Adv Ther (2023) 40:4695–4710
https://doi.org/10.1007/s12325-023-02637-4

REVIEW

Peripheral Nervous, Hepatic, and Gastrointestinal Endpoints for AL Amyloidosis Clinical Trials: Report from the Amyloidosis Forum Multi-organ System Working Group

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Received: May 10, 2023 / Accepted: August 3, 2023 / Published online: September 2, 2023

ABSTRACT

Systemic immunoglobulin light chain (AL) amyloidosis is a heterogeneous rare disease driven by a destructive monoclonal gammopathy and typified by misfolded immunoglobulin light and/or heavy chains which aggregate and deposit in organs as insoluble amyloid fibrils. Disease heterogeneity is driven by the degree of multi-systemic involvement; cardiac, renal, neurological, and gastrointestinal (GI) systems are affected to varying degrees in different patients. While prognosis is primarily driven by hematologic response to treatment and outcomes associated with cardiac events and overall survival, the involvement of the peripheral nervous, hepatic, and GI systems can also have a significant impact on patients. The Amyloidosis Forum (https://amyloidosisforum.org) is a public–private partnership between the nonprofit Amyloidosis Research Consortium (www.arci.org) and the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research formed to advance drug development for the treatment of systemic amyloid disorders. A series of virtual workshops focused on the development of novel, patient-relevant endpoint components and analytical strategies for clinical trials in AL amyloidosis. This review summarizes the proceedings and recommendations of the Multi-Systemic Working Group which identified, reviewed, and prioritized endpoints relevant to the impacts of AL amyloidosis on the peripheral nervous, hepatic, and GI systems. The Working Group comprised amyloidosis experts, patient representatives, statisticians, and representatives from the FDA, Medicines and Healthcare products Regulatory Agency (MHRA), and pharmaceutical companies. Prioritized neuropathy/autonomic endpoints included a modified form of the

Portions of this work were previously presented at the Amyloidosis Forum Meeting, Considerations for Novel Endpoint Development in AL Amyloidosis, held on 22 January 2021 (available at https://amyloidosisforum.org/workshop/).

Members of the Amyloidosis Forum Working Group Participants are listed in the Supplementary Information.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-023-02637-4.

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Neuropathy Impairment Score (NIS + 7) and the Composite Autonomic Symptom Score (COMPASS-31), respectively. Alkaline phosphatase was identified as the most relevant indicator of liver involvement and disease progression. Following extensive review of potential GI endpoints, the Working Group identified multiple exploratory endpoints. These recommended components will be further explored through evaluation of clinical trial datasets and possible integration into composite endpoint analysis.

Keywords: AL amyloidosis; Light-chain amyloidosis; Clinical trial endpoint; Multi-systemic; Peripheral nervous, hepatic, gastrointestinal

Key Summary Points

Immunoglobulin light chain (AL) amyloidosis is a rare, systemic disease caused by a plasma cell dyscrasia and characterized by amyloid fibril deposition in different organs.

The multi-systemic nature of AL amyloidosis warrants consideration of innovative approaches to analyses of clinical outcome data for patients without cardiac involvement.

The Amyloidosis Forum is a public–private partnership with the US Food and Drug Administration to facilitate development of new therapies for amyloidosis in the precompetitive domain.

Following review of evidence, the Multi-organ System Working Group prioritized peripheral nervous, hepatic, and gastrointestinal candidate endpoints for use in AL amyloidosis clinical trials.

INTRODUCTION

AL Amyloidosis is a Multi-systemic Disorder

Systemic immunoglobulin light chain (AL) amyloidosis is a heterogeneous rare disease affecting adults with an estimated prevalence between 1/17,000 and 50,000 in the USA and Europe (ORPHA: 85443). The pathobiological hallmark of AL amyloidosis is a destructive monoclonal gammopathy typified by misfolded monoclonal immunoglobulin light and/or heavy chains which aggregate and are deposited as insoluble amyloid fibrils in target organs [1, 2]. Disease heterogeneity is driven by the degree of multi-systemic involvement; cardiac, renal, neurological, and gastrointestinal (GI) systems are affected to varying degrees in different patients (Fig. 1) [3, 4]. In rare cases, non-plasma cell B cell clones may also lead to AL amyloidosis and the latter has been associated with GI involvement [5, 6]. Most patients have one or two organs affected (primarily the heart and kidney) [3]. However, in patients with multi-organ involvement, other organ systems involved include the nervous (22%), liver (17%), and GI (16%) systems [3]. While the majority of clinical trials in AL amyloidosis focus on primary drivers of disease progression, i.e., hematologic response and outcomes associated with cardiac events and overall survival, the involvement of the peripheral nervous, hepatic, and GI systems significantly impacts patients with AL amyloidosis, but such involvement is often not fully investigated in clinical trials.

