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Article

The Effectiveness of Teclistamab in Patients With Relapsed/Refractory Light Chain Amyloidosis: A Multicenter Retrospective Study

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Abstract

Aims/Background: Teclistamab is a B-cell maturation antigen (BCMA)-directed bispecific monoclonal antibody recommended for relapsed/refractory multiple myeloma (RRMM) management. However, some small-scale studies support the application of teclistamab in relapsed/refractory light chain (RRAL) amyloidosis, primarily secondary to multiple myeloma (MM). Therefore, this study evaluated the efficacy and safety profile of teclistamab in daratumumab-pretreated RRAL amyloidosis patients. **Methods**: After dose escalation, 19 patients across five centers, enrolled from October 2024 to July 2025, received teclistamab at a fixed dose (60 mg, n = 13) or weight-based administration (1.5 mg/kg, n = 6). Patients were followed up, and treatment response was monitored by evaluating hematologic, hepatic, cardiac, and renal involvement, as well as by examining the associated complications. The dosing frequency was reduced as hematologic efficacy improved, adjusted by the treating physician. **Results**: At a median 4.0-month follow-up (interquartile range [IQR], 3–8), teclistamab demonstrated profound hematologic responses and organ improvement. 94.7% of patients achieved a stringent difference between involved and uninvolved free light chain (dFLC) response at a median time of 18.5 days. The weight-based and fixed-dose groups had comparable time to stringent dFLC response (median 20.5 days [IQR, 18–26] vs 17.5 days [IQR, 11–27], p = 0.385). Furthermore, 68.4% of the patients showed a significant cardiac response. Adverse events observed following treatment included cytokine release syndrome (ten events, all $\leq$grade 2), immune effector cell-associated neurotoxicity syndrome (one event, grade 1), and associated infections (ten events, 4 $\geq$grade 3). **Conclusion**: These results indicate teclistamab as a practical option for daratumumab-exposed RRAL amyloidosis, supporting that fixed-dose strategy and timely reduction of dosing frequency guided by therapeutic efficacy appear to be feasible real-world approaches.

Keywords: amyloidosis; efficacy; safety; teclistamab

1. Introduction

Systemic light chain (AL) amyloidosis is a rare plasma cell disease in which clonal plasma cells produce misfolded immunoglobulin light chains that deposit as amyloid in multiple organs [1]. Current therapeutic strategies primarily focus on inhibiting pathogenic free light chain (FLC) production, and achieving a deep, sustained hematologic response is associated with improved organ response and prognosis [2]. Over the past two decades, treatment has progressed from melphalan- and bortezomib-based chemotherapy toward targeted therapies such as daratumumab, which binds cluster of differentiation 38 (CD38) on plasma cells [3]. Although daratumumab combined with cyclophosphamide, bortezomib and dexamethasone (Dara-CyBorD) can induce rapid, profound hematologic responses and improve organ outcomes, past-daratumumab relapse or treatment resistance remains a significant clinical concern [4].

Notably, advances in multiple myeloma (MM) treatment have significantly influenced the therapeutic landscape of AL amyloidosis. Bispecific T-cell engagers targeting B-cell maturation antigen (BCMA), such as teclistamab and elranatamab, are U.S. Food and Drug Administration (FDA)-approved for relapsed/refractory MM (RRMM), and teclistamab has shown an overall response rate of 63% [5]. However, these agents carry substantial safety concerns, including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and infections [6,7]. Early evidence in amyloidosis is promising: in a 17-patient cohort with relapsed/refractory AL (RRAL) amyloidosis (includ-

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ing 10 individuals with concomitant symptomatic MM), 100% achieved ≥hematologic very good partial response (hemaVGPR) with a median time to response of 18 days, while in another 7-patient cohort (6 with concurrent MM), 88% reported at least a hematologic very good partial response with a median time of 28 days [8,9]. Despite these encouraging results, robust evidence on the efficacy and safety of teclistamab specifically in primary RRAL amyloidosis remains limited.

