Linking changes in quality of life to haematologic response and survival in systemic AL amyloidosis

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Abstract

This study reports HRQL among newly-diagnosed AL patients (n=914) treated with a bortezomib-based regimen and its association with response depth and survival. Haematologic response/HRQL were assessed over 24 months in an ongoing, prospective study. HRQL change was calculated across haematologic/cardiac response levels. The relationship between baseline HRQL and survival was evaluated by the Cox proportional hazard model (PH). Shared random effects models (SREMs) estimated time-to-death conditional on current HRQL/longitudinal HRQL trajectory. At 3 months, there was consistent decline in 5/8 HRQL domains across all haematologic response levels. By 12 months, 3/5 declining domains improved among complete response (CR) patients. In contrast, the mean change in less-than-CR patients did not indicate improvement. Under the Cox PH, having a baseline HRQL score 5 points > sample mean was associated with 20% lower mortality risk. SREMs indicated a 5-point greater HRQL score at the event time correlated with a ~30% decrease in mortality risk. For each 1-point increase in HRQL score trajectory slope, mortality risk decreased by ~88%. Only CR patients had HRQL improvement, while partial response patients had less decline but no meaningful improvements. These data show the importance of HRQL serial assessments of AL patients and its importance as an endpoint.

Introduction

Immunoglobulin light chain (AL) amyloidosis is a rare, multi-systemic disorder, frequently affecting multiple organs, with the heart and kidneys being the most commonly Subcutaneous daratumumab, in combination with bortezomib, cyclophosphamide, and dexamethasone, has been recently approved in the United States (U.S.) and Europe for treatment of AL amyloidosis.[1,2] With the rapid expansion of agents available for the treatment of plasma cell neoplasms and their adoption for treatment of AL, it is expected that patient outcomes will improve further, building upon the increases in survival observed over the past 20 years.[3,4]

AL amyloidosis is often treated with anti-plasma cell treatment regimens targeting light chain production. A profound reduction in light chains is needed to halt ongoing organ damage and to allow for the slow macrophage-led clearance of amyloid deposits, ultimately leading to improved organ function. Treatment response assessment requires evaluation of both haematologic and organ response;[5] however, robust assessment of treatment benefit in subgroups with the same organ involvement profile remains challenging due to the rarity of the disease. Capturing global improvement in a patient's condition is an important objective that has yet to be studied thoroughly in this multisystem disease.

Although depth of haematologic response translates to improved symptoms and survival,[6] treatments remain poorly tolerated and are sometimes associated with worsening of symptoms.[7] The combined net effect on both survival and tolerability may be captured through patients' own evaluations of their treatment experiences. Poor tolerance of treatment negatively impacts health-related quality of life (HRQL) and, conversely, effective treatments lead to improvements in HRQL over time.[8,9,10] Despite reports of HRQL scores following treatment initiation, there is no data on the impact of depth of haematologic response (the key determinant of patient outcomes) on HRQL. Similarly, although studies have also shown that pre-treatment HRQL scores are prognostic of

survival,[8,11] it is currently unknown whether depth of HRQL response impacts the likelihood of survival, similar to what has been reported for haematologic response.[6]

This study evaluates changes in HRQL in a cohort of newly-diagnosed patients who were participants in a large, real-world study of AL amyloidosis treated with upfront bortezomib-based therapy (AL amyloidosis chemotherapy [ALchemy]). Previous analyses of treatment response and survival among patients with AL amyloidosis treated with bortezomib showed that those achieving haematologic responses, especially deep responses, had durable response to treatment: 78% of patients were still alive and 71% had not progressed to further treatment at 5 years.[12] Despite these excellent survival and disease progression treatment-related outcomes, the impact on HRQL has not been evaluated among patients receiving bortezomib-based therapy. The present study evaluates the association of baseline HRQL and change in post-therapy HRQL, with depth of haematologic response[13] and survival, in this cohort.

Methods

Patients

Data come from a cohort of newly-diagnosed patients with AL amyloidosis from the UK National Amyloidosis Centre, who were participants in an ongoing, prospective study, Alchemy (REC Reference Number: 09/H0715/58), and treated with upfront bortezomib-based regimens. Over 95% of the patients in the cohort received cyclophosphamide-bortezomib-dexamethasone with remainder receiving bortezomib-dexamethasone or bortezomib-thalidomide-dexamethasone. HRQL data were collected from patients participating in ALchemy and then linked to clinical data including biomarkers, treatment outcomes (i.e., haematologic or organ response), disease progression, and vital status (death). Haematologic response was assessed at approximately 3, 6, and 12 months following treatment initiation and HRQL was collected at baseline, 3, 12, and 24 months. Haematologic responses were assessed by the international amyloidosis consensus criteria[14], and

categorized into the following: no response (NR), partial response (PR), very good partial response (VGPR), and complete response (CR). CR was defined as negative serum and urine immunofixation and normal serum-free chain ratio (0.26-1.65). VGPR was defined as dFLC < 40 mg/L, and PR was defined as > 50% dFLC reduction. Organ involvement and organ response were established as per amyloidosis consensus criteria.[5,14] Patients who completed the SF-36v2® Health Survey (SF-36v2) at baseline were included in the current study. Approval for analysis and publication was obtained from the National Health Service institutional review board; written consent was obtained from all patients in accordance with the Declaration of Helsinki.

