



# Adjuvant doxycycline to enhance anti-amyloid effects: Results from the dual phase 2 trial

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## ARTICLE INFO

### Article History:

Received 5 March 2020

Revised 16 April 2020

Accepted 20 April 2020

Available online xxx

### Keywords:

Doxycycline

Systemic light chain amyloidosis

Early mortality

## ABSTRACT

**Background:** Although, doxycycline use is associated with improved outcomes in amyloidosis in retrospective studies, evidence from clinical trials is limited.

**Methods:** This phase 2 trial of doxycycline (clinicaltrials.gov: NCT02207556) in newly diagnosed light chain (AL) amyloidosis enrolled 25 patients with systemic AL amyloidosis on treatment with doxycycline for 1 year along with chemotherapy. Outcomes of interest included mortality, organ response, and hematologic response rates at 1 year.

**Findings:** The median age was 62 years, 64% were male, and 68% had the AL lambda subtype. Patients had Mayo 2012 stage 3 in 24% and stage 4 in 28%. Cardiac involvement was present in 60% of patients, renal involvement in 72%, and 60% patients had 3 or more organs involved. Target organ was cardiac in 14(56%), renal in 7(28%), hepatic in 1(4%) and soft tissue in 3(12%). At 1 year, mortality was 20% (95% confidence interval, 8.9–41.6%) and organ response was 36% (18–57%). Hematologic response in 1-year survivors was 100%, including 30% complete and 55% very good partial response. Autologous hematopoietic cell transplant was performed in 60%; among transplanted patients, day-100 transplant-related mortality was 0. Doxycycline use was safe and not attributed to any grade 2 or higher toxicity.

**Interpretation:** In addition to a low 1-year mortality, doxycycline use was safe and associated with high transplant utilization rate. We thus contend that doxycycline should be studied in a placebo-controlled study in newly diagnosed AL patients in the first year, particularly among patients with advanced disease and cardiac involvement.

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## 1. Introduction

The amyloidoses are a diverse group of protein misfolding diseases wherein deposits of insoluble amyloid fibrils occur [1]. Immunoglobulin light chain (AL) amyloidosis is one of the most common subtypes of systemic amyloidosis, with an estimated incidence of 9.7 to 14 cases per million person-years in the United States [2]. This disease is associated with high morbidity and early mortality as current AL therapies are primarily directed at the underlying plasma cell clone producing the pathogenic light chain with chemotherapy and/or stem cell transplant [3]. There are no known effective fibril-directed therapies in AL which results in an inevitable delay and

unpredictability in organ response even after hematologic response is established. Light chain amyloidosis is also a disease of delayed diagnosis [4]. Both, delayed diagnosis and lack of fibril-directed therapies, result in a disease associated with high early mortality.

Early mortality is a significant problem in AL amyloidosis. Data from the Mayo Clinic showed that AL amyloidosis was associated with nearly 40% mortality in the first year after diagnosis with no improvement from 1977 to 2009, and more recently between 2010 and 2014 at ~35%, despite the availability of more effective chemotherapies during this time period [5,6]. Patients with advanced cardiac amyloidosis are known to have even higher early mortality. The staging system for amyloidosis which is heavily weighted by the severity of cardiac involvement shows that patients with stage 4 amyloidosis have 1-year mortality of upwards of 60% [7]. Strategies to lower early mortality and restore organ function are thus critically needed in order to improve outcomes for AL patients in the first year after diagnosis. There is a high interest in amyloid-directed therapies

The results of this study were reported in part as a poster at the 60th Annual Meeting of the American Society of Hematology.

