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Renal Response Criteria for Clinical Trials in Amyloid Light Chain Amyloidosis

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Immunoglobin light chain (AL) amyloidosis is a rare disease characterized by organ deposition of amyloid fibrils, most commonly in the heart and kidney. Disease heterogeneity necessitates organ-specific assessment to determine prognosis and response or progression. To facilitate development of new therapies, the Amyloidosis Forum (a public-private partnership between the US Food and Drug Administration and the nonprofit Amyloidosis Research Consortium) held a series of meetings and formed multiple working groups to identify clinical trial end points and analytic strategies. This report summarizes the recommendations of Renal Working Group. Estimated glomerular filtration rate (eGFR) and proteinuria were selected to evaluate eligibility, response, and/or progression in the context of investigational clinical trials for patients with AL amyloidosis. Accurate response assessments at the earliest possible time point were emphasized. The context of use, specific patient population, and the investigational therapeutic mechanism should ultimately drive selection of appropriate end points to evaluate renal response/progression in AL amyloidosis clinical trials.

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Immunoglobulin Light Chain Amyloidosis

Misfolded monoclonal light chains that form amyloid fibrils are the pathogenic basis for AL amyloidosis.[1] The AL fibrils can deposit in all organs and tissues but most commonly in the heart and kidney.[2] Because not all organs are affected to the same degree in an individual patient, separate assessment is necessary for each organ to determine the prognosis and response or progression.[3] Mortality, especially within the first 6 months of presentation, is determined by the severity of the heart involvement.[4,5] Conversely, kidney involvement can be found in 60% to 70% of patients and is usually an early sign of AL amyloidosis.[2] Renal impairment may progress to end-stage renal disease (ESRD), which is a major morbidity for these patients.[6]

The prognosis of patients with AL amyloidosis has transformed rapidly in the last 2 decades. Particularly for patients without advanced cardiac disease, AL amyloidosis may now be considered a treatable disease with the possibility of long term survival. In the era of melphalan and prednisone therapy, the median overall survival (OS) was 18 months, and longer if there was no cardiac involvement.[7] In highly selected patients, OS increased to 4.6 years with the introduction of autologous stem cell transplantation in the late 1990s.[8] However, treatment-related mortality with autologous stem cell transplantation can be high in patients with severe cardiac involvement or multiorgan involvement.[9] Melphalan with dexamethasone was found to be a good alternative to autologous stem cell transplantation with significantly lower treatment-related mortality.[10,11] Further improvement in OS was observed with bortezomib-based regimens such as cyclophosphamide/bortezomib/dexamethasone or

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bortezomib/melphalan/dexamethasone introduced in the early 2010s, which provided a faster and deeper hematologic response.[12,13] Most recently, daratumumab with cyclophosphamide/bortezomib/dexamethasone exhibited substantial improvement in hematologic complete responses and organ response rates.[14] Although survival advantage could not be demonstrated due to the short follow up of the trial, the better hematologic and organ response rates will most likely prove beneficial for OS.

To date, most therapies target the underlying plasma cell dyscrasia, whereas new therapies in clinical development target amyloid deposits in various organs. Given advances in current treatment paradigms and new therapeutic modalities on the horizon, better assessment of organ response and progression are needed in order to manage patients more effectively and to compare the efficacy of different treatment approaches.

The Amyloidosis Forum End Point Development Series

To bridge the gaps that pose barriers to drug development for the treatment of systemic amyloid disorders, a public-private partnership was formed between the nonprofit Amyloidosis Research Consortium (www.arci.org) and the US Food and Administration Center for Drug Evaluation and Research.[15] The Amyloidosis Forum (https://amyloidosisforum.org) leverages expertise of stakeholders from academia, industry, and regulatory agencies, complimented by patient perspectives.