HRQL Measure

HRQL was measured using the SF-36v2, a generic, self-report survey that takes 5-10 minutes to complete. Responses to the SF-36v2 result in scores for 8 dimensions of functional health and well-being: Physical Functioning (PF), Role-Physical (RP; role limitations due to physical problems), Bodily Pain (BP), General Health Perceptions (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE; role limitations due to emotional problems), and Mental Health (MH).[15] In addition, 2 summary scores (Physical Component Summary [PCS] and Mental Component Summary [MCS]) are calculated through a linear combination of the 8 domain scores. All SF-36v2 scores are scored to have a mean of 50 and a standard deviation of 10 based on the U.S. general population. Thus, scores above and below 50 are above and below the U.S. general population average, respectively, with higher values on all SF-36v2 scores implying better HRQL. Interpretation of group differences and individual changes in SF-36v2 scores can also be made using thresholds that have been developed for this purpose.[15] The current study uses these values to better interpret findings related to HRQL scores.

Statistical Analysis

Mean change from baseline for every SF-36v2 score was calculated to evaluate changes in the HRQL of patients experiencing different levels of haematologic response. The primary analyses relied on all available cases at 2 timepoints where haematologic response and HRQL were both assessed: 6 and 12 months after treatment initiation**.** A secondary set of analyses relied on the subset of patients who were alive at least 24 months after baseline. HRQL change was also evaluated among patients with and without cardiac response, as cardiac involvement is highly prognostic of survival.

Another key objective of the current study was to evaluate the relationship between HRQL and survival in the ALchemy cohort. PCS was used as the HRQL score for these analyses for 2 key reasons. First, it aggregates information from multiple HRQL domains, making it an ideal score to assess the trajectory related to global physical well-being. Additionally, it exhibits a greater variability, making it a more tractable score for fitting more complex models. The relationship between HRQL and survival was first investigated using a Cox proportional hazard (PH) model using baseline PCS as the covariate. However, since the primary goal was to estimate whether differences in patients' HRQL trajectories (and not just the initial HRQL level) significantly impacted probability of survival, additional models were needed to account for the longitudinal variation present in repeated HRQL assessments and the dependence of probability of survival on HRQL scores. For these reasons, subsequent models were based on shared random effects models (SREMs).[16] In this approach, the true individual HRQL trajectory is estimated using a random effects model and then used as a time-dependent covariate in a Cox model. The 2 models share random effects, which induce correlation between the longitudinal and survival components. A linear mixed effects sub-model was used to fit the longitudinal process (the HRQL trajectory). The survival process was modeled using a parametric proportional hazards model, with a Weibull baseline hazard. The association structure was set up by assuming that the time-to-death depended not just on the current HRQL value but also on the rate of change of the HRQL trajectory, while allowing for time-independent covariates. This specific

parameterization was selected through an assessment of significance of model parameters and comparison of 2 measures of model fit, Akaike's information criterion (AIC), and Bayesian information criterion (BIC),[17] for different ways of modeling the survival process.

To illustrate the impact of baseline HRQL scores on the probability of survival, the results of the PH model were graphically depicted by evaluating the probability of survival according to 3 different baseline PCS values: 1) the sample mean; 2) 10 points (1 standard deviation) below the sample mean; 3) 10 points above the sample mean. Similarly, in addition presenting parameter estimates from the SREMs, the impact of HRQL trajectory on the estimated survival was illustrated by depicting the estimated survival at the study assessment visits (baseline and 3 post-treatment assessments) for a selected patient in the study cohort.

To overall prognostic value of HRQL, baseline PCS was estimated using Harrell's concordance index[18], which measures the discriminatory accuracy of biomarkers for a single survival outcome. This measure was also evaluated for 2 common AL amyloidosis clinical markers. In biomedical applications, Harrell's concordance index often ranges between 0.6 and 0.75, with a value of 0.5 representing no predictive value.[19]

Statistical analyses were conducted using SAS/STAT software, Version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA) and R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria, JM package, version 1.4-8).[20]