Diagnosis of AL amyloidosis is often delayed because symptoms and clinical presentation are often non-specific and vary depending on the organ system(s) affected [3, 7]. Patients with AL amyloidosis often have a severe impact on health-related quality of life (HRQOL) due to both the underlying disease process and arduous systemic chemotherapeutic regimens to treat the underlying plasma cell dyscrasia [8–12]. Treatment modalities for AL amyloidosis tend to follow multiple myeloma treatment paradigms, including monoclonal antibodies,

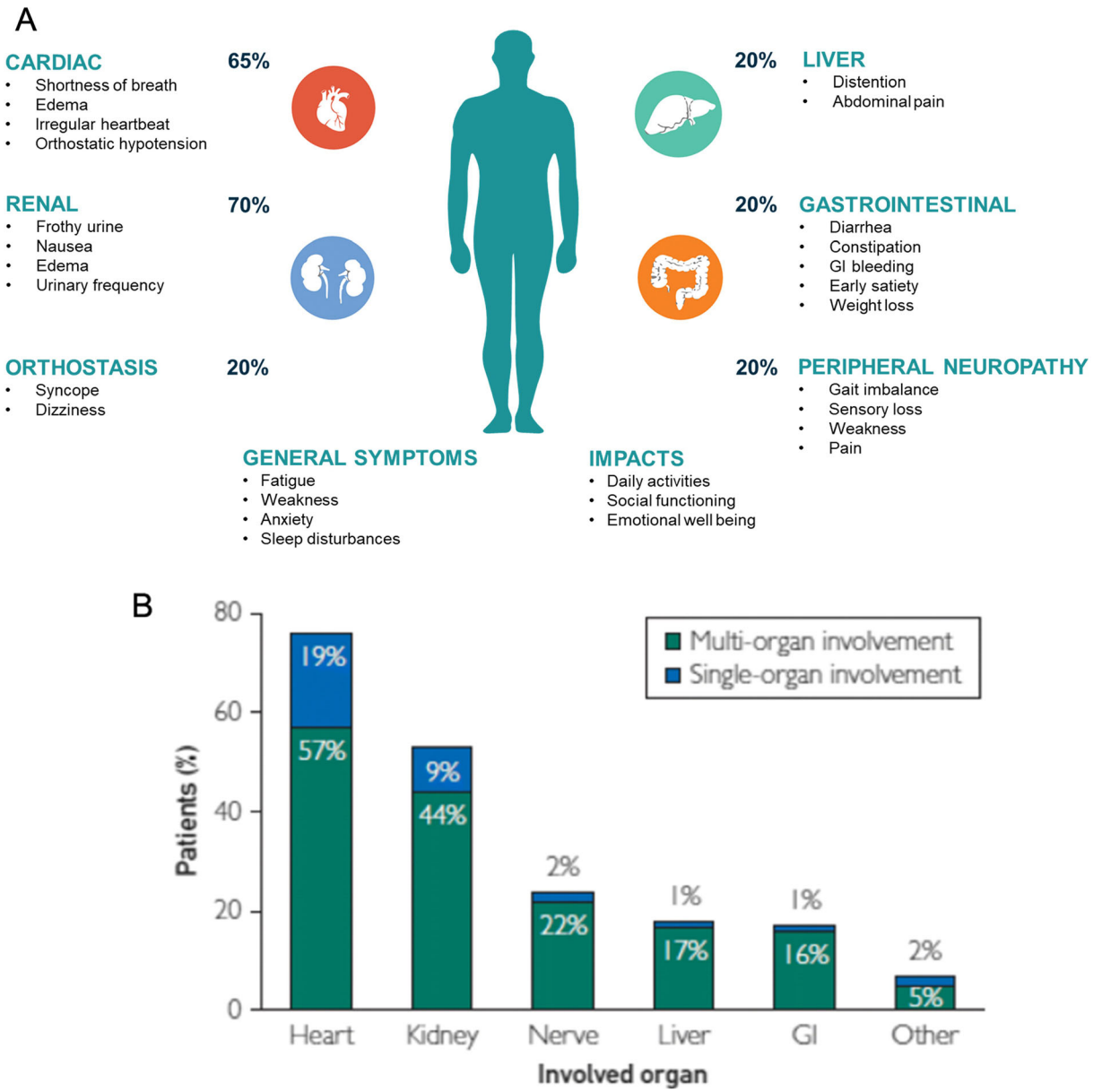

Fig. 1 Prevalence of presenting symptoms and organ involvement. Most common presenting symptoms in patients with AL amyloidosis based on global patient survey results (**A**); adapted with permission [50]. Organ involvement distribution (**B**) in patients with mass spectrometry (MS)-verified typing of AL amyloidosis (N = 592); reproduced with permission [3]

chemotherapeutics, and stem cell transplant. Predictors of organ response to available therapies include the degree of hematological response, severity of organ dysfunction at diagnosis, and time from diagnosis to treatment [13].

While much progress has been made in the advancement of therapies that target the underlying plasma cell disorder [14], there are currently no therapies specifically directed at correcting the amyloid fibril deposition that results in organ system dysfunction (i.e., anti-amyloid treatments). Clinical trials to assess

effectiveness of new anti-amyloid therapies must be designed with clinically meaningful endpoints that will measure and capture improvement in multiple organ systems over time and reflect the interventional product's mechanism of action. Namely, traditional hematologic response criteria would not reflect drug activity of an anti-amyloid therapy, and organ response criteria may need revision based on the different mechanisms of action.