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<https://doi.org/10.1016/j.eclinm.2020.100361>

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## Research in Context

**Evidence before this study:** Systemic AL amyloidosis is a difficult disease to treat. The disease is often associated with delayed diagnosis with over half of patients being advanced stage at diagnosis. While there are many chemotherapeutic drugs that can control the underlying plasma cell neoplasm, these have no effect on the insoluble amyloid fibrils. Consequently, in the first year after diagnosis, mortality rates of 30–40% are reported. Decreasing early mortality in AL amyloidosis is an unmet need. Doxycycline has been reported to have anti-amyloid properties. Before writing our clinical protocol in October 2014, we reviewed all publications using PubMed and Google Scholar on doxycycline and amyloidosis. This search was updated on November 15, 2018. All abstracts were reviewed in detail by AD.

**Added value of this study:** This trial is the first one to prospectively study the added benefit of doxycycline in conjunction with chemotherapy in newly diagnosed systemic AL amyloidosis. Doxycycline is readily available and cheap. Our results show a low early mortality in AL patients, as well as consequent high stem cell transplant utilization, which was safe and associated with 0 transplant-related mortality. Doxycycline use was safe and not associated with undue toxicity.

**Implications of all the available evidence:** Our study confirms preclinical and retrospective clinical evidence regarding benefit of doxycycline in AL amyloidosis. A randomized clinical trial would be the next step in proving the benefits seen in our study are caused by doxycycline. Our study lays the groundwork for doing a larger multicenter randomized trial. Until such a study is performed, these results provide evidence for clinicians to use doxycycline in newly diagnosed systemic AL amyloidosis patients through the first year of treatment.

and 3 fibril-directed therapies have been tested including NEOD-001 and anti-SAP antibody, both of which were discontinued due to lack of benefit [8] or change in benefit/risk profile [9] and CAEL-101 [10] which is currently under investigation.

Doxycycline has been shown to have beneficial properties in amyloidosis for many years. This effect has been shown *in vitro* studies of tetracyclines and A beta amyloid [11], *in vivo* mouse models in transthyretin (ATTR) [12] and AL amyloidosis [13]. It is thought that matrix metalloproteinase (MMP) inhibition by doxycycline is associated with its fibril-directed properties [14]. Doxycycline use was also supported by a retrospective report of survival benefit in AL amyloidosis patients who underwent hematopoietic cell transplantation and received doxycycline compared to penicillin antimicrobial prophylaxis in those who had a hematologic response to transplant [15]. Similar findings were reported by the National Amyloidosis Center in the United Kingdom where patients with advanced AL amyloidosis treated with doxycycline in addition to chemotherapy had lower early mortality when compared to historical controls [16].

In ATTR, a phase 2 study from Pavia, Italy showed that oral doxycycline 100 mg twice daily combined with tauroursodeoxycholic acid administered for 12 months was safe and associated with stability in cardiomyopathy and neuropathy impairment [17]. A more recent Canadian trial using doxycycline and ursodiol in ATTR cardiomyopathy showed a 11% rate of discontinuation with no change in functional class of heart failure, cardiac biomarkers or echocardiographic parameters at a follow up of 22 months [18]. Since the natural history of ATTR cardiomyopathy is much longer (years to decades), any benefit of doxycycline would likely be difficult to establish compared with AL amyloidosis where early morbidity and mortality is high. We hypothesized that doxycycline use will be safe and efficacious in improving early mortality compared to the standard of care therapy

in AL amyloidosis. We conducted a phase 2 prospective clinical trial, DUAL (Doxycycline to Upgrade response in AL amyloidosis), to study the safety and efficacy of doxycycline combined with plasma cell-directed therapy in newly diagnosed AL amyloidosis. In this paper, we report the results of patients with systemic AL amyloidosis treated on study.

## 2. Methods

### 2.1. Study design

This was a single center, single arm, open label, phase 2 clinical trial evaluating the safety and efficacy of oral doxycycline for one year in newly diagnosed AL amyloid patients treated additionally with the standard of care anti-AL therapy. The study was performed after approval by the Medical College of Wisconsin Institutional Review Board in accordance to the provisions of the Declaration of Helsinki guidelines. All patients provided written informed consent. It is registered under ClinicalTrials.gov with the identifier NCT02207556.