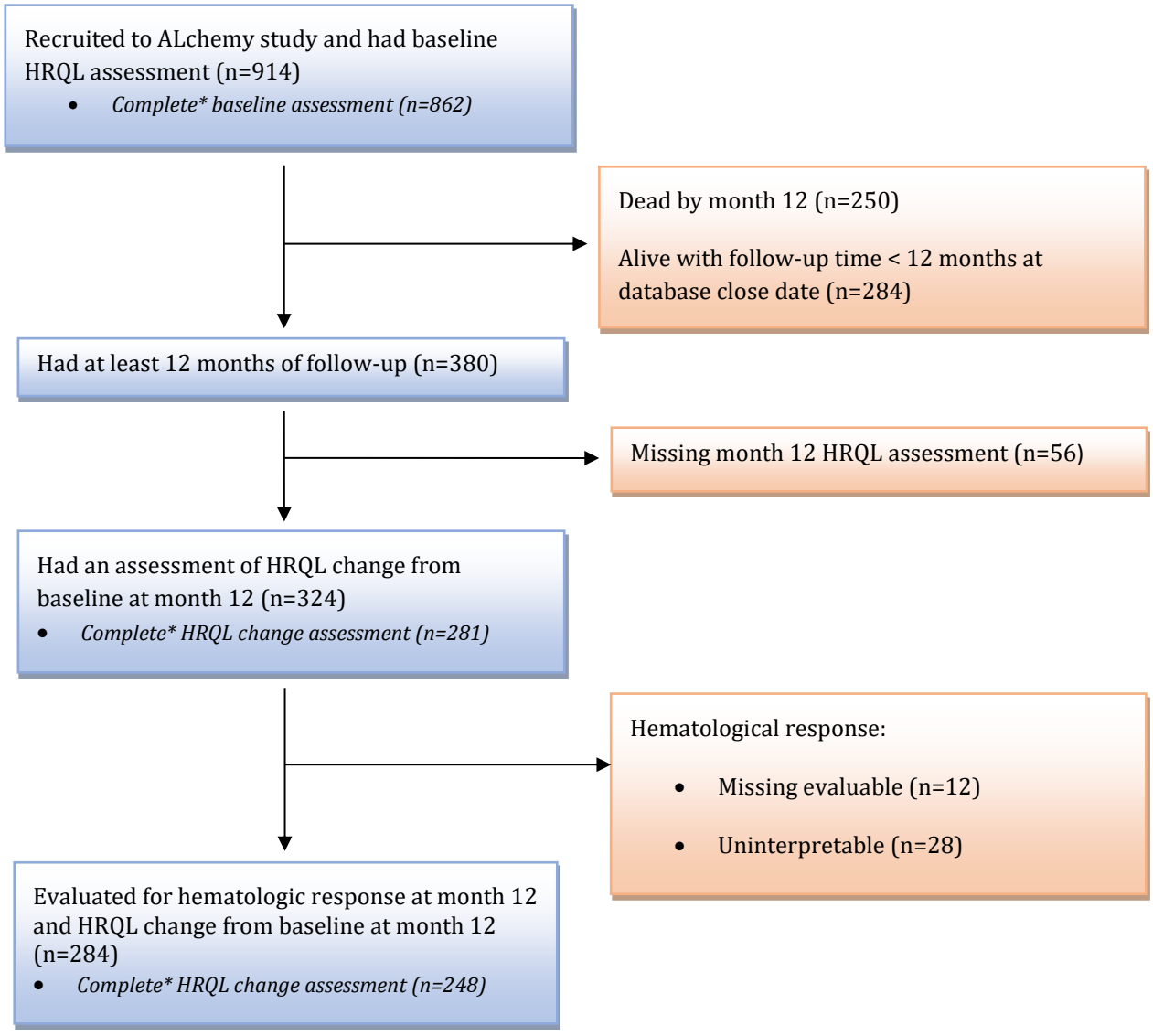
Results

Patients

Data from 914 patients were used in the analyses (Table 1). Approximately 40% of patients were female, and median age was 69 years (range, 39-90). Cardiac involvement was present in 63% (n=578) of patients, 69% (n=628) had renal involvement, and 38% (n=347) had both heart and renal

involvement. Based on the European modification of Mayo 2004 Staging,[21] patients were classed as: Stage I (n=153; 17%), Stage II (n=309; 34%), Stage IIIa (n=337; 37%), and Stage IIIb (n=106; 12%). Median N-terminal probrain natriuretic peptide (NT-proBNP) and dFLC were 2,097 ng/L (range, 0-70,000) and 180 mg/L (range, 0-15,898), respectively. A total of 328 patients died during the study period, with 76.2% (n=250) of these dying within 12 months of initiating treatment (Figure 1). A total of 380 were observed through a period of 12 months or longer following treatment initiation, but among these, 56 did not complete the 12-month HRQL assessment, leaving a total of 324 patients for whom change in HRQL from baseline to month 12 could be evaluated. The demographic and clinical characteristics of the 56 patients who were excluded due to missing HRQL data as well as the 324 patients for whom such evaluation was possible are provided in a supplementary file. Briefly, with few exceptions, the 324 patients were in most respects similar to the entire sample of 914: lower median NT-proBNP was observed among the final HRQL analytic sample (1,223 ng/L compared to 2,097 ng/L for the full sample) as well as a lower percentage of patients in the most severe disease stage (1.5% or 5 patients were EU modified 2004 Mayo Stage IIIb compared to 11.6% in the full sample). The 56 patients who were excluded due to missing HRQL data were slightly older than the HRQL analytic sample (median age of 73 versus 68) and had an even gender distribution (50% were male compared to 62% in the HRQL analytic sample). At the 12-month study visit, a total of 284 patients were assessed for both HRQL and haematologic response (Figure 1). The percentage of patients with CR or VGPR at 12 months was 63% (n=102 and n=78, respectively; Table 2). Organ response, evaluated 12 months following treatment initiation, indicated that among the 181 patients with cardiac involvement at baseline and a HRQL change score at 12 months, 152 had evaluable data (uninterpretable: n=20; missing: n=9) and 71 (39.2%, on an intent to treat basis) had a cardiac response (Table 2).