The Amyloidosis Forum Endpoint Development Series

Given the multitude of challenges to develop new therapies for rare, multi-systemic disorders, the Amyloidosis Forum (https://amyloidosisforum.org) was founded as a public–private partnership between the nonprofit Amyloidosis Research Consortium (ARC; www.arci.org) and the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) to advance drug development for the treatment of systemic amyloid disorders [15]. The Amyloidosis Forum hosts meetings, workshops, and other scientific activities in the precompetitive domain to bring together representatives from academia, industry, and regulatory agencies, complemented by patient perspectives. All activities through the Amyloidosis Forum are governed under CDER's Manual of Policies and Procedures ([MAPP] 4100.2).

As previously described, the Amyloidosis Forum conducted a series of virtual workshops to focus on the development of novel, patient-relevant endpoint components and analytical strategies for clinical trials in AL amyloidosis (Fig. 2) [16, 17]. This review summarizes the proceedings and recommendations of the Multi-Systemic Working Group (hereafter referred to as the "Working Group") which identified, reviewed, and prioritized endpoints relevant to the impacts of AL amyloidosis on the peripheral nervous, hepatic, and GI systems. The content of this article is therefore based on previously conducted studies and does not contain any new studies with human participants or animals.

The Multi-organ System Working Group comprised a chairperson (MLM), patient representative, two statisticians, and a panel of AL amyloidosis experts representing academia, industry, and regulatory agencies (FDA, Medicines and Healthcare products Regulatory Agency; MHRA). The Working Group heard patient testimonials and reviewed pertinent literature to identify known and potential endpoints that impact peripheral nerve, autonomic, GI, and hepatic involvement in AL amyloidosis. All outcome measures considered by the Working Group are summarized in Table 1.

Prioritized endpoints were considered in the context of available data from clinical trials in AL amyloidosis or in other forms of amyloidosis. However, the Working Group proceeded with the recognition that the relative utility of the various endpoint components might be different in the context of a trial evaluating an anti-amyloid therapy (i.e., a therapy targeting the removal of amyloid fibril deposits) for AL amyloidosis. The Working Group reported their findings and recommendations at the Amyloidosis Forum Meeting: Considerations for Novel Endpoint Development in AL Amyloidosis (available at https://amyloidosisforum.org/workshop/). Summary characteristics of the prioritized endpoint components are shown in Table 2 and discussed briefly below.

Prioritized Neurologic Endpoints

Neuropathy involvement in AL amyloidosis may be autonomic (e.g., orthostatic intolerance, erectile dysfunction) and/or somatic (e.g., lack of sensation, weakness). In a retrospective medical records review in a cohort of 26 patients with amyloid neuropathy confirmed by sural nerve biopsy, symptoms in at least 58% of patients included paresthesia, muscle weakness, and numbness [18]. The median duration of symptoms before diagnosis was 29 months; other organs were involved in most patients. Neuropathy was chronic, debilitating, and showed relentless progression. The median survival (treated and untreated) was 25 months [18].

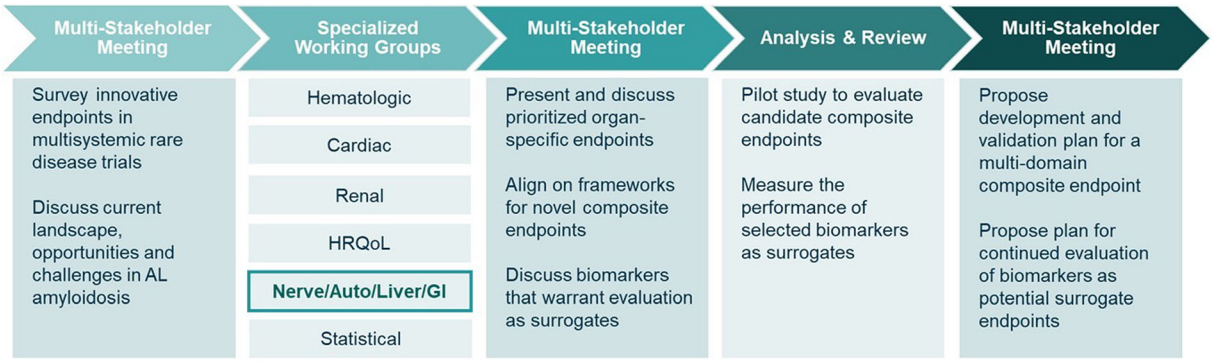

Fig. 2 The Amyloidosis Forum set out to develop a novel multidomain composite endpoint and/or analyses methods for use in clinical trials for immunoglobulin light chain (AL) amyloidosis. Specialized working groups identified and prioritized organ specific and health-related quality of life (HRQOL) endpoints; an additional working group focused on statistical approaches to analysis of clinical trial data. From these recommendations and post hoc analysis of available clinical trial data, the Amyloidosis Forum will develop and evaluate candidate composite endpoints and potential surrogate endpoints to facilitate drug development in AL amyloidosis

Composite neurological scores that incorporate the clinical, electrophysiological, and autonomic attributes assessed by trained personnel are considered an appropriate measure of treatment response/regression [15]. With limited data in AL amyloidosis, the Working Group extrapolated from hereditary transthyretin amyloidosis (ATTRv, also referred to as hATTR) due to similarity in the peripheral neuropathy phenotype with length-dependent, symmetric, sensory, motor, and autonomic involvement with relentless progression.

The Working Group also reviewed and considered the potential utility of a patient-reported outcome measure to capture clinical impact on HRQOL and activities of daily living (ADL), or whether a biomarker could provide an objective marker of neurological disease progression or response.