### 2.2. Participants

All newly diagnosed systemic AL amyloidosis patients who had not been started on systemic chemotherapy or doxycycline and seen at our cancer center during the study period were screened and approached for enrollment.

### 2.3. Eligibility

Inclusion criteria required a diagnosis of biopsy-proven AL amyloidosis with measurable amyloid organ involvement of a vital organ. Adult patients aged 18 or older were eligible and required to have a creatinine clearance of >25 ml/min. A negative pregnancy test was required for women of child-bearing potential. Patients with severe malabsorption, known intolerance or allergy to doxycycline, and prior chemotherapy for AL were excluded.

### 2.4. Procedures

#### 2.4.1. Study intervention

Oral doxycycline monohydrate 100 mg twice daily was administered and continued for one year as long as there was no contraindication to take doxycycline. Patients were counseled regularly to use appropriate sun protection though what was used was not mandated. Patients were followed monthly with a physician visit, performance status assessment, monoclonal protein studies, free light chain assay, cardiac biomarkers, along with routine blood counts and comprehensive metabolic panel. Patients completed a health-related quality of life (HRQL) assessment at monthly visits. At 3 monthly intervals, assessment of the target organ was included, additionally a 2-dimensional echocardiogram in patients with cardiac involvement, liver span in patients with hepatic involvement, and 24-hour urine protein assessment in patients with renal involvement.

#### 2.5. Response assessment

Patients were staged using the 2012 revised staging system [7]. The consensus guidelines for the conduct and reporting of clinical trials in systemic AL amyloidosis [19] were followed. Cardiac, renal, and hepatic organ involvement, hematologic and organ response/progression criteria were designated using the consensus guidelines and the revised criteria for response [20]. Target response was assigned based on which organ was involved. If cardiac involvement was present, the target organ was considered cardiac, followed by renal followed by hepatic.

## 2.6. Correlative studies

**Matrix metalloproteinase activity-** we obtained MMP-1, MMP-3, MMP-8, MMP-9, MMP-10 and tissue inhibitors of matrix metalloproteinases (TIMP)-1 levels at baseline, 6 months and 12 months of doxycycline.

**Health-related quality of life-** we followed HRQL using the Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Survey. The Global Physical Health and Global Mental Health summary score were calculated and analyzed.

## 2.7. Statistical analysis

**Sample size calculation:** An exact single-stage phase 2 design was considered. If the experimental regimen of doxycycline combined with chemotherapy were no more effective than conventional chemotherapy alone with an assumption that the true probability of organ response at 1 year is 25% (p0) and the probability of organ response with doxycycline would be 50% (p1), in statistical terms, we tested the null hypothesis H0:  $p \leq 0.25$ , versus the alternate H1:  $p \geq 0.5$ , where p is the probability of organ response. For 80% power to detect the designed difference in organ response at 1 year at a 5% significance, we needed 26 patients. We increased the sample size by 15% to account for patients with advanced disease who may die prior to response. **Stopping/safety rules:** Development of grade 3–4 adverse events related to doxycycline in 6 or more patients mandated halting further patient accrual until review by the Data Safety Monitoring Board.

## 2.8. Outcomes

The primary outcome of this study was to evaluate early mortality rate with doxycycline in systemic AL amyloidosis. Early mortality was defined as death due to any cause within the first year after diagnosis. Secondary outcomes included organ response/stable rates at 6 and 12 months and hematologic response rate at 12 months. The 6- and 12-month cumulative organ response rates with 95% confidence intervals were reported. Kaplan-Meier estimates were used to estimate overall survival.

For MMP activity analysis, a mixed model was developed to study changes compared to baseline testing in addition to the effect of time, stage, organ response and transplant status. A p-value of  $<0.05$  was considered significant and was adjusted for multiple comparisons using the Dunnett-Hsu method [21]. Similarly, HRQL was analyzed using a latent mixed models to account for within-patient correlations with repeated measures as well as missing data due to death.

Statistical analysis was conducted using SAS v9 (Cary, NC).