Therefore, this study aims to report outcomes from 19 consecutive patients diagnosed with daratumumab-RRAL amyloidosis without concurrent symptomatic MM, treated with teclistamab across five academic medical centers, to evaluate real-world safety and efficacy.

2. Methods

2.1 Study Population

This study included patients with RRAL amyloidosis who received teclistamab (JS20240024, Janssen-Cilag International NV, Beerse, Belgium) at five university hospitals in China. Patients who received at least one dose of teclistamab between 1 October 2024, and 17 July 2025, were included, and disease stage was assigned using the 2004 Mayo Clinic criteria with European modifications [10]. The data cutoff date was 6 August 2025.

2.2 Treatment Protocol and Data Collection

Teclistamab was administered subcutaneously using a step-up dosing regimen: 0.06 mg/kg on day 1, 0.3 mg/kg on day 3, and either 1.5 mg/kg or a fixed 60 mg dose on day 5, followed by weekly administration of 1.5 mg/kg (referred to as the weight-based group) or 60 mg (referred to as the fixed-dose group). Dose selection was determined by each center according to local treatment protocols. Group assignment followed the original treatment plan. For instance, the "weight-based group" included all patients initially scheduled to receive 1.5 mg/kg, even if later doses were reduced due to various reasons such as toxicity.

The dosing frequency of teclistamab is presented in **Supplementary Table 1**. Treatment intervals were dynamically adjusted over time, applying a response-adapted approach that was consistent across participating centers, aiming to reduce treatment burden and potential long-term immunosuppression. Frequency de-escalation was considered after a ≥hemaVGPR was achieved and sustained, alongside evidence of clinical stability or improving organ function. The timing of de-escalation was ultimately determined by the treating physician based on a comprehensive assessment that included the depth and durability of hematologic response, organ response trends, and patient-specific factors such as treatment tolerance and infection history.

Baseline laboratory data, prior treatment history, and efficacy and safety assessment details from each subsequent treatment cycle were retrieved from the hospital information system. CRS and ICANS were graded using the American Society for Transplantation and Cellular Therapy consensus, and managed with tocilizumab and dexamethasone in accordance with the International Myeloma Working Group guidelines [11,12]. Pre-treatment hypogammaglobulinemia was defined as an immunoglobulin G (IgG) level of ≤4 g/L [13]. All patients received prophylaxis against Herpes simplex virus and Pneumocystis jirovecii pneumonia and monthly intravenous immunoglobulin (IVIG) [14]. Infections were documented only when consistent clinical features were accompanied by objective confirmation, either microbiologic evidence (e.g., positive culture, multiplex polymerase chain reaction [PCR], or severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] testing) or radiographic findings (e.g., chest computed tomography confirming pneumonia), consistent with standard clinical practice.

2.3 Treatment Response Criteria

Hematologic response was defined as follows: for patients with a baseline difference between involved and uninvolved free light chain (dFLC) ≥50 mg/L, hematologic partial response (hemaPR) required a >50% reduction in dFLC; hemaVGPR was defined as dFLC <40 mg/L; hematologic complete response (hemaCR) required negative serum and urine immunofixation electrophoresis with a normal FLC ratio, and FLC levels; and a stringent dFLC response was defined as dFLC <10 mg/L. For patients with baseline dFLC ≥20 and <50 mg/L, only hemaCR and stringent dFLC response were assessed. An early, high-quality hematologic response was defined as achieving a stringent dFLC response within one month [15,16]. Refractoriness was defined as failure to achieve ≥hemaPR after two cycles or ≥hemaVGPR after three cycles [17]. Hematologic relapse was defined as reappearance of monoclonal protein or an abnormal FLC ratio with doubling of involved FLC (iFLC) in hemaCR; or, for patients in hemaVGPR or hemaPR, a ≥50% increase in serum monoclonal protein to >5 g/L or urine monoclonal protein to >200 mg/day with a visible peak, with a concomitant 50% increase in iFLC to >100 mg/L [15].