Modified Neuropathy Impairment Score

Measures to assess polyneuropathy, including the Neuropathy Impairment Score (NIS), the NIS-lower limb, and the modified NIS (mNIS + 7), have been used in ATTRv trials [19–22]. However, the heterogeneous impairment and the aggressive disease course led to modification of these new scales to better assess sensation loss, autonomic dysfunction, and nerve conduction abnormalities in ATTRv amyloidosis and to avoid ceiling effects [22]. The modified tools assessed weakness, reflexes, sensation, nerve conduction attributes, and autonomic endpoints (postural blood pressure) versus heart rate response to deep breathing, to provide an objective measure of the motor and sensory involvement of the peripheral neuropathy in ATTRv amyloidosis. The utility of the lower limb function test was an exploratory endpoint in Neuro-TTR and assessed the patient's ability to walk on their toes, walk on their heels, and rise from a kneeling position and shown to be able to detect change in neuropathy impairments in those with early disease over 15 months [21]. Clinical relevance of the NIS + 7 and mNIS + 7 has been demonstrated in multiple ATTRv trials.

Previous studies in diabetic neuropathy established that a mean 2-point change in the NIS score in the treatment versus placebo group was clinically meaningful. A bilateral change in dorsiflexion strength by 25%, Achilles reflexes from normal to unequivocally decreased, or pinprick sensation from normal to decreased represent a 2-point change. Other trials have demonstrated the natural history of progression by demonstrating deterioration in NIS and NIS + 7 in patients with untreated ATTRv.

The Working Group agreed that a measure similar to the mNIS + 7 iteration should be developed for use in AL amyloidosis trials. This

Table 1 Summary of other multi-systemic endpoints in AL amyloidosis

Endpoints considered	Prioritized
Neuropathy	
Neurologic examination scores and scales	
-Neuropathy Impairment Score (NIS)	✔ (mNIS + 7)
-Medical Research Council (MRC) Sum Score	
-Hughes Functional Grading Scale	
-Lower Limb Function (LLF) score	
Patient-reported/clinician-reported composite	
-Overall Disability Sum Score (ODSS)	
-Neuropathy Symptoms and Change Score	
-Overall Neuropathy Limitation Score (ONLS)	
Patient-reported outcomes/health-related quality of life	
-Rasch-built Overall Disability Scale (R-ODS)	✔
-Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QOL-DN)	✔
-Chronic Acquired Polyneuropathy Patient Reported Index (CAPPRI)	
Anatomical/physiological assessments	
-Nerve conduction studies	✔ (as part of mNIS + 7)
-Quantitative sensory testing	
-Skin biopsy	
Biomarkers	
-Neurofilament light chain	✔ (experimental)
Autonomic	
Anatomical/physiological assessments	
-Composite Autonomic Scoring Scale (CASS)	
-Heart rate deep breathing	
-Postural hypotension (passive standing)	
Patient-reported outcomes/health-related quality of life	
-Composite Autonomic Symptom Score (COMPASS-31) questionnaire	✔
-Scales for Outcomes in Parkinson's Disease–Autonomic Dysfunction (SCOPA-AUT) questionnaire	
Hepatic	
Anatomical/physiological assessments	
-Liver dimensions	
-Fibro elastography	
Biomarkers	
-Alkaline phosphatase	✔ (w/ further validation)
-Aspartate transaminase (AST)/ alanine transaminase (ALT), bilirubin	
Gastrointestinal	
Anatomical/physiological assessments	
-Gastrointestinal tract biopsies	
-Imaging	
-Motility testing	
Patient-reported outcomes/health-related quality of life	
-Gastrointestinal Symptom Rating Scale (GSRS)	
-Patient-Reported Outcomes Measurement Information System (PROMIS-GI)	✔ (modified short form)

Table 1 continued

Endpoints considered	Prioritized
-Nutritional parameters/dietary flexibility	
Nutritional parameters	
-Modified Body Mass Index	✔

adapted instrument would also be a composite NIS but will not incorporate a quantitative sensation testing component, nor the heart rate response to deep breathing because of specialized equipment demands and the likelihood of excessive inter-site variability. The Working Group does not recommend use of postural blood pressure testing as a neuropathy endpoint because of the influence of confounding factors associated with cardiac and renal involvement. The Working Group also stressed the importance of consistent training and standardization of methodology across sites in multicenter trials to ensure integrity of the data.

Rasch-Built Overall Disability Scale

A Rasch-built Overall Disability Scale (R-ODS) was developed for immune-mediated peripheral neuropathies consisting of 24 items assessing ADLs and social participation [23]. The R-ODS captures the ability of an individual to function independently in daily life and has been found to correlate with grip strength. The scale is subjective and has been validated in other neuropathies including Guillain-Barré syndrome, chronic immune thrombocytopenia, and IgM neuropathy [23, 24]. In the phase 3 APOLLO trial in patients with ATTRv, differences between placebo and patisiran were observed as early as month 9, with R-ODS continuing to decline (worsen) in patients assigned to placebo [25]. The utility of the R-ODS has not been established in AL amyloidosis.