The Amyloidosis Forum conducted a series of virtual workshops to advance patient-focused end point components and analytical strategies for clinical trials in AL amyloidosis (Figure 1). Specialized working groups were formed in the areas of cardiac, hematological, renal, and other (gastrointestinal, peripheral nerve/autonomic, and hepatic) organ systems impacting the heterogeneous AL amyloidosis patient population.[16,17] Additional working groups reviewed potential health-related quality-of-life measures and novel statistical approaches to analysis of clinical trial data.[18,19] Each working group reported their findings and recommendations at a subsequent Amyloidosis Forum meeting (available at: https://amyloidosisforum.org/workshop/).

This review summarizes the proceedings of the Renal Working Group (hereafter referred to as the "Working Group"), which comprised a patient representative, 2 statisticians, and a panel of AL amyloidosis experts representing academia, industry, and regulatory agencies (US Food and Drug Administration, and UK Medicines and Healthcare Products Regulatory Agency). Over a series of 4 meetings, the working group chairperson and members heard patients' testimonials, reviewed available literature, and consulted data from registrational clinical trials in various amyloidosis indications to identify known and potential end points representative of kidney involvement in AL amyloidosis (Table 1). Outcome measures were prioritized based on clinical relevance, available natural history data and/or clinical experience, relevant time horizon to detect change, meaningful thresholds or minimal clinically important differences, and gaps in knowledge regarding that end point. Consensus was reached through the working group meeting format and presented at a subsequent Amyloidosis Forum meeting, Considerations for Novel End Point Development in AL Amyloidosis, held on January 22, 2021 (available at: https://amyloidosisforum.org/workshop/). Characteristics of the prioritized renal outcome measures are summarized in Table 2 and discussed hereafter.

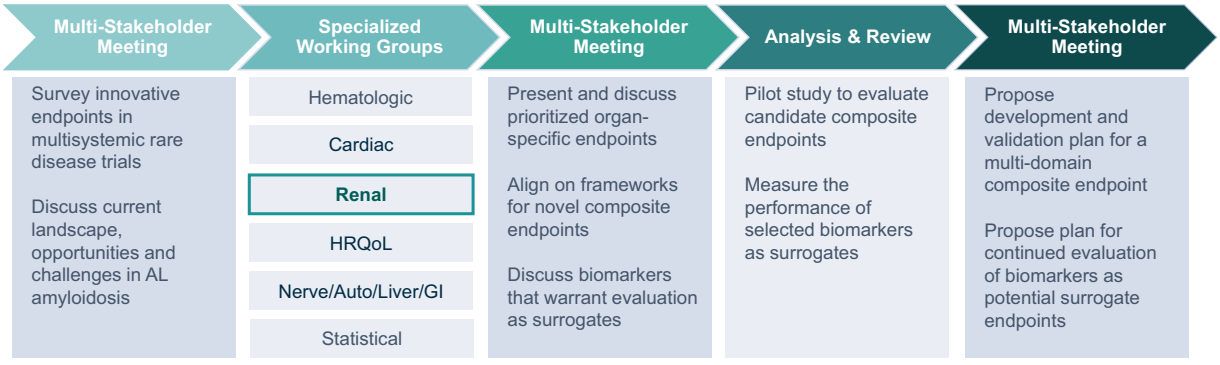

Figure 1. A community approach to end point evaluation for AL amyloidosis trials. The Amyloidosis Forum set out to develop a multidomain composite end point and/or analyses methods for use in clinical trials for AL amyloidosis. Specialized working groups identified condition specific and health-related quality of life (HRQoL) outcome measures; an additional working group focused on statistical approaches to analysis of clinical trial data. The Renal Working Group sought to identify outcome measures to facilitate patient focused drug development for patients with AL amyloidosis kidney involvement.

Table 1. Outcome measures assessed by the Amyloidosis Forum Renal Working Group

Renal endpoints considered	Prioritized
Biomarkers	
Cystatin C	
Estimated glomerular filtration rate	√
Proteinuria by 24 h urine collection	√
Serum creatinine	
Albumin-to-creatinine ratio	
Protein-to-creatinine ratio	

Summary based on presentations from Amyloidosis Forum Meeting: "Considerations for Novel End point Development in AL Amyloidosis" (22 January 2021; available at: https://amyloidosisforum.org/considerations-for-novel-endpoint-development-in-al-amyloidosis/).