Cardiac involvement was defined as the interventricular septal thickness greater than 12 mm on echocardiography in the absence of other causes, or N-terminal pro-B-type natriuretic peptide (NT-proBNP) greater than 332 pg/mL without renal insufficiency [18]. Cardiac response was graded as follows: cardiac no response (carNR), <30% reduction from baseline NT-proBNP or brain natriuretic peptide (BNP); cardiac partial response (carPR), 31–60% reduction; cardiac very good partial response (carVGPR), >60% reduction; cardiac complete response (carCR), a nadir NT-proBNP ≤350 pg/mL or BNP ≤80 pg/mL [19].

Renal involvement was defined as a 24-hour urine protein excretion (24hUP) >0.5 g, predominantly albumin. Renal response was graded as follows: renal no response (renalNR), ≤30% reduction in 24hUP; renal par-

Table 1. Baseline characteristics of the study participants at teclistamab initiation.

Variable	n = 19
Male sex assigned at birth, n (%)	7 (36.8)
Age, median (IQR), years	66 (55.5–70.0)
Involved light chain, λ, n (%)	16 (84.2)
ECOG, median (IQR)	1 (1–2)
t(11;14), n (%) [a]	5 (45.5)
1q21 amplification, n (%) [b]	4 (50.0)
Mayo 2004, II/IIIa/IIIb, n (%)	13 (68.4)/2 (10.5)/4 (21.1)
Involved organs, n (%)	
Heart	19 (100.0)
Kidney	12 (63.2)
Liver	1 (5.3)
Peripheral nerve system	3 (15.8)
Gastrointestinal tract	3 (15.8)
Lab values, median (IQR)	
cTnI, µg/L	0.064 (0.039–0.101)
NT-proBNP, pg/mL	3410 (1974.75–9361.75)
24hUP, g	0.66 (0.18–1.55)
eGFR, mL/min/1.73 m^2	49 (36–72)
ALP, U/L	90 (70–107)
IgG, g/L	4.79 (2.75–7.44)
M protein, g/L	0 (0.00–1.79)
dFLC, mg/L	97 (59.47–242.20)
Number of prior lines of therapy, median (IQR)	2 (1–3)
EFS of prior daratumumab-based treatment, median (IQR), m	12.2 (6.5–27.9)
Triple class refractory, n (%)	9 (47.4)
Time from diagnosis to teclistamab initiation, median (IQR), m	17 (7.0–48.5)
EFS of the last-line therapy prior to initiating teclistamab, median (IQR), m	7.7 (5.90–12.95)

[a] Only 11 patients were tested for t(11;14).

[b] Only 8 patients had available results for 1q21 amplification.

Abbreviations: IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; 24hUP, 24-hour urine protein; eGFR, estimated glomerular filtration rate; ALP, alkaline phosphatase; IgG, immunoglobulin G; dFLC, difference between involved and uninvolved free light chain; EFS, event-free survival.

tial response (renalPR), 30–60% reduction in 24hUP; renal very good partial response (renalVGPR), >60% reduction in 24hUP; and renal complete response (renalCR), a nadir 24hUP ≤200 mg/d [20].

Hepatic involvement was defined as total liver span >15 cm or alkaline phosphatase (ALP) >1.5 times the institutional upper limit of normal, in the absence of drug-induced liver injury or biliary obstruction. Hepatic response was graded as follows: hepatic no response (hepaNR), ≤30% reduction from baseline; hepatic partial response (hepaPR), 31–60% reduction from baseline; hepatic very good partial response (hepaVGPR), >60% reduction in ALP from baseline to a nadir that remained above two times the lower limit of normal; and hepatic complete response (hepaCR), a nadir ALP ≤2× lower limit of normal [21].

