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The Clinical Trials Landscape in Immunoglobulin Light Chain Amyloidosis: A Systematic Review

Tracking no: ADV-2024-012737R1

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Abstract:

Conflict of interest: COI declared - see note

COI notes: COI: ERSC receives research funding from Arnold Ventures. RC: Consulting/Advisory Board-Janssen, Sanofi, Adaptive Biotech

Preprint server: No;

Author contributions and disclosures: R.R abstracted the data and wrote the first draft of the manuscript. D.S. participated in writing the manuscript along with R.R. C.L. and V.S. abstracted the data. R.C. designed the research, edited the manuscript, and approved the final version. V. Sanchoralwala, S.L., and E.C. provided critical input and approved the final draft of the manuscript.

Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: Not Appicable

Clinical trial registration information (if any):

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COI: ERSC receives research funding from Arnold Ventures.

RC: Consulting/Advisory Board-Janssen, Sanofi, Adaptive Biotech

Manuscript Word Count: 1198

To the editor,

Immunoglobulin light chain (AL) amyloidosis is a rare hematologic disorder characterized by end-organ damage from deposition of fibrillar aggregates of unstable light chains[1]. The key to successful management of AL is rapid and profound reduction of amyloidogenic FLCs using plasma cell clone-directed therapies[2]. The treatment armamentarium in AL is therefore mostly borrowed from that of multiple myeloma. However, while drug development in myeloma has proceeded rapidly, with >15 new therapies approved since 2010, just one therapy has received FDA accelerated approval specifically for AL amyloidosis: anti-CD38 monoclonal antibody daratumumab (2021)[3]. Potential reasons for this discrepancy include the rarity of AL amyloidosis and its historically poor prognosis, especially patients with cardiac amyloid with baseline N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) >8500 pg/mL[4,5], who often have early mortality or cardiac adverse events that might deter pharmaceutical companies from investing in this space.

Furthermore, the lack of contemporary criteria to standardize assessment of hematologic progression complicates trial design in AL, especially in the relapsed/refractory setting. The 2005 International Society of Amyloidosis (ISA) criteria for hematologic progression requires the iFLC (involved FLC) to be at least 10mg/dL to define hematologic progression in most patients[6]. However, a recent survey of global amyloidosis experts revealed their discomfort to wait until such an iFLC elevation[7]. Another challenge is that clinical trials often exclude patients with advanced cardiac and renal dysfunction. We performed a systematic review to define the current landscape of clinical trials in AL amyloidosis and highlight unmet needs in this population.

A search on clinicaltrials.gov was performed on September 2023, using the term ‘Amyloidosis’ under the field Condition/disease. We included all trials in AL amyloidosis testing a

pharmaceutical agent and that are currently ongoing, defined as having an enrollment status of 'Not yet recruiting', 'Recruiting', 'Active, not recruiting', and 'Enrolling by Invitation'. We excluded studies that had 'suspended', 'withdrawn', or of 'unknown' status. Data on key elements of the study design (inclusion/exclusion criteria, intervention, endpoints, sponsor) were extracted by two independent reviewers (R.R. and V.S.), and discrepancies were resolved by a third reviewer (R.C.).

Our search generated 280 unique entries, among which 32 trials that tested a pharmaceutical agent in systemic AL amyloidosis were included for analysis. The PRISMA flowchart is shown in Supplementary Appendix I. The characteristics of included trials are summarized in **Table I**. Notably, the majority of trials were in patients with previously-treated AL amyloidosis (17/32; 53%), followed by the newly-diagnosed setting (12/32; 38%). Just 9/32 trials (28.1%) tested novel agents for AL amyloidosis rather than those approved for myeloma. Most trials (23/32; 71.9%) were multi-center and just a minority were industry-sponsored (8/32; 25%). Among the 5 phase III trials, 3 were industry-sponsored registrational trials. The mean estimated sample size for industry-sponsored vs non-industry-sponsored trials was 143 (±28.8) vs 59 (±16.6) patients respectively (p=0.0174). The mean sample size of multi-center trials was significantly higher than that of single-center trials [95±18 vs 42±29 respectively; p=0.025]. Industry-sponsored trials had a substantially higher likelihood of being in newly diagnosed setting (62.5%) compared to non-industry-sponsored trials (29.2%) (p=0.146). Of 32 trials, 31 reported the cut-off in difference between involved and uninvolved FLC (dFLC) used for trial inclusion. The most common cut-off was 5 mg/dL (16/31; 52%), followed 2 mg/dL (8/31; 26%). Of two trials which had no dFLC cut-off, one evaluated different durations of daratumumab maintenance (NCT05898646) and one tested siltuximab to reduce symptom-burden after auto-transplant (NCT03315026). Serum M-spike was allowed as measurable disease in 10 trials, with the most common cut-off being 0.5 g/dL (n=9). Among 27 trials with available data on the