185 Figure 1. CONSORT Diagram Depicting Patient Flow



*Complete assessment indicates that all SF-36v2 scores could be calculated

Table 1. Baseline Characteristics (N=914)

Characteristic	Median (range) or n (%)
Age	69 (39-90)
Males/females	560 (61.3)/ 354 (38.7)
ECOG class±	
0	220 (24.1%)
1	321 (35.1%)
2	268 (29.3%)
3	42 (4.6%)
Not recorded	63 (6.9%)
Cardiac involvement	578 (63.2%)
NT-proBNP (ng/L)	2,097 (0-70,000)
Disease Stage (EU Modif. 2004 Mayo Staging)	
I	153 (16.7%)
II	309 (33.8%)
IIIa (NT-proBNP=8500 ng/L)	337 (36.9%)
IIIb (NT-proBNP>8500 ng/L)	106 (11.6%)
Not recorded	9 (1.0%)
Systolic blood pressure	118 (0-190)
Renal involvement	628 (68.7%)
CKD stage¥	
1	190 (20.8%)
2	325 (35.6%)
3	246 (26.9%)
4	107 (11.7%)
5	40 (4.4%)
Not recorded	6 (0.7%)
Palladini Stage§	
Stage I	182 (19.9%)
Stage II	278 (30.4%)
Stage III	133 (14.6%)
Not recorded / No renal involvement	321 (35.1%)
Proteinuria, g/24 h	3 (0-33)
Estimated glomerular filtration rate, mL/min)	64 (10-100)
Creatinine, µmol/L	96 (27-1,077)
Liver involvement	119 (13.0%)
Soft tissue involvement	146 (16.0%)
Peripheral nerve involvement	85 (9.3%)
Autonomic nerve involvement	86 (9.4%)
Gastrointestinal involvement	44 (4.8%)
Other organ involvement	2 (0.2%)
Number of involved organs	1 (1-4)
6 Minute Walk Test (meters)	350 (0-708)
Difference between involved and free light chains	
< 20 mg/L	65 (7.1%)
20-50 mg/L	56 (6.1%)
> 50 mg/L	737 (80.6%)
Not recorded	56 (6.1%)

Abbreviations: CKD, Chronic kidney disease; ECOG, Eastern Cooperative Oncology Group; GFR=Glomerular filtration rate; NT-proBNP, N-terminal probrain natriuretic peptide;

‡ECOG Classes: 0 – Asymptomatic; 1 – Symptomatic but completely ambulatory; 2 – Symptomatic, <50% in bed during the day; 3 – Symptomatic, >50% in bed, but not bedbound

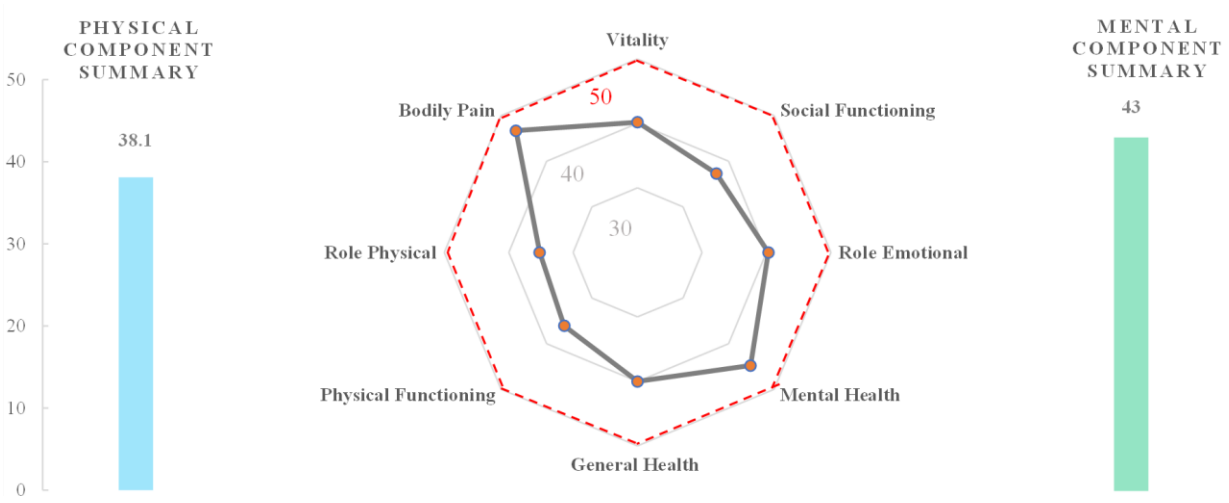
¥CKD stage: 1= GFR 90 or higher; 2 = GFR 60-89; 3 = GFR 30-59; 4 = GFR 15-29; 5 = GFR < 15

§Palladini Stages: I: both proteinuria ≤5 g/24 h and eGFR ≥50 mL/min per 1.73 m^2; II: either proteinuria >5 g/24 h or eGFR <50 mL/min per 1.73 m^2; III: both proteinuria >5 g/24 h and eGFR <50 mL/min per 1.73 m^2

Quality of Life Scores

SF-36v2 scores indicated large decrements in HRQL at baseline, with mean scores ranging between 35.2 (RP) and 46.7 (BP) across the 8 domains (Figure 2). At baseline, patients in this study presented with greater impacts on physical health, with a mean PCS of 38.1, more than 10 points below the normative mean of 50 points, whereas mean MCS was 43.0.