## 2.9. Role of funding source

An American Cancer Society Institutional Research Grant # 86–004–26 funded the clinical trial enrollment, drug procurement, and follow up. Correlative studies were performed using funds from a KL2 TR001438 and K23 HL141445.

## 3. Results

The study enrolled between December 2014 and July 2017. The study enrolled 31 patients: 25 systemic and 6 localized AL amyloidosis. However, owing to differences in detecting responses and low early mortality in localized AL, the results of the localized AL will be reported separately. Table 1 shows the baseline characteristics of enrolled patients. The median age was 62 years, 64% were male, and 68% had the AL lambda subtype including 1 patient with AHL (mu lambda). Stage was advanced with stage 3 in 24% and stage 4 in 28%

**Table 1**  
Baseline patient characteristics.

Characteristic	Number (N = 25)
Median age at diagnosis (range), years	62.1 (38.8 - 78.4)
Race	
White	21 (84%)
African American	4 (16%)
AL subtype	
Kappa	8 (32)
Lambda	16 (64)
Mu/Lambda	1 (4)
2012 AL stage	
1	3 (12.0)
2	9 (36.0)
3	6 (24.0)
4	7 (28.0)
Median hemoglobin (range), g/dL	12.3 (9.7 - 16.5)
Median albumin (range), g/dL	3.7 (1.1 - 4.8)
Median creatinine (range), mg/dL	1.1 (0.6 - 2.4)
Median alkaline phosphatase (range), U/L	77.0 (42.0 - 498.0)
Median NT-proBNP (range), pg/ml	2564 (65.0 - 18,333)
Median troponin t (range), ng/ml	0.017 (<0.01 - 0.342)
Median kappa (range), mg/L	20 (4.2–1007)
Median lambda (range), mg/L	131.5 (5.8–588.2)
Median M-spike (range), g/dL	0.9 (0–10.1)
Median bone marrow plasma cells (range),%	15 (3–40)
CRAB criteria,%	4 (15)
Cardiac involvement,%	14 (56)
Renal involvement,%	18 (72)
Liver involvement,%	6 (24)
Peripheral nerves involvement,%	2 (8)
Autonomic nerves involvement,%	5 (20)
Gastrointestinal involvement,%	7 (28)
Number of organs involved	
1	4 (16)
2	6 (24)
≥3	15 (60)
Median follow-up of survivors (range), months	21.4 (12.2–40.3)

patients. Cardiac involvement was present in 56% of patients, renal involvement in 72%, and 60% patients had 3 or more organs involved. Median bone marrow plasma cell percentage was 15 (range, 3–40)%. The median follow-up was 21.4 (12.2–40.3) months. Target organ was cardiac in 14 (56%), renal in 7 (28%), hepatic in 1 (4%) and soft

**Table 2**  
Target organ response at 6 and 12 months.

Patient	Target organ	Organ response at 6 months	Organ response at 12 months
1	Renal	response	response
2	Cardiac	died at 4.3 months	died at 4.3 months
3	Renal	response	response
4	Cardiac	progression	died at 7.8 months
5	Cardiac	progression	response
6	Cardiac	response	response
7	Renal	progression	progression
8	Renal	stable	stable
9	Cardiac	progression	progression
10	Soft tissue	stable	stable
11	Cardiac	progression	died at 8.2 months
12	Renal	response	response
13	Cardiac	progression	progression
14	Soft tissue	stable	stable
15	Cardiac	died at 1.3 months	died at 1.3 months
16	Renal	stable	stable
17	Cardiac	response	response
18	Cardiac	died at 2.1 months	died at 2.1 months
19	Cardiac	stable	stable
20	Cardiac	stable	response
21	Hepatic	stable	response
22	Renal	response	response
23	Soft tissue	stable	stable
24	Cardiac	progression	stable
25	Cardiac	progression	stable

tissue in 3 (12%). The median NT-proBNP was 2564 (65–18,333) pg/ml and median TnT was 0.017 (<0.01–0.342) ng/ml.

