings have important pathophysiological and therapeutic implications.

Pathophysiology of amyloid deposition: still unresolved issues!

Determinant factors of amyloid are borne by the precursor light chain (LC), as suggested by recurrence in the renal graft and by induction of amyloid deposits in mice injected with LCs from patients with AL amyloidosis [4]. Pathophysiological studies are made difficult by the unique structural heterogeneity of the precursor, each monoclonal LC being different from all others (Figure 1).

Several LC characteristics are considered amyloidogenic. In AL amyloidosis, the \(\lambda\) isotype is approximately 3- to 6-fold more frequent than the \(\kappa\) isotype. A rarely expressed homology family of LC variable regions, the \(\text{V}_{\lambda,\text{VI}}\) variability subgroup, is found only in amyloid-associated monoclonal immunoglobulins and represents 41% of amyloid LCs [5].

The essential role of the variable domain is further supported by analyses of extracted fibrils, which showed it to be the main amyloid constituent. This finding suggests a role of proteolysis in fibrillogenesis, and may partly account for the weak reactivity of anti-LC antibodies in some patients.

The search for primary sequence peculiarities of the LC variable domains led to disappointing conclusions,
domain that is always different from one patient to another, and a constant domain. The $\lambda$ domain is encoded after the rearrangement of structural determinants of amyloidogenic potential are borne by the $\lambda$ domain, some in the CDRs that may influence the binding specificity, others in the framework regions where aminoacid substitutions may either increase the thermodynamic stability or favour dimerization.

![Diagram of immunoglobulin structure](image)

**Fig. 1.** A monoclonal immunoglobulin $\lambda$-light chain includes a variable ($V_L$) domain that is always different from one patient to another, and a constant domain. The $V_L$ domain is encoded after the rearrangement of a $V$ and a $J$ gene segment, and its variability is essentially restricted to three separate peptide portions termed 'complementarity determining regions' (CDR1, 2 and 3); the remaining $V_L$ sequence ('framework regions') supports the globular antiparallel beta-sheet structure of the domain. All structural determinants of amyloidogenic potential are borne by the $V_L$ domain, some in the CDRs that may influence the binding specificity, others in the framework regions where aminoacid substitutions may either increase the thermodynamic stability or favour dimerization.

Although an analysis of nearly 200 LC sequences identified 12 positions in $\kappa$-chains and 12 in $\lambda$-chains where certain aminoacid residues were associated with amyloidosis [6]. Because of their high dimerization constants, LCs from patients with AL amyloidosis could behave as antibodies for extracellular structures. This may also explain why $\lambda$-chains, which are more prone to form dimers than $\kappa$, are more frequent in amyloidosis.

Molecular bases of organ tropism in AL amyloidosis remain essentially unclear. Gertz et al. [2] first showed that patients with renal amyloid are far more likely to have a monoclonal $\lambda$ LC. The ratio of $\lambda$ to $\kappa$ patients in their cohort was 4:1 in patients with non-renal amyloid compared to 12:1 in those with renal amyloid ($P = 0.02$). Conversely, patients with $\kappa$ LCs are more likely to have dominant hepatic involvement [7]. The tropism of organ involvement may be influenced both by the germ line gene segment used for the LC variable region ($V_L$) and by somatic mutations occurring in the secreting clone [8]. Patients expressing a monoclonal LC of the $\lambda_{III}$ subgroup are more likely to present with dominant renal involvement, while cardiac and multisystem disease is less frequent [7]. Organ-specific environmental factors are also involved, including high intrarenal concentrations of urea that enhance fibril formation by reducing the nucleation lag time [9].

Five percent of the Mayo Clinic's patients [2] with apparently no renal manifestation, ultimately required dialysis. These patients may have had asymptomatic renal amyloid deposits at presentation. Tissue injury is mostly the consequence of extensive deposition of amyloid. However, at least in some tissues, the infiltration alone does not correlate well with the degree of organ failure or survival. This suggests that soluble LCs may exert direct cellular toxicity. LCs from AL-amyloid patients incubated with human mesangial cells induced a macrophage-like phenotype, whereas those from patients with non-amyloid deposition disease induced a myofibroblastic phenotype [10].