Figure 2. Health-Related Quality of Life at Baseline: SF-36v2 Scores



Note: All SF-36v2 scores can be interpreted with respect to a value of 50 representing the mean of the U.S. general population, with higher values implying better HRQL

Change in HRQL across Haematologic Response Status

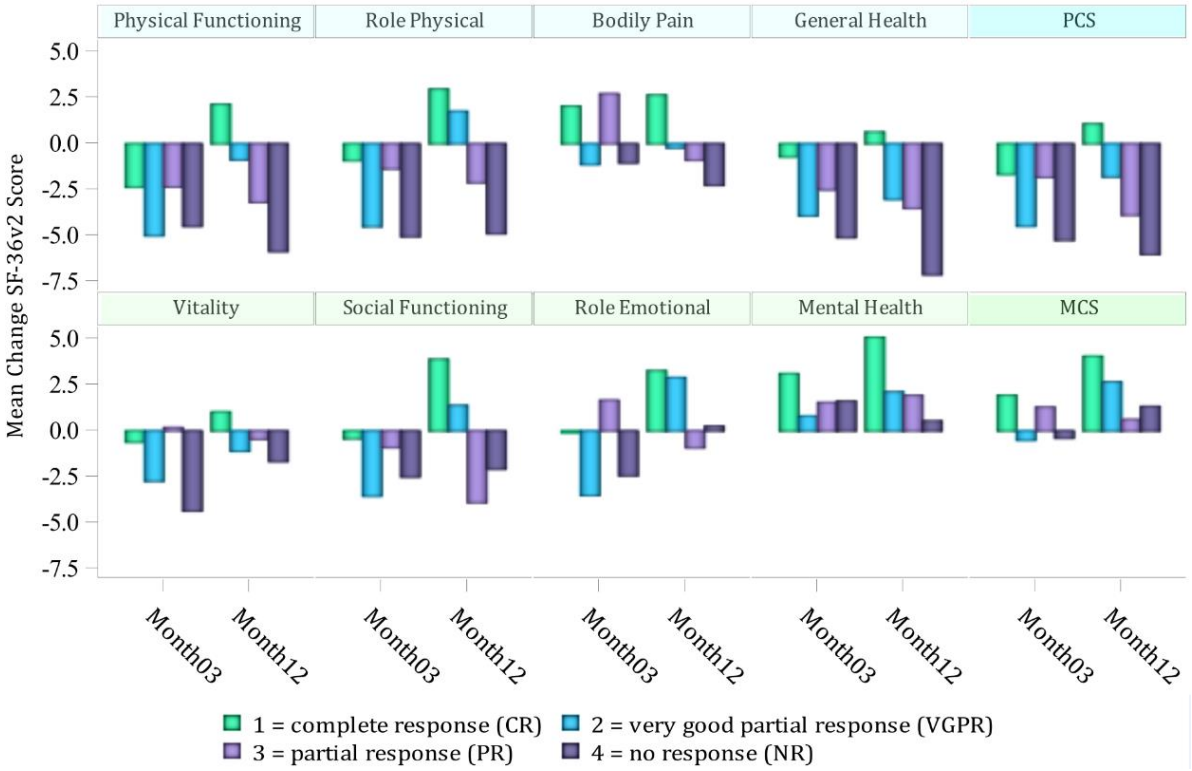
HRQL assessments 3 months following treatment initiation indicated that patients primarily experienced a decline in HRQL at that time, with PCS declining on average by -3.6 points, a value that exceeds the minimum for meaningful within-person change for this score[15] (3.4 points). By month 12, among patients who remained alive and had a HRQL measurement, PCS had declined by an

average of -2 points relative to baseline. BP, MH, and MCS showed a slightly different pattern, with change being minimal.

Across levels of haematologic response, mean change (Δ) in HRQL domains after 3 months of treatment indicated a consistent absolute decline for all groups in 5 of the 8 SF-36v2 domains—PF, RP, GH, VT, and SF (Figure 3) —as well as in PCS. However, by month 12, patients with CR reported improvement in 3 SF-36v2 domains (Figure 3; Table 2): PF (Δ = 2.1; n=101), RP (Δ = 2.9; n=99), and SF (Δ = 4.4; n=100). Further, patients who *remained* in CR through month 24 reported further substantial improvement in HRQL: PF (Δ = 3.3; n=46), RP (Δ = 5.5; n=45), and SF (Δ = 8.0; n=44). In contrast, the mean change in other response groups was not indicative of improvement. Among patients with VGPR, improvement was either absent or too small to be considered meaningful (Δ < 2 points); mean change among patients with PR or NR indicated a decline in HRQL across nearly all domains (Figure 3). These trends were unchanged when only patients surviving ≥ 24 months were included.

Cardiac response at 12 months was associated with improvement in HRQL across all SF-36v2 scores, although differences in BP, VT, MH, and MCS did not reach the clinically-relevant levels (< 2 in all cases). In agreement with results for haematologic response, the largest gains were observed in PF (Δ = 4.2), RP (Δ = 5.5), and SF (Δ = 5.9). Differences between those achieving a response and those who did not were equally largest in these domains of HRQL.

