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SHORT REPORT

Using a Modified Delphi Panel to Estimate Health Service Utilization for Patients with Advanced and Non-Advanced Systemic Light Chain Amyloidosis

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Purpose: Patients with diagnosed with systemic light chain (AL) amyloidosis at advanced Mayo stages have greater morbidity and mortality than those diagnosed at non-advanced stages. Estimating service use by severity is difficult because Mayo stage is not available in many secondary databases. We used an expert panel to estimate healthcare utilization among advanced and non-advanced AL amyloidosis patients.

Patients and Methods: Using the RAND/UCLA modified Delphi method, expert panelists completed 180 healthcare utilization estimates, consisting of inpatient and outpatient visits, testing, chemotherapy, and procedures by disease severity and organ involvement during two treatment phases (the 1 year after starting first line [1L] therapy and 1 year following treatment [post-1L]). Estimates were also provided for post-1L by hematologic treatment response (complete or very good partial response [CR/VGPR], partial, no response or relapse [PR/NR/R]). Areas of disagreement were discussed during a meeting, after which ratings were completed a second time.

Results: During 1L therapy, 55% of advanced patients had ≥1 hospitalization and 38% had ≥2 admissions. Rates of hematopoietic stem cell transplant (HSCT) in advanced patients were 5%, while pacemaker or implantable cardioverter defibrillator (ICD) placement were 15%. During post-1L therapy, rates of hospitalization in advanced patients remained high (≥1 hospitalization: 20-43%, ≥2 hospitalizations: 10-20%), and up to 10% of advanced patients had a HSCT. Ten percent of these patients underwent pacemaker/ICD placement.

Conclusion: Experts estimated advanced patients, who would not be good candidates for HSCT, would have high rates of hospitalization (traditionally the most expensive type of healthcare utilization) and other health service use. The development of new treatment options that can facilitate organ recovery and improve function may lead to decreased utilization.

Keywords: consensus, hematology, outcomes research, mayo stage, cardiac failure

Introduction

Systemic light chain (AL) amyloidosis is rare, with an incidence of 10–14 affected adults per million person-years in the United States.[1] AL amyloidosis is caused by the misfolding of proteins, leading to unstable tertiary structure and formation of fibrils that deposit in organs and tissues.[2] The disease is staged using the revised Mayo system, which incorporates serum markers of cardiac damage and clonal proliferation.[3] Survival is measured in months for the most severely affected (stage 4) patients compared to years for those with stage 1 or 2 disease.[4]

Estimating health service utilization is crucial for understanding the burden of disease. As is common for rare diseases, information on the health service use associated with AL amyloidosis is limited.[5,6] Healthcare claims data usually provide the largest easily obtainable sample to study utilization in rare conditions, but prior to 2017, there was no ICD-10 diagnosis code specific for AL amyloidosis and even now, ICD-10 coding for AL amyloidosis (E85.81) does not indicate disease stage or severity.[7] Recent studies in AL amyloidosis used administrative healthcare claims data to estimate utilization in AL amyloidosis[5,6] but did not have access to key laboratory test results and could not reliably measure utilization by Mayo stage (ie, disease severity). Further, with the approval of daratumumab, an injection commonly used for patients with multiple myeloma[8] and approved for use for patients with AL amyloidosis in 2021,[9] the treatment paradigm has changed.

The RAND/UCLA modified Delphi panel method[10] (also called the RAND/UCLA Appropriateness Method or RUAM) was developed in the 1950s[11] and adapted in the 1980s for use in the medical setting.[12] It is a formal group consensus process that systematically and quantitatively combines expert opinion and evidence by asking panelists to rate, discuss, then re-rate items.[10,13] The method is useful when clinical evidence is lacking or emerging (eg, recent medication approvals).[14] Given the limitations of prior real-world studies and difficulty obtaining adequate data from other sources, we used this validated expert consensus method to estimate current health service use associated with AL amyloidosis.