All patients received induction chemotherapy with triplet combination of bortezomib, cyclophosphamide and dexamethasone (CyBorD). Doxycycline was given at 100 mg twice daily. Side-effects attributed to doxycycline use were grade 1 photosensitivity in 3 patients and clostridium difficile diarrhea in 1 patient. This patient had multiple hospitalizations for end stage cardiac failure and was found to have C difficile diarrhea during his last admission. One patient discontinued doxycycline at 5 months owing to renal amyloid progression and worsening creatinine clearance.

### 3.1. Outcomes (Table 2)

**Early mortality:** No deaths were seen in the first month, 1 (8%) at 3 months, 3 (12%) at 6 months and 5 (20%) at 12 months. Overall survival at 6 months was 92% (95% confidence interval; 71.6–97.9%) and 80% (58.4–91.1%) at 12 months. All deaths were seen in patients with stage 3 or 4 AL amyloidosis with target cardiac organ involvement. One-year survival is shown in Fig. 1.

**Organ response:** At 6 months, organ response was seen in 6 (24%), stable disease in 8 (32%), progression in 8 (32%) and death in 3 (12%). The 6-month cumulative incidence of response was 24% (9.4–45%). At 12 months, organ response occurred in 9 (36%), stable disease in 8 (32%), organ progression in 3 (12%) and death in 5 (20%). The 12-month cumulative incidence of organ response was 36% (18–57%).

**Hematologic response at 12 months:** Among patients who survived to 1 year, a hematologic response was seen in all patients including 30% complete, 55% very good partial and 15% partial response.

**Transplant utilization:** Fifteen patients underwent autologous hematopoietic cell transplantation after initial CyBorD. Among patients who underwent transplant, day 100 transplant-related mortality was 0. Of the 10 patients who did not have a transplant, 5 were those that died within year 1, all of whom presented in stage 3 or 4 AL amyloidosis with cardiac involvement. Of the remaining 5 patients, 4 patients did not undergo transplant owing to severe cardiac AL (2 with stage 3 and 2 with stage 4) and 1 patient had

coexistent myelofibrosis in addition to AL amyloidosis with coexistent multiple myeloma and therefore not felt to be an appropriate transplant candidate. Among the 15 patients who underwent transplant, 6 had cardiac involvement, including 4 patients with stage 3 or 4 AL amyloidosis. Of the 13 patients with stage 3 or 4 AL amyloidosis at diagnosis, 5 (38%) died, 4 (31%) survived but did not undergo transplant owing to transplant ineligibility and 4 (31%) underwent transplant safely.

### 3.2. Correlative studies

**MMP activity:** Serum MMP-1, MMP-3, MMP-8, MMP-9, MMP-10 and TIMP-1 expression and activity were measured at study enrollment, 6 months and end of study. Activity showed an overall effect of time with end of study with MMP-1 levels 14% higher than at enrollment (p 0.001), MMP-3 12% higher p 0.003), MMP-8 20% higher (p 0.004). These changes were more pronounced with stage 3/4 compared to stage 1/2. Transplant led to reduction MMP activity across all MMP subtypes but was statistically significant only for MMP-10 activity: estimate ratio 0.67 (95% CI 0.45, 1.00), p 0.05. Patients with organ progression had higher MMP-3 activity at 12 months compared to patients with organ response/stable disease. No changes were seen in MMP or TIMP-1 expression. (Supplementary Table 1 and Supplementary Fig. 1 for MMP analysis)

**HRQL:** PROMIS Global Physical Health and Global Mental Health summary scores were assessed at every 3 months. Average summary scores showed an initial small decline at 3 months compared to baseline after which they showed a gradual increase. A significant increase was seen for PROMIS Global Mental Health summary score over time and with organ response. (Fig. 2, Supplementary Table 2).