upper limit of NT pro-BNP cut-off for exclusion, the most common cut-off was 8500 pg/mL (17/27; 63%), followed by 1800 (2/27; 7%), 5000 (2/27; 7%), and 7500 (1/27; 4%). Of 5 trials that did not exclude patients based on NT-proBNP, four were specifically targeted to patients with stage IIIb disease, and one was a pragmatic trial that included all-comers. Notably, 23 trials excluded patients with renal function below a specified eGFR cut-off: most commonly 40 ml/min/1.73m^2 (6 trials), 30 (6 trials), and 20 (6 trials). Only two trials with an eGFR cut-off tested experimental drugs that are excreted renally (lenalidomide [NCT03252600] and pomalidomide [NCT04270175]).

The most common primary endpoints were hematologic response rate (13/32; 41%) and safety-related endpoints (13/32; 41%); overall survival (OS) was a primary endpoint in just 4/32 (13%) trials. Industry-sponsored trials had a higher incidence of having safety as primary endpoint compared to non-industry-sponsored trials (75% vs 29.2% respectively; p=0.022). Health-related quality of life (HRQoL) was measured as a pre-specified endpoint in just 12/32 trials (38%). The majority of interventions were fixed-duration (26/31; 84%); industry-sponsored trials were significantly more likely to treat until progression than non-industry sponsored trials (50% vs 4.4%; p=0.0045).

We demonstrate substantial heterogeneity in the eligibility criteria and definitions of measurable disease used in current AL clinical trials. Two-thirds of trials continue to exclude patients with NT-proBNP >8500 pg/mL, despite an improved prognosis for these patients in the daratumumab era[8,9]. As early mortality in the era of Dara-VCd frontline therapy predominantly occurs in patients with stage IIIb disease (i.e. baseline NT-proBNP>8500 pg/ml)[10], it will be more difficult for emerging therapies to demonstrate an OS benefit in a reasonable time-frame without including this high-risk group. Additionally, trials in relapsed/refractory setting shouldn't exclude patients with stage IIIb disease at diagnosis since

the steep drop in survival slope is limited to the 1st year after diagnosis. Despite the availability of validated PRO instruments in AL and a well-defined HRQoL trajectory[11-15], only one third of trials measured a PRO endpoint.

We also observed discordance in the dFLC cut-offs used for measurable disease. Notably, the current hematologic response criteria in AL amyloidosis defines very good partial response (VGPR) as dFLC<4 mg/dl, and requires a baseline dFLC ≥5 mg/dl to be considered response-evaulable[16]. However, several seminal studies have now demonstrated the strong prognostic impact of achieving dFLC<1 mg/dl at the end of treatment, highlighting that even small amounts of persistent clonal light chain can lead to ongoing organ damage[17-20]. Additionally, several groups had proposed a new response category named "low-dFLC PR" for patients with baseline dFLC of 2-5 mg/dl, defined as a post-treatment dFLC<1 mg/dl without achieving a CR[21-23]. Since hematologic response evaluation is now feasible for all patients with dFLC≥2 mg/dl (due to creation of the new response category-low-dFLC PR), regulatory authorities should encourage inclusion of these patients in clinical trials. Furthermore, novel assays to check light chain burden such as mass spectrometry-based FLC assays[24] should be evaluated in clinical trials. While significant advances have been made in clone-directed therapy – in large part thanks to successful development in myeloma – therapies targeting light chain cytotoxicity and deposited amyloid fibrils in vital organs remain an unmet need, and should be tested in RCTs. Furthermore, since patients with AL are frailer compared to myeloma, trials should be designed with the shortest possible treatment duration needed to achieve the desired efficacy. Table 2 highlights some suggestions in clinical trial design in AL, along with areas of unmet need.