Materials and Methods

We used the RAND/UCLA modified Delphi panel method[10] in this study. An overview of this methodology is outlined in Figure 1. The primary steps in the process include identification of a relevant group of experts, providing them with a systematic review of evidence, generating a rating form made up of hypothetical patient scenarios designed to elicit estimates of the parameters of interest, completing first-round ratings prior to a meeting where areas of disagreement are discussed, followed by second-round ratings and analysis of those ratings.

We recruited 12 geographically diverse clinical experts; nine oncologists/hematologists, two cardiologists, and one non-physician patient advocate. All physicians practiced in US academic settings. Physicians had 6–39 (median 15) years of experience treating AL amyloidosis patients and were caring for 20–450 (median 75) AL amyloidosis patients.

Panelists were provided with an up-to-date systematic review and asked to estimate utilization (eg, inpatient admissions, outpatient visits, laboratory testing, chemotherapy, procedures) by phase of treatment and disease severity. We defined two phases of treatment: the 1-year of first line treatment following diagnosis (1L) and the 1-year after completing first-line treatment or during relapse (post-1L). We stratified post-1L by hematologic response (complete response [CR] or very good partial response [VGPR], or partial, no response [PR/NR respectively] or relapse). We defined advanced as encompassing two groups: patients with Mayo stage 3 or 4 during 1L and those with elevated troponin and/or NT-proBNP during post-1L, indicating cardiac involvement. All other patients were classified as non-advanced. Patients were further stratified by renal or other non-cardiac organ involvement.[15,16] For simplicity, in the remainder of the manuscript, we refer to this as "renal involvement." The interaction of treatment phases and patient characteristics produced 20 distinct patient groups. For each group, panelists estimated utilization for a variety of services (eg, laboratory tests, inpatient admissions), providing a total of 180 individual estimates.

Panelists provided these estimates both before (first-round) and after (second-round) a virtual meeting. For each of these 180 estimates, we calculated the panel median, range, and mean absolute deviation from the median. Based on these calculations, items were classified into areas of agreement and disagreement. Agreement was defined when ≥9 panelist ratings were within 1 mean absolute deviation from the median. Items were categorized as "some disagreement" when 6–8 ratings were within 1 mean absolute deviation from the median and "more disagreement" when ≤5 ratings
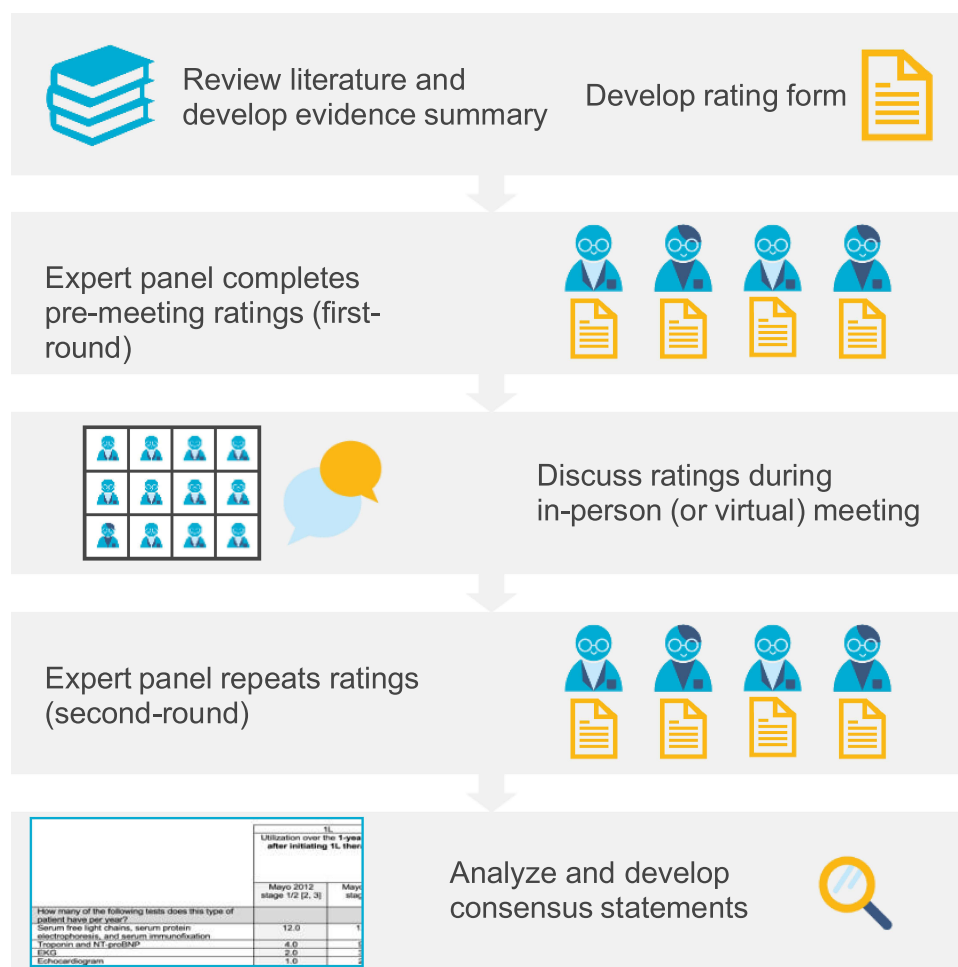
Figure 1 RAND/UCLA modified Delphi panel process.