## 4. Discussion

Our trial studied the safety and efficacy of doxycycline in newly diagnosed systemic AL amyloidosis. High one-year mortality in AL amyloidosis is an unmet need in managing patients with this complex disease. Despite 52% of our study patients being stage 3 or 4 AL and 56% patients with cardiac involvement, we saw low early mortality in our study of just 20% at 1 year. Early mortality of only 20% has

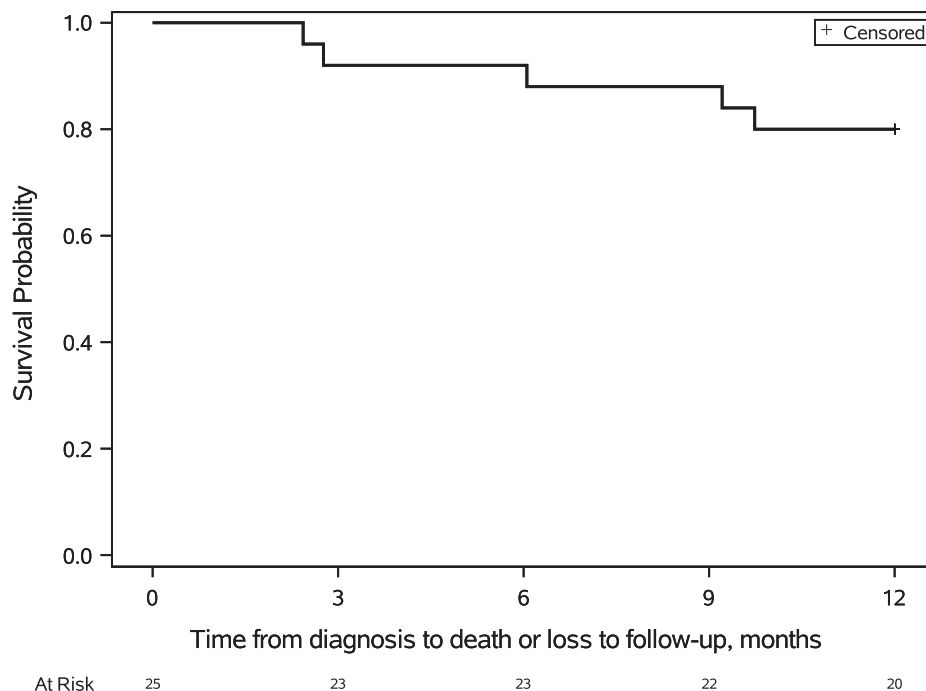
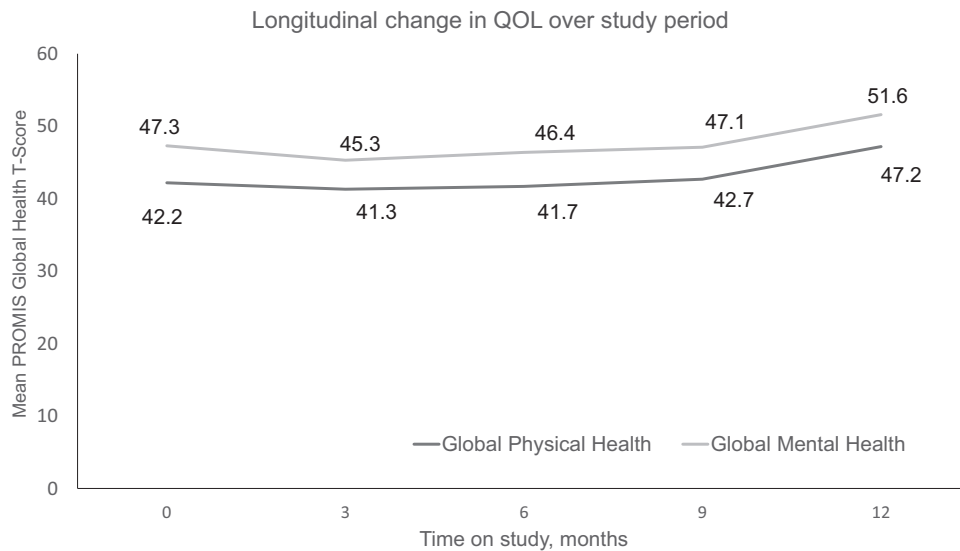


Fig. 1. Kaplan-Meier estimates of overall survival.