Patient-Reported Outcome: Norfolk QOL-DN

The Norfolk Quality of Life Questionnaire–Diabetic Neuropathy (Norfolk QOL-DN) consists of 35 questions assessing neuropathy in five domains: ADL, autonomic neuropathy, large fiber neuropathy/physical functioning, small fiber neuropathy, and symptoms [26, 27]. The instrument was considered appropriate for use in an observational, cross-sectional study in 61 patients with V30M transthyretin familial amyloid polyneuropathy (TTR-FAP) and 16 healthy volunteers [27]. The instrument is subjective and represents a clinically relevant measure of neuropathy symptoms, neuropathy complications, ADL, and chronic health status. The Norfolk QOL-DN has also been shown to correlate with the NIS.

Natural history for the Norfolk QOL-DN has been delineated for patients with ATTRv but has not yet been established for patients with AL amyloidosis. At present, there are no established responder-level estimates available to be considered a minimal clinically important difference (MCID). Change status was determined on the basis of the distribution for each domain and total score of better, same, or worse determined using 0.5 of a standard deviation of the baseline score [28].

Biomarkers: Neurofilament Light Chain

Circulating biomarkers may provide a subjective measure of drug pharmacodynamics and/or effectiveness. Neurofilament light chain (Nfl) is a biomarker in cerebrospinal fluid and plasma that reflects axonal damage in a wide variety of neurological disorders. In patients with ATTRv, plasma Nfl was elevated in patients with ATTRv compared to healthy volunteers [29]. Levels of Nfl correlated with disease severity and increased with disease progression. In a phase 3 study in patients with ATTRv, Nfl levels decreased with patisiran and correlated with mNIS + 7 [30]. In a retrospective study, patients with polyneuropathy associated with AL amyloidosis had increased levels of serum Nfl [31]. Nfl has also been used as a biomarker of axonal injury in chemotherapy-induced peripheral neuropathy and may have value in the setting of a treatment with nerve toxicity.

Autonomic Endpoint: COMPASS-31

The Composite Autonomic Symptom Score (COMPASS-31) is a 31-item instrument

Table 2 Prioritized other multi-system endpoints for clinical trials in AL amyloidosis

System	Neurologic				Autonomic	Hepatic	Gastrointestinal/nutritional	
Characteristic	**mNIS + 7**	**R-ODS**	**Norfolk QOL-DN**	**Neurofilament light chain**	**COMPASS-31**	**ALP**	**mPROMIS-GI**	**Modified BMI**
Objective	Yes	No	No	Yes	No	Yes	No	Yes
Clinically relevant	A similar version used in multiple ATTRv trials, Measures weakness, reflexes, sensation, nerve conduction attributes, and lower limb function	Measures ADL and independent functioning Correlates w/grip strength	Assess patients' perception of symptoms associated with nerve fiber damage Correlates with ATTRv disease severity and NIS	Elevated in ATTRv vs. healthy controls Correlates with disease severity, mNIS + 7	Assesses multiple domains of autonomic function	Correlates with liver function and symptoms	Significant morbidity and impact on HRQOL GI involvement is common but heterogeneous, symptoms may not reflect GI involvement	Correlates with morbidity and mortality
Meaningful threshold	NIS and mNIS + 7 2-point change vs. placebo	Responsiveness comparison at individual level using standard errors	Not established Change gated as better, worse, or same	Not established	Not established	Consensus response is 50% reduction in elevation	Not established	Not established
Time horizon	Continual progression	9–18 months	9–18 months	Not established	18 months	Not established	Not established; may be drug dependent	Not established
Natural history	Data in ATTRv	Data in ATTRv	Data in ATTRv	Data in ATTRv	Data in ATTRv	Not established	Unknown	Not established

Table 2 continued

System	Neurologic				Autonomic	Hepatic	Gastrointestinal/nutritional	
Characteristic	mNIS + 7	R-ODS	Norfolk QOL-DN	Neurofilament light chain	COMPASS-31	ALP	mPROMIS-GI	Modified BMI
Potential limitations	Intra-site variability; requires strict and consistent training across sites	Subjective	Time consuming; subjective	Exploratory: requires further validation; may be impacted by treatments used for AL amyloid (neurotoxic)	Time consuming, subjective	Relation to survival not established; most datasets underpowered to assess	Modified short form tailored to AL amyloidosis required; currently exploratory endpoint	Not a marker of solely GI involvement and likely a more global endpoint

ADL activities of daily living, *ALP* alkaline phosphatase, *ATTRv* hereditary transthyretin amyloidosis, *BMI* body mass index, *COMPASS-31* Composite Autonomic Symptom Score, *HRQOL* health-related quality of life, *NIS* Neuropathy Impairment Score, *Norfolk QOL-DN* Norfolk Quality of Life–Diabetic Neuropathy, *PROMIS-GI* Patient-Reported Outcomes Measurement Information System,*R-ODS* Rasch-built Overall Disability Scale

assessing multiple domains of autonomic function. The COMPASS-31 was derived from the much longer 161-item Autonomic Symptom Profile and the 84-item COMPASS [32]. During development of the COMPASS-31, experts also reviewed individual items to include not only scientifically important questions but also retained items of clinical importance.