Assessment of Kidney Function

Glomerular Filtration Rate

The kidney performs many functions; however, the function that has the most clinical importance is solute filtration measured by the glomerular filtration rate (GFR), which represents the rate at which the kidney clears the blood of a substance.[20] GFR is best measured by a urinary clearance test with an exogenous substance; however, the assessment requires expertise which is usually available only at academic centers, thereby limiting widespread use.

In clinical practice, serum creatinine is the most common biomarker used to assess kidney function. Measured creatinine clearance can be performed but its accuracy is dependent on a stable serum creatinine concentration, an accurate collection of the urine for 24 hours, and an accurate quantitation of serum creatinine.[20-24] Although creatinine is far from the ideal marker for measuring GFR (e.g., secretion by the kidney and the gut, interference by medications and cooked meat, and high dependence on muscle mass), it has been used for nearly 100 years and is widely available.[21,23] Mathematical formulas have been developed to estimate GFR based on serum creatinine concentration. The Modification of Diet in Renal Disease Study and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations have been validated in different populations.[25-28] Most laboratories now report an eGFR with the serum creatinine concentration based on one of these formulas.

Cystatin C is another marker used clinically, which has some advantages over creatinine.[28] Cystatin C is less dependent on muscle mass, which makes it better in elderly or patients with sarcopenia.[29,30] However, cystatin C is manufactured by all nucleated cells, including cancer cells, and thus raises some concern about accuracy in patients with cancer, especially before and after treatment.[31-33] The gene encoding cystatin C is also upregulated by ∼50-fold in myeloma cells and has been implicated as a marker of tumor burden.[34-36] For these reasons, cystatin C may have limited interpretability in patients with cancer, especially those with plasma cell clones. Recently, a combined serum creatinine cystatin C formula was developed which also has the benefit of eliminating the need for race declaration for the calculation of eGFR.[28]

Proteinuria

Aside from a loss in GFR, kidney injury in amyloidosis can also be manifested by proteinuria. In patients with AL amyloidosis, proteinuria >5 g/d is associated with a higher risk for progression to ESRD.[37] Proteinuria can be separated into albuminuria from glomerular injury and nonalbuminuria, which can be either from tubular injury or overflow such as occurs with Bence Jones proteinuria. Although Bence Jones proteinuria is common for patients with multiple myeloma, albuminuria from glomerular injury is the most common renal defect in AL amyloidosis,[38] and is associated with loss of the filtration barrier to albumin.

Table 2. Prioritized renal end points for clinical trials in AL amyloidosis

Characteristic	Prioritized Renal Outcome Measure: eGFR	Proteinuria
Objective	Yes	Yes
Clinically relevant	Calculated from serum creatinine, age, sex, and race of the patient; used in numerous trials of kidney disease	Used in clinical trials in amyloidosis and other kidney diseases
Meaningful threshold	Established staging system with eGFR thresholds	5 g/d (for prognostication) Proteinuria: eGFR ratio >30 as risk factor and > 100 as high risk factor for progression to ESRD Urine albumin-to-creatinine ratio >3600 mg/g equivalent to proteinuria > 5000 mg/d
Time horizon	Minimum 6 mo continual progression; correlates with need for renal replacement therapy	12 mo time point recommended for response assessment (based on time to 50% reduction of proteinuria in AL amyloidosis after stem cell transplantation)
Natural history	25% decrease in eGFR predictive of end-stage kidney disease in 2 separate cohorts	Reduction of proteinuria associated with renal response (which is associated with decreased risk of loss in kidney function) 30% reduction of proteinuria associated with decreased risk of ESRD 25% reduction of proteinuria: eGFR ratio associated with decreased risk of ESRD
Potential limitations	Limited to creatinine with nonideal body weight: overload patients, sarcopenic patients	Dependent on accuracy of collection

AL amyloidosis, immunoglobulin light chain amyloidosis; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.