In conclusion, our study highlights the urgent need to harmonize definitions of measurable disease and hematologic progression criteria in AL clinical trials, greater inclusion of patients with advanced organ involvement, and increased use of PRO endpoints.

Contributions

R.R abstracted the data and wrote the first draft of the manuscript. D.S. participated in writing the manuscript along with R.R. C.L. and V.S. abstracted the data. R.C. designed the research, edited the manuscript, and approved the final version. V. Sanchoralwala, S.L., and E.C. provided critical input and approved the final draft of the manuscript.

Conflicts of Interest

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Table 1. Characteristics of clinical trials in AL Amyloidosis

Variable	**Number of trials (%), except where indicated**
Disease Setting:	
Newly Diagnosed	12 (37.5)
Previously Treated	17 (53.1)
Mixed	3 (9.4)
Trial Sponsor:	
Investigator-sponsored	17 (53.1)
Industry-sponsored	8 (25.0)
Co-operative group	7 (21.9)
Trial Phase:	
I	7 (21.9)
II	14 (43.8)
I/II	6 (18.8)
III	5 (15.6)
Randomized	11 (34.4)
Estimated sample size, median (range)	45 (12-416) patients
Trial location:	
US	17 (53.1)
Ex-US	10 (31.3)
Both US and ex-US	5 (15.6)

Primary endpoint: Safety Overall survival Hematologic response rate	 13 (40.6) 4 (12.5) 13 (40.6)
HRQoL measured:	12 (37.5)
Nature of investigational agent: Clone-directed Fibril-directed Other	 27 (84.4) 4 (12.5) 1 (3.1)
Biomarker-selected*	5 (15.6)
dFLC cut-off for inclusion (mg/dl): 2 4 4.5 5 18 No cut-off Not available	 8 (25.0) 2 (6.3) 1 (3.1) 16 (50.0) 2 (6.3) 2 (6.3) 1 (3.1)
Upper limit of NT-proBNP (pg/ml) for exclusion 1800 5000 7500 8500 No upper limit Not available	 2 (6.3) 2 (6.3) 1 (3.1) 17 (53.1) 5 (15.6) 5 (15.6)
NYHA class for exclusion@: III or higher IIIb or higher IV	 10 (55.6) 6 (33.3) 2 (11.1)

Lower limit of ANC for exclusion[$] : 1000/cc 1500/cc	 21 (91.3%) 2 (8.7%)
Treatment duration[#]: Fixed-duration (n; %) Treatment until progression (n; %)	 26 (83.9) 5 (16.1)

[*]All biomarker-selected trials were in patients with t(11;14) cytogenetic abnormality
[@]Data available for 18 trials
[$]Data available for 23 trials
[#]Data available for 31 trials

Table 2. Suggestions for Clinical Trial Design in AL Amyloidosis

Key considerations in trial design:

- Uniform implementation of measurable disease criteria in trials of relapsed/refractory AL amyloidosis
- Preference for time-limited therapy to reduce physical and financial toxicity
- Response-driven de-escalation strategies
- Inclusion of patients with advanced disease (e.g. NT-proBNP>8500 pg/mL, ESRD, and autonomic neuropathy)
- Incorporate correlative studies on novel assays for measuring tumor burden (e.g. free light chain-mass spectrometry)
- Incorporate patient-reported outcome (PRO) assessment to measure health related quality of life
- Functional assessment (6MWT) with clinically meaningful differences

Key areas of unmet need:

- Standardization of supportive care regimens
- Rare entities such as IgM amyloidosis
- Treatment and natural history studies of localized AL amyloidosis
- Determine the most appropriate imaging modalities for assessing disease burden and response, considering factors such as sensitivity, specificity, and feasibility
- Therapies targeting amyloid fibrils and misfolded light chains

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