COMPASS-31 measures autonomic symptoms across six domains: orthostatic intolerance, vasomotor, secretomotor, GI, bladder, and pupillomotor, and has been validated for use in patients with diabetes and is used to assess patients with other autonomic disorders (e.g., postural tachycardia, multiple system atrophy, dementia with Lewy bodies). In APOLLO, a phase 3 trial of the RNAi therapeutic patisiran in patients with ATTRv, baseline COMPASS-31 was 30, compared to a baseline score of 8.9 in healthy volunteers. Following 18 months of patisiran treatment, COMPASS-31 scores improved (least-squares mean change from baseline, − 5.3; 95% CI − 7.9, − 2.7) as did individual domains of orthostatic intolerance and GI symptoms; placebo scored worsened by 2.2 points [33].

Normative data for the COMPASS-31 was derived from 405 healthy controls. The instrument provides both a global autonomic severity score and domain scores which is advantageous for use in trials with varying populations and drug classes. There are currently no established MCID estimates in patients with AL amyloidosis.

Prioritized Hepatic Endpoints

Overall 15% of patients with AL amyloidosis have liver involvement. In a natural history study of 98 patients with hepatic involvement, the median survival was 8.5 months [34]. However approximately two-thirds of patients with liver involvement also have cardiac or renal involvement which are competing causes of death. Only 5% of patients are estimated to have dominant liver amyloidosis. The consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis states hepatic involvement is implicated when

amyloid is diagnosed at another site in a patient with hepatomegaly (total liver span greater than 15 cm by radionuclide scanning or computed tomographic imaging) or the serum alkaline phosphatase (ALP) value is 1.5 times the institutional upper limit of normal [35]. Hepatic involvement is confirmed by interstitial deposits of amyloid on biopsy and evidence of organ dysfunction [35]. Clinical features of patients with hepatic involvement confirmed by biopsy are consistent, with at least 72% presenting with involuntary weight loss, hepatomegaly, proteinuria, elevated serum ALP, and either serum or urine monoclonal protein [34].

Symptoms of hepatic involvement are generally vague: weight loss, early satiety, or dysgeusia are common. In a natural history study, clinicians considered amyloidosis as the differential diagnosis for only 26% of patients before liver biopsy [34]. The patient representative on the Working Group described her own path to diagnosis as complex in part due to non-specific symptoms, e.g., hardened/enlarged liver, loss of appetite, and pain after eating. Eventually GI symptoms led to diagnosis and successful treatment. For patients with liver and GI involvement, dietary management and appetite as meaningful endpoints were paramount indicators of HRQOL.

The Working Group assessed serum chemistry parameters and liver dimensions as candidate endpoints; fiber elastography was considered as an exploratory endpoint. The consensus of the Working Group was that transaminases (i.e., AST and ALT), while common indicators of liver damage, were not sensitive enough and were relevant only late in the AL amyloidosis disease process.

Alkaline Phosphatase Levels

The Working Group agreed circulating ALP levels represented an objective measure of disease process and could be qualified as a clinical trial endpoint in AL amyloidosis trials. By consensus, response has been reported as 50% reduction of the ALP elevation [35, 36].

The Working Group also noted several limitations: most available datasets are underpowered to statistically establish the value of ALP reduction. ALP has not been validated as surrogate endpoint for survival nor has a receiver operating characteristic curve been constructed to find the optimal percentage decline associated with outcomes (i.e., 25%, 75%), and the time to response is likely therapy dependent. Organ responses were observed after 1 year on a melphalan-based regimen, compared to responses observed after 3–6 months following bortezomib-based regimens.

Prioritized Gastrointestinal Endpoints

GI involvement is common with AL amyloidosis but can be heterogeneous and affect various parts of the gut; there is not one pattern that is pathognomonic. AL amyloid deposition typically occurs in the muscularis mucosa, submucosa, and muscularis propria, often leading to the formation of protrusions and bowel obstruction. Deposition can also occur in the neuromuscular layer of the GI tract, leading to abnormal peristalsis, abnormal GI transit times, and dysmotility [37, 38].

GI symptoms are multifactorial and can be affected by other organ involvement and medications and therefore may not reflect GI involvement. Patients with AL amyloidosis often report abdominal pain, nausea, vomiting, early satiety, unintentional weight loss, diarrhea, constipation, and GI bleeding [15, 39]. Intestinal pseudo-obstruction and protein-losing enteropathy are severe manifestations, albeit uncommon. Limited data suggest GI symptoms may be more common in some subtypes of amyloidosis [40, 41]. GI symptoms generally worsen with longer disease duration and may improve with successful therapy [42].

On the basis of patient-reported testimonials, GI involvement in AL amyloidosis causes significant morbidity and has a key impact on HRQOL. Symptom-directed therapy may improve GI symptoms and is often independent of the results of amyloid-directed therapy, thereby presenting a challenge in the design of clinical trials for AL amyloidosis. The Working Group did not identify any GI-related clinical outcome endpoints considered valid for use in a clinical trial setting. The Working Group

therefore does not recommend a primary GI endpoint based on currently available information but encourages exploration of endpoints in early stages of clinical development where data may be used to develop a drug- or disease-specific outcome measure for use in future trials.