Table 3. Renal staging, progression, and response criteria algorithms

Criteria	Gertz *et al.*[3]	Palladini *et al.*[37]	Kastritis *et al.*[43]
Baseline			
Stage I		24-h UPr <5000 and eGFR >50	24-h UPr/eGFR ratio <30
Stage II		24-h UPr >5000 or eGFR <50	24-h UPr/eGFR ratio 30–99
Stage III		24-h UPr >5000 and eGFR <50	24-h UPr/eGFR ratio ≥100
Renal progression	50% increase in 24-h UPr (≥1000 mg/d) or ≥25% worsening of Scr or CrCl	≥25% decrease in eGFR	≥25% increase in 24-h UPr/eGFR ratio or 24-h UPr/eGFR ratio ≥100
Renal response	50% decrease in 24-h UPr (≥500 mg/d) without ≥25% worsening of Scr or CrCl	≥30% decrease in 24-h UPr or 24-h UPr <500 in the absence of renal progression	≥25% decrease in 24-h UPr/eGFR ratio or 24-h UPr/eGFR ratio <100 (if initially >100)

24-h UPr, 24-h urine protein in mg/d; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate in ml/min per 1.73 m^2; Scr, serum creatinine.
Adapted from Drosou *et al.*[46].

Traditionally, the gold standard of proteinuria measurement is by a 24-hour urine collection. Unfortunately, the assessment is cumbersome for the patient and can be challenging to collect all of the urine in an exact 24-hour period.[22] Measurement from spot urine collection has been used as a substitute for 24-hour collections. Urine dipstick, though a popular and inexpensive screening tool, is qualitative and only semiquantitative, and usually cannot detect Bence Jone proteinuria. Therefore, for patients with AL amyloidosis, urine dipstick is a good screening tool, but is generally not recommended to quantify response in a clinical trial setting. There may also be diurnal variance; therefore, first morning urine samples are generally preferred.

Protein-to-creatinine ratio (PCR) and albumin-to-creatinine ratio (ACR) are quantitative, convenient, and have good correlation with 24-hour urine collection. ACR may miss some nonalbumin proteinuria and the accuracy of both may diminish at the extremes (<0.5 g/d and >10 g/d). Due to the drawback of 24-hour urine collection, ACR and PCR have been tested in AL amyloidosis populations. The first study from Pavia, Italy was conducted in 64 patients newly diagnosed with AL amyloidosis; a high correlation ($r = 0.90$) was observed between 24-hour urine protein and ACR.[39] The cutoff for renal involvement (>0.5 g/d of proteinuria) was an ACR of 500 mg/g and for staging (>5 g/d of proteinuria by 24-hour urine) was 3600 mg/g.

A larger study published by the Mayo Clinic involving 575 patients who had a spot urine collected within 7 days of a 24-hour urine confirmed the high correlation between ACR and 24-hour urine proteinuria ($r = 0.87$).[40] In this study, the ACR cutoff for involvement was 280 mg/g and 3580 mg/g for staging. Using cutoffs of 300 mg/g and 3600 mg/g, a sensitivity of 92% and 93% and specificity of 97% and 94%, respectively were noted for renal involvement and staging. No significant difference in the correlation or the cutoffs was found between spot urines collected on the same day and those collected within 1 to 7 days of the 24-hour urine collection. PCR ($n = 286$) demonstrated good correlation with 24-hour urine proteinuria ($r = 0.83$) as well. However, PCR differed significantly between AM and PM collected urine samples where the cutoff for 0.5 g/d of proteinuria would change from 563 mg/g in the AM to 877 mg/g in the PM. This difference was not found in ACR; thus, the authors concluded that ACR was superior to PCR in patients with AL amyloidosis. Importantly, the correlation between ACR and 24-hour urine proteinuria was maintained after treatment.