were within that range. The median of items in the second-round ratings was used to estimate healthcare utilization. In Table 1, we report utilization estimates for patients with renal involvement. Utilization estimates for patients without renal involvement are presented in the Supplemental Appendix.

This study was non-interventional and did not involve human subjects as defined in 45 CFR part 46, thus ethical institutional review board (IRB) approval was not required. All panelists are included as authors of this manuscript and agree to the publication of the Delphi panel results.

Results

Before the meeting, out of 180 items rated, 38% (n = 68) were agreed on by the panel; 48% (n = 86) were classified as "some disagreement" and 14% (n = 26) were classified as "more disagreement". Following the meeting, 64% (n = 116) of items were agreed on (a substantial increase typical with the modified Delphi panel method); 33% (n = 60) were classified as "some disagreement" and only 2% (n = 4) were classified as "more disagreement." Considering only the 1L period, 68% (41/60) of utilization estimates were agreed upon and, during the post-1L period, 62.5% (75/120) were agreed upon.

1L Period
Treatments
Across patients, most were treated with a recently approved[17] daratumumab-containing regimen (93% of advanced patients and 90% of non-advanced patients).

Table 1 Utilization Estimates

	IL		Post-IL			
	Utilization Over the 1-Year Period After Initiating 1L Therapy[a]		**Utilization Over the 1-Year Period after completing 1L Therapy in Patients Who Have a Complete/Very Good Partial Hematologic Response[a]**		**Utilization Over the 1-Year Period after completing 1L Therapy in Patients Who Have a Partial/no Hematologic Response, or the 1-Year Period After Relapse [a]**	
	Mayo 2012 Stage 1/2[b,c]	**Mayo 2012 Stage 3/4**	**Without Cardiac Involvement**	**With Cardiac Involvement[d]**	**Without Cardiac Involvement**	**With Cardiac Involvement[d]**
How many of the following tests does this type of patient have per year?						
Serum free light chains, serum protein electrophoresis, and serum immunofixation	12.0	12.0	4.0	6.0	12.0	12.0
Troponin and NT-proBNP	4.0	9.0	2.0	4.0	3.5	7.0
EKG	2.0	3.5	1.0	2.0	1.0	2.5
Echocardiogram	1.0	2.0	1.0	2.0	1.0	2.0
How many patients out of 100 would be treated with the following in 1 year?[e]						
Daratumumab (dara) containing regimen	90.0	92.5	25.0	42.5	50.0	50.0
Other non-dara containing chemotherapy	12.5	12.5	10.0	10.0	55.0	60.0
Hematopoietic stem-cell transplantation	30.0	5.0	10.0	3.0	22.5	10.0
How many patients out of 100 would have the following in 1 year?						
Bone marrow biopsy/aspiration	25.0	25.0	5.0	5.0	50.0	50.0
Pacemaker or Implantable Cardioverter Defibrillator (ICD) placement	1.5	15.0	0.0	10.0	0.0	10.5
Heart transplant	0.0	1.0	0.0	1.5	0.0	2.5
Kidney transplant	0.0	0.0	4.0	1.0	0.0	0.0
Carpal tunnel syndrome release	5.0	4.0	5.0	2.0	5.0	4.0
Initiation of chronic dialysis	5.0	7.0	5.0	7.0	10.0	10.0
Any amyloidosis related inpatient admissions	12.5	55.0	5.0	20.0	15.0	42.5
Two or more amyloidosis related inpatient admissions	5.0	37.5	2.5	10.0	6.0	20.0