228 Figure 3. Mean Change from Baseline in SF-36v2 Scores by Haematologic Response



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230 Note: Change from baseline to the study visit concurrent with haematologic response assessment

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Table 2. Mean Change from Baseline to Month 12 in SF-36v2 Scores by Haematologic and Cardiac Response (Observed Cases)

SF-36v2 Score*†	Haematologic Response: Complete Response (n=102)	Haematologic Response: Very Good Partial Response (n=78)	Haematologic Response: Partial Response (n=67)	Haematologic Response: No Response (n=37)	Cardiac: Response (n=71)	Cardiac: No Response (n=81)
PF	**2.07**	**-0.88**	-3.39	-5.31±	**4.15**	-1.38
RP	**2.93**	**1.76**	-2.55	-3.85	**5.49**±	0.49
BP	**2.69**	-0.23	-1.39	-1.67	2.02	0.28
GH	**0.30**	**-3.03**	-3.99	-5.89	**0.77**	-2.37
VT	**1.39**	-1.11	-1.08	-2.35	1.76	1.23
SF	**4.36**	1.39	-4.41	-1.53	**5.93**	1.35
RE	3.50	2.90	-1.07	0.40	4.15	2.04
MH	**5.39**	2.12	1.48	-0.29	4.90	3.61
PCS	**0.86**	**-1.81**	-4.23±	-4.89±	**2.35**	-1.93
MCS	**4.55**	2.66	0.17	0.66	4.29	3.67

Note: Mean changes in SF-36v2 scores across haematologic response levels were based on 284 patients; mean changes in SF-36v2 scores across levels of cardiac response were based on 152 patients; values shown in bold font indicate a difference from the "No Response" group ≥ (in absolute value) the smallest value indicating a meaningful between-group difference.

* Smallest values indicating a meaningful individual-level change: PF, 4.3; RP, 4.0; BP, 5.5; GH, 7.0; VT, 6.7; SF, 6.2; RE, 4.6; MH, 6.7; PCS, 3.8; MCS, 4.6

† Smallest values indicating a meaningful group-level difference: PF, 3; RP, 3; BP, 3; GH, 2; VT, 2; SF, 3; RE, 4; MH, 3; PCS, 2; MCS, 3

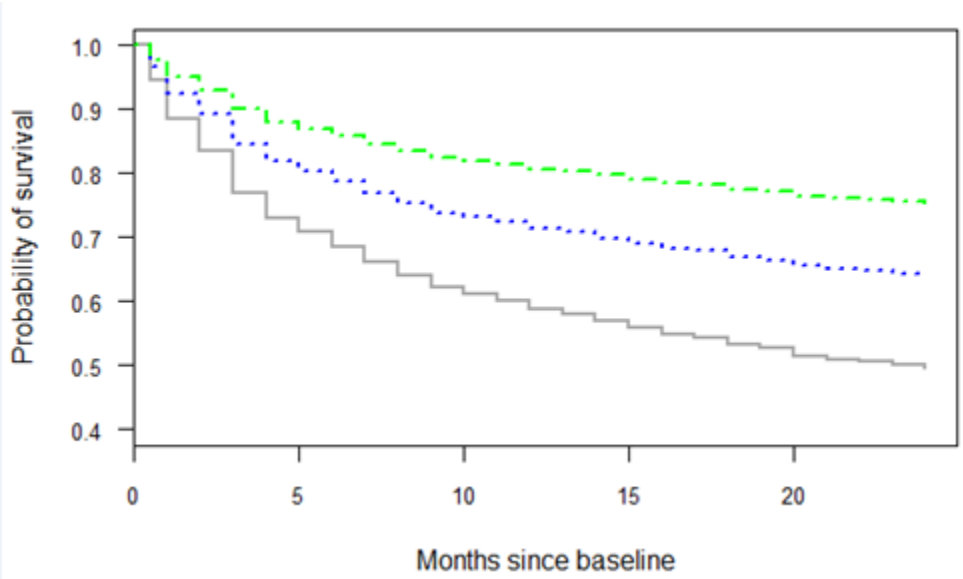
± Indicates an average within-person change ≥ the smallest meaningful individual-level change.

Abbreviations: BP, Bodily Pain; GH, General Health Perceptions; MCS, Mental Component Summary; MH, Mental Health; PCS, Physical Component Summary; PF, Physical Function; RE, Role Limitations due to Emotional Problems; RP, Role Limitations due to Physical Problems; SF, Social Functioning; VT, Vitality

246 ***Value of HRQL Assessment on Prediction of Survival***

247 Under the traditional Cox PH model, a 2-point higher PCS baseline score, a value approximately equal
248 to the MID, was associated with a decrease in the death hazard of approximately 9% (hazard ratio =
249 0.087; 95% confidence interval = [0.903, 0.923]; $p < 0.001$). Figure 4 presents the estimated survival
250 curve through 24 months for baseline PCS scores equal to the sample mean (38 points), as well as 10
251 points below, and 10 points above, the sample mean. There is a clear inverse relationship between
252 baseline PCS and the probability of survival, with the 3 curves being well-separated almost the entire
253 24-month period. Smaller differences in PCS scores similarly translate into significant differences in
254 outcomes: a patient with a baseline PCS score 5 points greater than the sample mean of 38, has a 20%
255 lower mortality risk. In terms of overall prognostic value, baseline PCS alone performed reasonably
256 well, resulting in a value of 0.66, based on Harrell's measure of prediction accuracy[18] (for reference,
257 this measure is slightly below that of NT-proBNP, at 0.72, and slightly above left ventricular global
258 longitudinal strain, at 0.62, 2 common AL amyloidosis clinical markers).