As a result of the significant impact of AL amyloidosis on HRQOL and ADL, patient-reported outcomes may be reasonable to include in early phase clinical trials to assess the GI symptom and impact burden to help inform future clinical trial endpoints. Nutritional parameters, while not necessarily GI-specific, may be a useful exploratory endpoint as limited food tolerance and nutritional concerns are key issues to patients and worsened nutritional parameters have been associated with overall mortality. Modified Body Mass Index (modified BMI, defined as [weight divided by square of height] × albumin level) was considered the most compelling of the nutritional parameters available for inclusion. Other potential nutritional parameters discussed, including individual vitamins and serum albumin, were deemed nonspecific and potentially reflective of other non-GI processes.

Modified PROMIS-GI

In patients with GI involvement, signs and symptoms could potentially be collected directly from patients using a patient-reported instrument(s) to obtain a meaningful measure of clinical benefit; however, these symptoms are often confounded by adverse drug effects and currently there is no AL amyloidosis-specific instrument available.

The Patient-Reported Outcome Measurement Information System (PROMIS) initiative developed new ways to measure patient-reported outcomes such as pain, fatigue, physical functioning, emotional distress, and social role participation that have a major impact on quality-of-life across a variety of chronic diseases (www.nihpromis.org). A PROMIS-GI symptom scale was developed by literature review, focus groups in 102 patients with diverse GI conditions, and evaluated for reliability and validity [43].

The PROMIS-GI symptom assessment comprised 60 items across eight scales: gastroesophageal reflux (13 items), disrupted swallowing (7 items), diarrhea (5 items), bowel incontinence/soilage (4 items), nausea and vomiting (4 items), constipation (9 items), belly pain (6 items), and gas/bloat/flatulence (12 items) [43]. Responsiveness and MCID estimates have been developed for patients with GI disorders including gastroesophageal reflux disease, inflammatory bowel disease, irritable bowel syndrome, systemic sclerosis, and other common GI disorders [44].

The Working Group recommends development of a modified PROMIS-GI short form specifically tailored to GI symptoms commonly occurring in patients with AL amyloidosis with consideration for the mechanism of action of the target therapy, along with potential side effects of the therapy and/or concomitant medications. A modified PROMIS-GI scale for AL amyloidosis would build upon existing datasets, be of limited burden/risk to the patient (other than time), and may reflect an important outcome measure for patients.

Modified Body Mass Index

Significant differences in modified BMI interval change were observed in a subgroup analysis in the phase 3 APOLLO trial in patients with ATTRv [45]. Extrapolation to include modified BMI in AL amyloidosis trials is reasonable with the caveat that this endpoint reflects global involvement and is not a GI-specific outcome measure. For example, patients with cardiac and autonomic involvement may have changes in absorption, activity, muscle mass, or food intake that could affect nutritional parameters through mechanisms unrelated to GI system involvement. In addition, nutritional intake may be strongly affected by medications and supportive non-amyloid therapy.

DISCUSSION

Given the systemic, multi-organ, heterogeneous nature of AL amyloidosis, the Amyloidosis Forum is working toward identifying appropriate endpoints and analytical methodologies for use in clinical trials investigating novel therapies. Composite endpoints may have the

potential to account for specific organ involvement in an individual patient but measure meaningful clinical change with treatment.

Neurological, hepatic, and GI endpoints are relevant to include in the design of interventional trials given the devastating impact of organ involvement and the multisystemic nature of AL amyloidosis. The Multi-organ System Working Group prioritized identification of endpoints as the next step toward development of a novel multi-domain composite endpoint for use trials in AL amyloidosis.

The Working Group identified seven potential endpoints based on established natural history and clinician experience. The optimum timing for assessments, particularly the timing of imaging assessments, to gauge treatment response, may vary depending on the therapeutic mechanism of action (i.e., anti-plasma cell or anti-amyloid). For example, in the context of anti-plasma cell therapy, which does not directly target existing deposits, a long-time course (6 to 12 months) may be required to demonstrate meaningful changes in target organ outcomes. Furthermore, many treatments used to treat AL amyloidosis can cause and/or worsen peripheral neuropathy, and the utility of an endpoint would need to be considered with this caveat in the design of a clinical trial.

In the context of organ-targeted new therapies, several imaging modalities were discussed as interesting future endeavors. For example, liver elastography (via ultrasound or magnetic resonance imaging) could be developed as a pharmacodynamic biomarker and surrogate serial change in liver stiffness [46–49]. A big challenge is the need to assess the time to a meaningful difference as this may be heavily dependent on an individual patient, disease stage, or drug mechanism of action.

The biggest limitation to the Working Group was the lack of available data in patients with AL amyloidosis. The Working Group identified only one prior trial in AL amyloidosis with a neuropathy endpoint. Most of the recommendations were extrapolated from the clinical experience in ATTRv or other forms of amyloidosis. In the case of ALP, most available datasets are underpowered to clearly establish the value of ALP reduction in assessing liver response to treatment.

From the patient perspective, limited food tolerance and nutritional concerns were discussed as key issues impacting HRQOL and ADL. Because of their clinical meaningfulness, capturing data on these outcomes may be useful in order to explore their potential utility as clinical trial endpoints. However, nutritional intake is multifactorial and not necessarily a marker of any specific system function. It may be confounded by medications, non-amyloid therapies, and other external factors. The Working Group could not identify any prior amyloid studies where food tolerance/nutrition data have been collected nor could the Working Group identify a qualified survey that explores this topic. The Working Group concluded limited food tolerance and nutritional concerns are clinically meaningful to patients but would be difficult to pursue as a trial endpoint at present.