A large prospective study of 531 patients from Pavia confirmed the cutoffs of 300 mg/g for renal involvement and 3600 mg/g for staging and the use of ACR for assessment of renal response.[41] After 36 months of follow-up, no patient with ≥30% reduction in ACR required dialysis versus 16% to 36% of patients with <30% reduction required dialysis. In contrast, another study from Boston University suggested that although cumbersome, 24-hour urine collection is superior to PCR in some cases because of disagreements in kidney staging and organ response in 10% to 20% of cases, especially affecting patients with nephrotic range proteinuria.[42]

Kidney Involvement in AL Amyloidosis

Three classification algorithms have been independently developed to assess staging, response, and progression of renal involvement for patients with AL amyloidosis (Table 3). Kidney involvement in AL amyloidosis is defined by 0.5 g/d or more of proteinuria with or without renal impairment.[3] The demonstration of AL amyloidosis deposits in the kidney is definitive but not required if the deposits have been confirmed in another organ and the manifestation is classic for amyloidosis.[43] Previous studies have shown that 30% albuminuria is a differentiating cutoff between AL amyloidosis and light chain cast nephropathy with

virtually no overlap.[38] The albuminuria is the result of glomerular basement membrane injury from the deposition of amyloid.[44] In approximately 5% of patients with AL amyloidosis, renal involvement is manifested by progressive loss of GFR and minimal proteinuria (< 1 g/d).[45] In these patients, the amyloid is deposited in the vessel walls and interstitium rather than in the glomeruli.

In patients with low grade proteinuria or those who mainly excrete Bence Jones proteinuria, a kidney biopsy may be required to demonstrate kidney involvement. Although proteinuria of >0.5 g/d establishes renal involvement, proteinuria >1 g/d is required for reliable response assessment in clinical trials due to day to day variation.[3] One study found that patients with PCR <177 mg/g had a day to day variability of ±160% versus ±50% in patients with PCR <1768 mg/g.[47]

Assessment of Renal Response

The first renal response criteria for AL amyloidosis were published by the International Society of Amyloidosis in 2004.[3] Using this definition, the median time to renal response was 10 to 11 months after autologous stem cell transplantation in responders.[48] Renal response was highly correlated with the depth of hematologic response. Proteinuria reduction was also inversely correlated with increase in serum creatinine by ≥25%. Proteinuria reduction >75% was associated with improved OS but a lead time bias could not be excluded.[49]

Palladini *et al.*[37] published new renal response criteria in 2014 based on data from an Italian cohort and validated with data from a German cohort. In both cohorts, patients who achieved a renal response had a significantly lower risk (hazard ratio: 0.15; $P < 0.001$) of developing ESRD at 2 years. In this model, renal response was not associated with improvement in OS. Palladini criteria enabled assessment of renal response as early as 6 months after treatment initiation.

A third renal response criteria were introduced by Kastritis *et al.*[50] Response criteria were used to assess renal response as early as 3 months after treatment initiation. Patients with renal response had a significantly lower risk of progression to ESRD than those without (0% vs. 22% respectively, $P < 0.001$). OS was not evaluated based on response in this study.

Assessment of Renal Progression

Renal progression in AL amyloidosis is defined slightly differently among the 3 sets of criteria (Table 3). In the Palladini study, progression was defined by >25% decrease in eGFR. Patients who had a 50% increase in proteinuria were more likely to have decline in renal function; however, this finding did not reach statistical significance.[37] Patients who met progression criteria per Kastritis were found to have an increased risk of progression to ESRD regardless of the criteria.[50] The relative risk of progression to ESRD was 4.233 ($P = 0.003$) using the Kastritis model.

Comparison of Models

The models were compared using a single cohort of 495 patients from the Mayo Clinic.[51] Protection or association with ESRD based on response or progression was analyzed using C-statistic at 3, 6, and 12 months. Renal progression was found at 3 months per International Society of Amyloidosis criteria; Palladini criteria predicted a higher risk of ESRD with hazard ratios of 2.5 ($P = 0.04$) and 2.8 ($P = 0.001$), respectively, but renal response was not associated with protection (i.e., decreased risk) of ESRD. Renal progression per Kastritis criteria was not associated with a higher risk of ESRD, but renal response was associated with protection (hazard ratio: 0.38, $P = 0.017$). After 6 and 12 months, all criteria predicted progression and protection against ESRD; C-statistics were similar.