259 Figure 4. Predicted Survival through 24 Months as a Function of Selected Baseline PCS Values



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261 Baseline PCS equal to: 28 points ; 38 points (sample mean); 48 points

262 Abbreviation: PCS, Physical component summary

To evaluate the impact of the entire HRQL trajectory on survival, we used an approach where the impact of both the level and the change of HRQL on the risk of death, was estimated using a joint model. The main model estimated the HRQL longitudinal process based on a quadratic function of time; the estimated latent HRQL trajectory was then used to model the survival process (model 1). A likelihood ratio test (LRT) comparing this model with a simpler model that included just the level of PCS (but not the change), indicated that modeling the effect of change provided a significantly better fit (LRT = 20.03; $p < 0.001$). A second model was fit, in which, in addition to the latent HRQL trajectory, baseline PCS was used to model the probability of survival (model 2). Table 3 shows the estimated parameters corresponding to the sub-models under the shared random effect approach, for models 1 and 2. Results for model 1 indicated that a 5-point greater PCS at the time of the event is associated with a decrease in the risk of death of about 30% ($\exp(5 \times (-0.070)) = 0.701$). Further, for each 1-point increase in the trajectory of PCS, the risk of death decreases by about 88% ($\exp(-2.111) = 0.121$). For model 2, which included baseline PCS as a time-independent covariate in addition to the latent estimated PCS score and its change, only the former remained statistically significant (expected due to the high correlation). Nevertheless, it is instructive to note that HRQL trajectory was a significant predictor of survival in both models. While model 2 resulted in slightly better measures of model fit (AIC and BIC are both smaller for model 2 than for model 1), these differences were small.

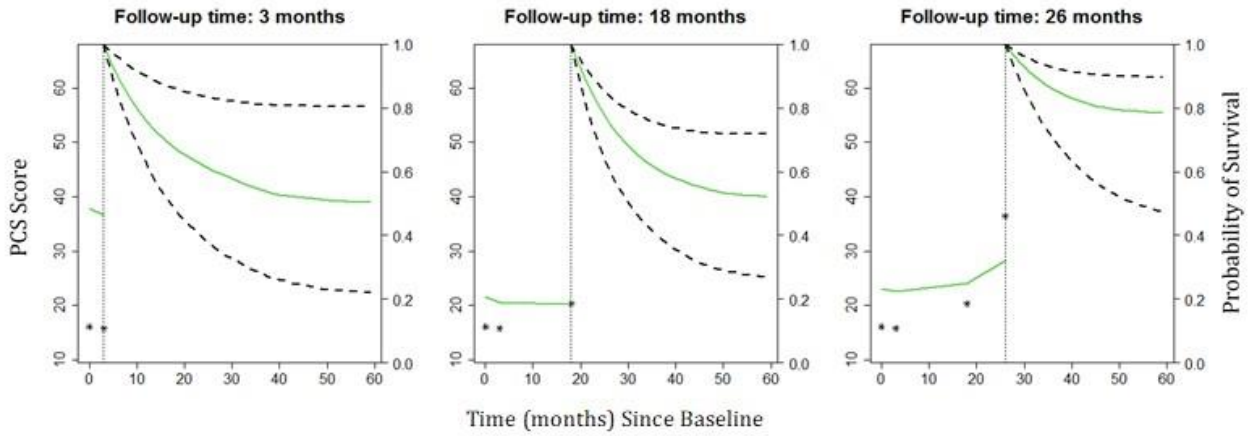
Table 3. Joint Modeling of Longitudinal PCS and Survival: Estimated Model Parameters

Parameter	**Model 1**			**Model 2**		
Longitudinal Process	**Estimate**	**SE**	**p**	**Estimate**	**SE**	**p**
Intercept	37.697	0.348	<.0001	37.852	0.346	<.0001
Months since baseline	-0.360	0.066	<.0001	-0.353	0.075	<.0001
Squared months since baseline	0.013	0.003	<.0001	0.015	0.004	<.0001
Survival Process						
PCS score	-0.070	0.010	<0.0001	0.039	0.030	0.2020
Change in PCS score	-2.111	0.857	0.0138	-2.588	0.820	0.0016
Baseline PCS				-0.076	0.022	0.0005
AIC	*15,509*			*15,497*		
BIC	*15,562*			*15,554*		

Note: N = 881; number of deaths = 315 (35.8%)
Abbreviation: AIC, Akaike's information criterion; BIC, Bayesian information criterion; SE = standard error

To illustrate how the model can be used to link HRQL trajectory and survival, we calculated the survival probabilities of a selected patient from the ALchemy sample over time, based on model 1. The figure below (Figure 5) shows how the survival curves are updated (right side of each plot) as new measurements in PCS (left side of each plot) occur over time. For this patient, 4 PCS measurements occurred: baseline, and 3, 18, and 26 months after treatment initiation. Figure 5 shows this patient followed a trajectory reflective of the overall pattern observed in the study with a slight initial decline in PCS followed by subsequent improvement. Consequently, the estimated survival (based on the median prediction) changes over time. For example, the estimated probability of survival at 48 months changes from 49% at 3 months (PCS = 15.8), to 53% at 18 months (PCS = 20.3), and 79% at 26 months (PCS = 36.4).