Notes: [a]May or may not have an organ response to their 1L treatments. [b]During 1L, non-advanced patients were those with Mayo stages 1/2 while advanced were those with Mayo stages 3/4. Post-1L, non-advanced patients were those without cardiac involvement while advanced were those with cardiac involvement. Additional utilization values for different subgroups are provided in Supplemental Appendix. [c]Revised Mayo 2012 model: stage 1 troponin ≥0.025 µg/L, NT-proBNP ≥1800 ng/L, dFLC ≥180 mg/L. For each stage, stage 1 is absence of any risk factors; stage 2 is presence of 1 risk factor; stage 3 is presence of 2 risk factors; and where applicable, stage 4 is all risk factors present. [d]Elevated troponin and/or NT-proBNP. [e]For each treatment, estimate the proportion of patients who are on this regimen regardless of the other treatments they may also be on.

HSCT is the only category where utilization was higher in non-advanced patients. Five percent of advanced patients had HSCT compared to 30% of non-advanced patients, as advanced patients are often too sick to undergo this procedure.

Procedures and Laboratory Tests

Initiation of chronic dialysis was higher among advanced patients (7%) than non-advanced patients (5%). Experts estimated 15% of advanced patients would have a pacemaker or implantable cardioverter defibrillator placed, compared to 2% of non-advanced patients. Laboratory tests unrelated to cardiac function (eg, serum free light chains) occurred with similar frequency across all patients (12 times per year). Advanced patients had more echocardiograms per year than non-advanced patients (2 vs 1). There was no difference in rates of bone marrow biopsies between advanced and non-advanced patients (both 25%).

Hospitalizations

Hospitalization, a key driver of cost, was higher in advanced patients: 55% would be hospitalized (ie, any amyloidosis-related inpatient admissions including renal, cardiac, other) at least once during the year and 38% two or more times. Frequency of hospitalizations among non-advanced patients was lower (13% once and 5% two or more times).

Post-1L Period

Treatments

Similar to the trend observed during the 1L period, fewer advanced patients with CR/VGPR had HSCT (3%) compared to non-advanced patients (10%) in the post 1L period. This difference was also observed in patients with PR/NR or relapse where non-advanced patients were approximately twice as likely to have a HSCT compared to advanced patients (23% vs 10%, respectively). Across both levels of severity, a greater proportion of patients with PR/NR or relapse were treated with a daratumumab-containing regimen (50% advanced and non-advanced) compared to patients with CR/VGPR (43% advanced, 25% non-advanced).

Procedures and Laboratory Tests

Among both advanced and non-advanced patients with CR/VGPR, 5% had a bone marrow biopsy. In patients with partial/no response or relapse, the estimate was much higher at 50% for both groups. Across both levels of response, advanced patients had up to 10 times the number of pacemaker/ICDs inserted (10% with CR/VGPR and 11% with PR/NR or relapse) compared to 0% in non-advanced patients. Among patients with CR/VGPR, initiation of chronic dialysis remained similar to the 1L period (7% advanced, 5% non-advanced). Those with PR/NR or relapse had similar estimates (10% among both advanced and non-advanced). The number of serum free light chain tests was higher among patients with PR/NR or relapse regardless of renal involvement (12 per year) than those with CR/VGPR (6 per year in advanced, 4 per year in non-advanced). Similar to the 1L period, echocardiograms occurred more frequently in advanced patients (2 per year), compared to non-advanced patients (1 per year) in both CR/VGPR and PR/NR or relapse patients.