Recommendations for Kidney Outcomes in AL Amyloidosis Clinical Trials

In AL amyloidosis with renal involvement, GFR and proteinuria are key parameters. GFR reflects the impact of the injury on the overall filtration function, whereas proteinuria reflects the degree of structural glomerular injury. eGFR and PCR have been validated in multiple cohorts for the assessment of renal response and progression in patients with AL amyloidosis, and have served as surrogate end points for either traditional or accelerated regulatory approval in other diseases (https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure). Although progression to dialysis is an important clinical outcome for patients with renal involvement due to AL amyloidosis, the size and duration of clinical trials required to demonstrate meaningful results based on dialysis would be prohibitive.

Although other biomarkers are being investigated, to date none have been used as clinical end points in prospective clinical trials. Growth differentiation factor 15 has been described as a new biomarker for survival and renal outcomes using 2 cohorts of patients with AL amyloidosis, but utility is currently limited to specialized academic centers.[46] Imaging radiotracers for use with positron emission tomography or computed tomography are also under development; preliminary findings suggest encouraging results in quantifying renal amyloid in patients with systemic amyloidosis.[52] Additional studies are required to evaluate the use of these imaging agents for monitoring change in renal

amyloid over time. Therefore, at present, eGFR and proteinuria are the recommended variables for primary end points to assess renal involvement, response, and progression in AL amyloidosis clinical trial end points.

GFR in Clinical Trials

Although the most accurate way to measure GFR is by iothalamate or inulin clearance, the methodologies are cumbersome and require specialized training. The most common alternative is to estimate GFR calculated by one of the Modification of Diet in Renal Disease Study or CKD-EPI formulas.[25-28] Kastritis *et al.*[50] used the Modification of Diet in Renal Disease Study formula for their study, the formula used in the Palladini study was not mentioned.[37] Although CKD-EPI seems to be superior in higher eGFR, and the Modification of Diet in Renal Disease Study in lower ranges, both equations perform well between 30 and 80 ml/min per 1.73 m^2 of eGFR.[53,54] Of available CKD-EPI equations; only the CKD-EPI creatinine formula has been extensively used in AL amyloidosis clinical trials. The nonrace-based creatinine-cystatin C formula has not been comprehensively studied to date in this population but should be adopted.

Proteinuria in Clinical Trials

Proteinuria assessment in patients with AL amyloidosis has traditionally been performed with 24-hour urine collection. This method was used in studies of markers of renal prognosis, response, and progression.[37,50] Studies have evaluated both PCR and ACR as alternatives to 24-hour urine in AL amyloidosis populations; overall, the results suggest ACR is the preferred alternative, not PCR.[42] Although 24-hour urine collection remains the gold standard, ACR is an accurate measurement of proteinuria in AL amyloidosis and may be able to substitute for 24-hour urine collection in the future.[40,41] In the low range ($<$ 500 mg/d for ACR, $<$1000 mg/d for PCR), 24-hour urine may still be needed to increase accuracy and should, at minimum, be collected at diagnosis and/or clinical trial baseline.

Conclusion and Future Directions

The Amyloidosis Forum Renal Working Group recommends eGFR and proteinuria to evaluate eligibility, response and/or progression in the context of investigational clinical trials in patients with AL amyloidosis. As therapy for AL amyloidosis improves, more accurate biomarkers of kidney function and kidney amyloid imaging are needed to assess prognosis, response, and progression.[55] The Working Group recommends continued investigation of new biomarkers and imaging modalities as exploratory end points in prospective clinical trials. These end points will become even more important for the assessment of combination therapy or antiamyloid therapies. Because rapid response is sometimes required for preservation of kidney function, accurate determination of response at the earliest possible time point is important to determine if a change in therapy is required. Ultimately, for drug development, the context of use in a regulatory evaluation, the specific patient population, and the investigational therapeutic mechanism should drive selection of appropriate end points.

APPENDIX

Additional Amyloidosis Forum Renal Working Group Participants

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