Furthermore, while there are challenges in designing trials with newly diagnosed patients, the study of patients with relapsed/refractory AL amyloidosis presents additional challenges outside the scope of the Working Group's initial efforts. More work is required to understand the utility of the endpoints prioritized by the Working Group and confounding factors in the context of drug development trials conducted in the relapsed/refractory setting. Trials should also be designed to understand long-term sequelae for patients with a good initial organ response but persistent issues such as worsening neuropathy or GI symptoms despite the lack of measurable hematological progression.

CONCLUSIONS

The multi-systemic nature of AL amyloidosis warrants consideration of innovative approaches to analyses of clinical outcome data. Overall, the Multi-System Working Group reached consensus

on clinically meaningful endpoints for patients with neurologic, autonomic, hepatic and/or GI involvement due to AL amyloidosis. The Working Group agreed that further evaluation of these prioritized endpoints is required across multicenter trial datasets. The Working Group identified the lack of available prospective data in AL amyloidosis for supporting several candidate endpoints as a key limitation to use in clinical trials. The Amyloidosis Forum seeks to obtain and analyze available datasets from prospective interventional trials to further assess these endpoints and identify measures predictive of response to therapy and clinical outcomes. Natural history studies or continued collaboration and data sharing across specialized centers may also provide supporting evidence. While intended to provide guidance for the use of novel endpoints/analyses, the context of use including specific research objectives, trial population, and investigational product for a particular trial will inherently drive selection of the appropriate endpoint definitions and composite analysis to detect meaningful change and enable patient-focused drug development. The community of patients with AL amyloidosis and the physicians who treat them stand ready to support further studies to this end.

ACKNOWLEDGEMENTS

The authors would like to recognize Kathy Koontz for presenting powerful patient perspectives as part of the Amyloidosis Forum Multi-System Working Group. Preston Dunnmon and Rosalyn Adigun acted as liaisons for the Amyloidosis Forum from the US Food and Drug Administration. Sarah Cairns-Smith, Kristen Hsu, and Robyn Himick of the Amyloidosis Research Consortium provided project management and administrative support.

Medical Writing/Editorial Assistance. Kimberly Denis-Mize, PhD provided professional writing services in the preparation of this manuscript and was funded by the Amyloidosis Research Consortium.

Author Contributions. Michelle L. Mauermann served as chairperson of the Multi-System Working Group and presented the Working Group findings at the Amyloidosis Forum meeting; Michelle L. Mauermann, William J. Litchy, and Laura Obici provided clinical expertise and assessment of neurological endpoints; Morie A. Gertz provided clinical expertise and assessment of hepatic endpoints; John O. Clarke provided clinical expertise and assessment of gastrointestinal endpoints. Michelle L. Mauermann, John O. Clarke, William J. Litchy, Laura Obici, and Morie A. Gertz contributed to the development of the manuscript; additional Working Group participants (Supplementary Material) participated in discussions and provided additional expertise. Isabelle Lousada is the ARC liaison for the Amyloidosis Forum responsible for the conception of this work and contributes patient perspective. All authors have reviewed the submitted manuscript. All Working Group participants attended meetings and provided additional expertise and perspectives.

Funding. The Amyloidosis Forum is funded by ARC. ARC is funded through private/philanthropic donations and grants from for-profit pharmaceutical and biotechnology companies. ARC retains all influence, control and autonomy over projects for which it has received external support. ARC received grants from AbbVie, Alexion, Caelum, GlaxoSmithKline, and Janssen in support of the Amyloidosis Forum Novel Endpoints and Analyses meeting series. ARC was responsible for designing the meeting series, co-developing each Amyloidosis Forum meeting agenda, establishing multi-stakeholder working groups, production of meeting materials, hosting each virtual meeting, and publications. Research reported in this publication was supported by the National Institute on Aging of the NIH (Award Number R13AG071150). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. ARC funded the Rapid Service Fees associated with this publication.

Data Availability. The Amyloidosis Forum meetings are publicly available (https://amyloidosisforum.org/). Recordings from the 15 October 2020 meeting, Novel Endpoints and Analyses in Multisystemic Rare Disease Trials, are available at https://amyloidosisforum.org/novel-endpoint-and-analyses/. Recordings from the 22 January 2021 meeting, Considerations for Novel Endpoint Development in AL Amyloidosis, are available at: Considerations for Novel Endpoint Development in AL Amyloidosis—The Amyloidosis Forum.

Declarations

Conflict of interest. Michelle Mauermann: Research funding from IONIS, Alnylam, EIDOS, Editorial board of *Mayo Clinic Proceedings*, Book royalties from Oxford Publishing. John O. Clarke: Consultant with Alnylam, Pfizer. William Litchy: Contracts with IONIS, Alnylam, EIDOS. Laura Obici: Speaker fees from Alnylam, SOBI, Pfizer and Akcea. Isabelle Lousada: None. Morie Gertz: DSMB: AbbVie, Celgene, Advisory Board: Ionis, Consulting: Akcea, Alnylm, Prothena, Honoraria and consulting, i3Health educational materials, Honoraria: Research to Practice, Ambry Genetics, Amgen, Janssen, Celgene, Karyopharm, Pfizer (to institution), Sanofi, Stock Options: Aurora Bio.

Ethical approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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