**Fig. 2.** Longitudinal Change in PROMIS scores over study period.

not been described before in newly diagnosed systemic AL amyloidosis. These data confirm prior retrospective evidence by Wechalekar and Whelan who showed, among 30 patients with cardiac AL when compared to 73 historical control patients, a reduction in mortality in cardiac AL with the greatest benefit in patients with Mayo stage IIIa and limited benefit in the very advanced stage patients [22].

The toxicity of doxycycline in our study was manageable and did not result in unexpected side effects beyond that of chemotherapy use. We expected photosensitivity in patients and therefore counseled patients regarding appropriate sun protection. Three patients (12%) developed photosensitivity reactions. This incidence is similar to a recently published ATTR prospective study which demonstrated 11% photosensitivity [18]. However, in our trial, these reactions were mild and self-limited without necessitating doxycycline discontinuation. One patient developed *Clostridium difficile* diarrhea during the study. However, this patient also had multiple hospitalizations related to heart failure and the positive *C difficile* test was found during a hospitalization.

Organ responses in amyloidosis follow hematologic response. Patients who have rapid and deep reduction in the involved amyloidogenic free light chain have the best organ outcomes [23]. One-year organ responses after diagnosis are not well understood as many studies such as transplant studies generally report best organ response and these exclude patients who die early as they would not get to transplant. Our study showed a target organ response of 36% and stable disease in 32%. These numbers could serve as a benchmark in other settings and trial design.

Among patients who survived to 1 year, a hematologic response was seen in all patients. Even though the type of hematologic treatment was not mandated, all patients received uniform induction with CyBorD followed by autologous hematopoietic cell transplantation when transplant-eligible. Current data suggest that only 15–20% of amyloid patients are transplant-eligible [3]. Among patients who undergo transplant, 100-day mortality can be high at 3–5% in the U.S. [24]. In our study, we noted a high autologous hematopoietic cell transplant utilization at 60%. Despite over half of the patients in this study reporting stage 3 or 4 disease, we saw high transplant utilization in this study. More importantly, the 100-day mortality among transplanted patients was 0. These data confirm previously reported retrospective data that doxycycline treatment allows greater proportion of patients to live long enough to achieve deeper clonal responses to chemotherapy [22]. Our data are also concordant to prior data showing a survival benefit among amyloid patients who received doxycycline antimicrobial prophylaxis after transplant

compared to penicillin prophylaxis in those who achieved a hematologic response [15].

Even though MMPs have been known to be markers of damage at the tissue level in cardiac and renal AL amyloidosis [25,26], serum MMP activity has never been tested in systemic AL patients to our knowledge. Because doxycycline is a potent MMP inhibitor, we tested a number of MMPs over the course of the study. While we did not observe reductions in serum MMP activity over time, we caution that because we did not have a control arm, changes that may be secondary to doxycycline may not be identified in our study design. Our results showed mild elevations in some MMP activity at the end of study compared to enrollment. We were intrigued to see that transplant led to overall reduction in MMP activity across subtypes though this was significant only for MMP-10. Organ progression was associated with higher MMP activity at 12 months compared to patients with organ response/stable disease. These exploratory results suggest that serum MMP activity may be useful biomarker of inflammation in AL disease and should be studied further in this setting.

Finally, HRQL was an important correlative objective of our study. There aren't published clinical trials in AL disease to date that have included patient-reported outcomes or HRQL as endpoints or objectives. We were not surprised to see worsening scores at 3 months as amyloidosis patients can have worsening in the first 3–6 months after diagnosis (in line with early mortality). Our results show a small but overall improvement in quality of life scores temporally after that period.