**Kidney and life survival: Is renal replacement therapy worthwhile?**

Gertz et al. [2] confirm the importance of cardiac involvement in predicting survival. Patients with renal AL amyloidosis had a better survival than patients without renal involvement (38 months versus 19 months; $P = 0.05$), mostly because of the higher prevalence of cardiac amyloidosis in patients without renal involvement. We recommend measuring N-terminal pro-brain natriuretic peptide (BNP) in all patients. BNP is a sensitive marker of myocardial dysfunction and response to treatment, and a powerful predictor of overall survival [12,13].

The management of patients with AL amyloidosis on haemodialysis is often complicated by persistent hypotension, gastrointestinal haemorrhage, chronic diarrhoea and difficulties in the creation and maintenance of vascular access. Peritoneal dialysis could have several advantages avoiding vascular access and deleterious effects on blood pressure, but it may enhance malnutrition.

As in their previous publication in the early 1990s [14], Gertz et al. [2] reported a poor outcome for patients with AL amyloidosis on dialysis. The median survival from the start of dialysis was 10.4 months, with 20% of patients dying within the first month and only 12% having a 5-year survival. Major causes of death were cardiac, voluntary cessation of dialysis and gastrointestinal tract involvement. Given the poor outcome and quality of life, one could legitimately ask whether patients should be put on a chronic dialysis programme. However, in two studies dating from the early 1990s on heterogeneous cohorts of patients with AL or AA amyloidosis [15,16], patients’ median survival from dialysis initiation ranged from 25 to 52 months, respectively. In a recent study [17], including 19 patients with AL amyloidosis undergoing dialysis, the median survival was 26 months (extremes, one to 96 months). The difference in overall survival may be explained by substantial progress in chemotherapy, as patients from the Mayo Clinic were enrolled in therapeutic protocols between 1993 and 1997 with none of them receiving high-dose melphalan (HDM) [2], while French patients were seen between 1995 and 2005 and received dexamethasone-based regimen or HDM [17].

The outcome remains poor in patients with cardiac involvement that may benefit from heart and kidney transplantation, provided that the underlying clonal plasma cell disease has remitted following chemotherapy [18–21].

**The hope of new therapies**

Given that amyloid deposits can regress, the objectives should be a complete haematologic remission assessed by measurement of serum-free LC [22,23]. Remission should be achieved as soon as possible to avoid early death related to cardiac involvement and/or extensive amyloidosis. AL amyloidosis benefited greatly from major advances in the treatment of multiple myeloma. HDM
(140–200 mg/m²) followed by autologous stem cell transplantation (ASCT) induces complete haematologic response and significant functional improvement in a substantial proportion of low-risk patients [24–27]. However, treatment-related mortality is higher than in ASCT-treated myeloma patients. Thus, an alternative to HDMA/ASCT consists of oral melphalan (10 mg/m²/day) and dexamethasone administered at a high dosage (40 mg/day) in 4-day cycles each month (M/Dex). A recent randomized, multicentre trial showed no significant difference in complete haematologic response between M/Dex and HDMA/ASCT [28]. Moreover, median survival was 56.9 months in the M/Dex group compared with 22.2 months in the HDMA/ASCT group (P = 0.04). Renal responses occurred in ~25% of the patients in either group.

The following recommendations may be proposed: (1) patients with severe organ dysfunction should receive M/Dex as a first-line treatment and (2) patients with less severe disease are eligible for M/Dex or HDMA/ASCT, still considered the reference treatment in experienced centres in the United States. In those who do not show haematologic responses after 3 to 6 months, treatment should be changed to alternatives such as lenalidomide (or thalidomide) or bortezomib-based regimens. These new regimens might become first-line reference treatments in the coming years.

With the eventual eradication of the LC secreting clone, regression of amyloid deposits can now be envisaged.

Conflict of interest statement. None declared.

(See related article by M. A. Gertz et al. Clinical outcome of immunoglobulin light chain amyloidosis affecting the kidney. Nephrol Dial Transplant 2009; 24: 3132–3137.)

References


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