Hospitalizations

Estimates of hospitalizations varied by hematologic response. Among patients with CR/VGPR, 20% of advanced patients were admitted at least once and 10% at least twice, compared to 5% and 3% of non-advanced patients, respectively. The same pattern was observed among patients with PR/NR or relapse: 20% of advanced patients had at least two admissions compared to 6% of non-advanced patients.

Discussion

AL amyloidosis is associated with significant morbidity and substantial healthcare utilization. As a result of the rarity of the condition and recent changes in the treatment paradigm, the precise nature of the healthcare utilization burden of AL amyloidosis has not been well characterized. Using the modified Delphi panel method, we found that pacemaker/ICD placements, initiation of chronic dialysis, and hospitalizations (generally key drivers of utilization and cost) were more common among advanced than non-advanced patients. Even in the setting of CR/VGPR, panelists estimated advanced patients would be more likely to have cardiac-related testing and procedures (eg, echocardiograms, pacemaker placement) as well as hospitalizations. These findings highlight the need for new treatment options that can clear amyloid from

organs in order to facilitate organ recovery and improve function, which may lead to decreased healthcare utilization among advanced patients.

HSCT is a major driver of cost because it typically results in a lengthy hospital stay.[18] HSCT was less common among advanced patients because most are not medically fit enough to tolerate it.[19] In our study, only 1–5% of these patients received this therapy 1L, compared to 30% of non-advanced patients. It is used as a potentially curative 1L treatment and salvage in later line thus increasing healthcare utilization across all disease stages. With newer therapies demonstrating higher rates of CR, we anticipate rates of HSCT to decrease.[16]

Our estimates of hospitalization are broadly consistent with earlier ones, which reported 26%[20] and 50%[5] of patients with at least one inpatient admission per year. However, it is difficult to make detailed comparisons because prior studies did not compare hospitalizations by stage and used data from an earlier treatment era.

This study has limitations. Our utilization estimates reflect the opinion of 11 clinical experts and one patient advocate. To mitigate this limitation, we used a well-validated, formal process. The modified Delphi panel process[20] is a valid method to gain clinical insight where this is emerging evidence.[21–24] This process is consistent with elicitation methods recently recommended as best practice for healthcare decision-making and for conducting health technology assessments.[14] Test-retest reliability (the same panelists repeating ratings at a later time) is high and independent panels reach similar conclusions. Experts were provided with a systematic review of the literature on which to base their initial estimates and the estimates were refined by consensus. The timing of the panel meeting might also have affected results. The meeting occurred less than a year after the Food and Drug Administration's approval of daratumumab for AL amyloidosis. Panelists found it challenging to estimate rates of daratumumab use in patients with PR/NR or relapse because they may have received 1L treatment before or after daratumumab approval.

Routinely collected (or "real world") data are commonly used to estimate utilization. When administrative data lack key measures such as disease stage, researchers may turn to data derived from electronic health records to estimate utilization. But as AL amyloidosis affects no more than 10–14 people per million, even data sources with millions of records are inadequate to produce reliable cost and utilization estimates. Further, the effects of changes to the treatment paradigm can take years to be reflected in these data sources. Utilization data may be collected from medical records although outpatient medical records often lack information on inpatient care (potentially the most expensive component), care provided by other specialists, or care at geographically dispersed locations.

Conclusion

Our expert consensus-based estimates of healthcare utilization in patients with AL amyloidosis may be the most accurate currently available. We hope these estimates contribute further understanding of the healthcare utilization and burden of this rare condition until actual real-world measurements are available to help contextualize the development of new therapies to reduce utilization and subsequent costs.

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