Figure 5. Longitudinal PCS Assessments and Conditional Survival Probabilities for a Selected Patient



Note: The vertical dotted line represents the time of the last HRQL measurement, with PCS scores up to this point shown to the left, and median survival (95% confidence interval in dashed lines) shown to the right

Abbreviation: PCS, Physical component summary

Discussion

This study evaluated whether meaningful changes in HRQL are associated with deeper haematologic response or increased survival among a large sample of patients with AL amyloidosis treated with upfront bortezomib-based regimens. At baseline, patients in this study reported significant impairment of baseline HRQL levels which were generally in line with those of previously published studies.[22]

Although reports exist that evaluate HRQL in patients with AL amyloidosis pre- and post-treatment, none to our knowledge have evaluated a link between depth of haematologic response and HRQL. Our results indicated that patients with CR report meaningful HRQL improvement after 1 year of treatment, reflected primarily in functioning domains (physical, role, and social functioning). Patients in other response levels, including VGPR and PR, did not, on average, report meaningful HRQL gains, in fact, patients in PR reported a decline in HRQL. Of patients with cardiac involvement, those who achieved a cardiac response reported a similar profile of response across the various domains of

HRQL, with a focus on the same 3 functioning domains. For the first time, we can show that deep responses to treatment translate to the patients "feeling better," which is not only a key goal of therapy but also one of the important evaluable aspects of therapy's effectiveness by global regulators. However, improvement takes time – there was no gain in HRQL at 3 months, and then it continued to improve to 24 months (the latest time point assessed in this study) – highlighting both benefits of the current therapies but also the limitations.

One important finding of this study was the marked decline in HRQL at early time points (3 months) and these results are similar to those from the Medical College of Wisconsin (MCW) and Mayo Clinic (MCW/Mayo cohort) study also showing significant worsening in multiple HRQL domains from baseline to 3 months.[8] Other studies have also recognized that patients may have early symptomatic and biomarker deterioration before improvements, particularly those with advanced amyloidosis.[23] In the MCW/Mayo cohort study, both physical and mental summary scores, as well as those for physical and fatigue domains, indicated meaningful worsening in the first 3 months following treatment initiation. Nevertheless, after 12 months, PRO scores were improved compared to the lowest decline at 3 months, suggesting overall trajectories similar to the ones observed in the current cohort. Despite this similarity, reports from the MCW/Mayo cohort study on the association between haematologic response and HRQL were limited to the comparison of cross-sectional scores across patients with VGPR (n=22) and those without VGPR (n=15).[8] Our results expand on those previously reported results. The striking fact was that only patients achieving CR had true improvement in HRQL and those with VGPR had less decline but no consistent improvements. It is established that organ responses in amyloidosis are linked to the depth of haematologic response. The results emerging from the current analyses show for the first time that patients' HRQL is concordant with those data. This raises important questions about the goals of therapy in AL amyloidosis – the final goal of any treatment is to improve HRQL. Since CR was the only depth of response correlating with improved HRQL, it supports recent publications which have shown substantially better outcomes and longer

times to next treatment in patients achieving CR; we now show that it also links with improved HRQL. This has important implications in planning future trials in AL amyloidosis with anti-plasma cell agents, where CR or better must be the treatment goal (rather than CR/VGPR which was considered adequate). With respect to differentiation across the various HRQL domains, our results indicated that, while most SF-36v2 domains were impacted by treatment, those related to physical functioning, namely PF, RP, and SF, ranked more highly in magnitude of change and were also more clearly linked to depth of haematologic response, which is in agreement with previous studies[24,25].

Previous studies have also examined the role of PRO scores as predictors of survival and disease progression. In the MCW/Mayo cohort,[8] it was concluded that nearly all HRQL domains were associated with higher risk of mortality; baseline scores in Anxiety, Depression, and Fatigue were associated with higher risk of 1-year mortality. These results are similar to those reported from the Boston University Amyloid Center's AL amyloidosis cohort.[10,22] In that study, it was shown that worse pre-treatment SF-36v2 PCS scores were associated with a greater risk of mortality in patients who received transplant or non-transplant chemotherapy, and that fatigue independently predicted survival in addition to stage and transplant.[11] Nevertheless, no prior studies established the value of sequential HRQL assessment in the prognosis of survival. Despite being limited in number, clinical markers in our study, such as NT-proBNP, fared similarly to HRQL in terms of prognostic value, showing that HRQL scores and their trajectories help predict survival and characterize treatment response.

In conclusion, our study indicates that HRQL assessment is an essential element in predicting survival and characterizing treatment response, with only CR being associated with meaningful HRQL improvement. It should be noted that the assessment instrument used in our study was developed with the general population in mind, while recent studies[26,27] have provided measurement frameworks that more fully reflect the experiences of AL amyloidosis patients and new tools[28] have

emerged that will likely be better suited to this patient population. Future studies should incorporate measurement of HRQL into the evaluation of treatment benefit, using instruments that specifically target concepts and symptoms that more fully reflect those most important to patients with AL amyloidosis.

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Data Sharing Statement

The authors are unable to share raw data due to patient confidentiality and consent limitations.

Conflicts of Interest Statement

The authors declare no competing financial interests.

Author Contributions

Oliver Cohen contributed to the paper by providing its conceptualization, by leading data curation, and by reviewing and editing drafts. Regina Rendas-Baum conceptualized the paper and the study's methodology, performed formal analyses, and wrote the paper. Kristen McCausland aided in the paper's conceptualization and reviewed and edited drafts. Darren Foard, Richa Manwani, Sriram Ravichandran, Helen Lachmann, Shameem Mahmood, Brendan Wisnioski, Philip Hawkins, and Julian Gillmore were involved in reviewing, editing, and approving the final paper. Kristen Hsu and Sabrina Rebello provided study funding and reviewed and edited the paper. Ashutosh Wechalekar was an investigator in the trial on which this study data is based, provided the resources necessary for analysis, and reviewed and edited the paper.

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