The main limitation of our study is the single arm design. Given the rarity of the disease as well as ease/availability of doxycycline, along with a single center design, it was not practical to conduct this study with a placebo arm. Thus, it is unclear whether our primary outcome is the result of doxycycline or some other 'latent' trial effect. While we intended to identify contemporaneous controls for these patients, this was heavily biased in that patients with cardiac AL and advanced disease were often placed on doxycycline by their treating physicians off protocol based on available retrospective data [15,16,22]. An additional flaw is our study design with organ response as the primary endpoint and a *a priori* hypothesis of organ response which was very arbitrarily obtained. It is unclear what the true 1-year organ response rate in systemic AL amyloidosis, as most studies report best organ response and many of these exclude patients who have already died. Moreover, our sample size calculation did not discriminate between localized versus systemic AL amyloidosis. Localized AL amyloidosis is a different disease not associated with early mortality and usually not treated with systemic chemotherapy or transplant (unless associated with lymphoma).

We therefore did not analyze these patients together and have only reported the systemic AL patients in this manuscript. Based on our statistical design, our study did not meet its primary endpoint. However, the key results of our study which included reduced early mortality, high and safe transplant utilization are unprecedented in systemic AL amyloidosis and therefore need further study. The Boston University Amyloid Center has performed a study of doxycycline in AL patients (localized and systemic) which did not show positive results and was associated with high rates of discontinuation due to photosensitivity [27]. Notably this study excluded patients with newly diagnosed systemic AL on active chemotherapy. Our trial is different from this study, especially among the systemic AL amyloidosis patients and in line with retrospective data from the National Amyloidosis Center, UK [22] and confirms their findings that any beneficial doxycycline effect may be in the first year after diagnosis of systemic AL patients, while on active chemotherapy.

In conclusion, we report the results of a phase 2 trial of doxycycline in newly diagnosed systemic AL in conjunction with bortezomib-based chemotherapy. In addition to an overall low early mortality, our study demonstrated the safety of doxycycline use along with high transplant utilization rate in AL amyloidosis. Given that our study population represented patients across all stages of disease we believe that these findings are generalizable in newly diagnosed systemic AL, although as a next step, a multicenter, placebo-controlled phase 3 study is needed. In the absence of such data, we contend that our results support the use of doxycycline in newly diagnosed amyloidosis patients in the first year of treatment, particularly among patients with advanced disease and cardiac involvement.

#### Authors' contributions

Anita D'Souza- literature search, study design, protocol development, data collection, data analysis, data interpretation, manuscript draft

Aniko Szabo- study statistical design, biostatistical analysis of data, figures, writing

Kathryn Flynn- study quality of life design, interpretation of QoL results, writing

Binod Dhakal- data collection, data interpretation, writing

Saurabh Chhabra- data collection, data interpretation, writing

Marcelo Pasquini- study design, data interpretation, writing

Dorothee Weihrauch- conducting MMP assays, MMP data interpretation, writing

Parameswaran Hari- study design, data collection, data interpretation, writing

#### Declaration of Competing Interest

AD- Grant funding and honoraria- Sanofi, EDO Mundipharma, TeneoBio, Takeda, Prothena, Pfizer, Imbrium, Akcea

BD- Grant funding and Honoraria- Takeda, Celgene, Janssen, Amgen and GSK

PH- Grant funding and honoraria – Takeda, Celgene/BMS, Janssen, Amgen, Sanofi, and Karyopharm

MP- Honoraria- Kite, Novartis, BMS, Celgene, Amgen, Medigene, Pfizer

KEF- Grant- Jazz, Incyte

AS, SC, DW have no conflicts to report

#### Acknowledgments

This study was funded by the [American Cancer Society](#) Institutional Research Grant # 86–004–26, the Research and Education Program Fund, a component of the Advancing a Healthier Wisconsin endowment at the Medical College of Wisconsin and Clinical and Translational Science Institute, and by a K23 HL141445 (AD). Its

contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. The funding was used to conduct the clinical trial.

#### Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.eclim.2020.100361](https://doi.org/10.1016/j.eclim.2020.100361).

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