Minimal residual disease (MRD) was assessed at a sensitivity of 10^{-6} according to EuroFlow protocols and standard operating procedures. Patients who died before response assessment and lacked any post-baseline assessment were categorized as having no response.

2.4 Statistical Analysis

Normality of continuous variables was assessed using the Shapiro-Wilk test. Because continuous variables do not conform to a normal distribution, they are summarized using the median (interquartile range); while categorical variables are expressed as counts (percentages). The nonparametric Mann-Whitney U test is used to compare continuous variables between two independent groups (e.g., a fixed-dose group versus a weight-based dosing group). Comparisons between categorical variable groups are performed using a continuity-corrected chi-square test. The event-free survival (EFS) for prior treatments was defined as the time from treatment initiation to disease progression, death, or start of the next treatment line; patients without these events

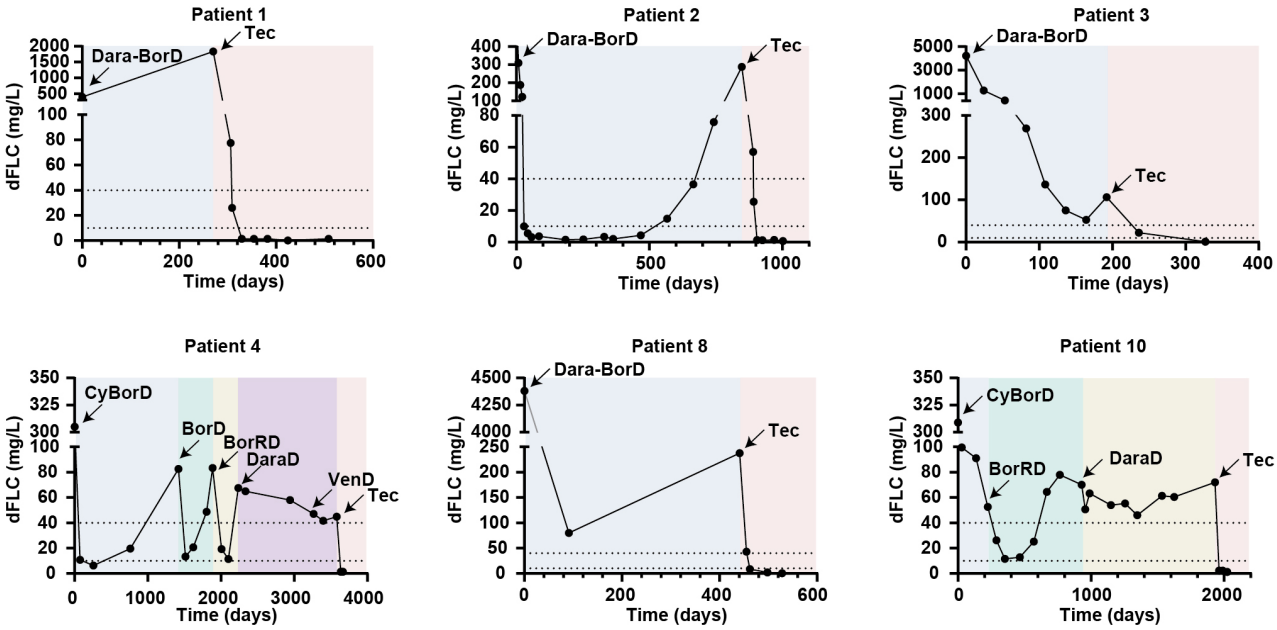


Fig. 1. Corresponding difference in free light chain (dFLC) across patients in the treatment process. Each regimen is outlined by a different shaded area color. The dashed line marks 40 mg/L and 10 mg/L dFLC for reference (Software: GraphPad Prism version 10.0 [GraphPad Software, Boston, MA, USA]). Dara-BorD, daratumumab, bortezomib and dexamethasone; CyBorD, cyclophosphamide, bortezomib and dexamethasone; BorD, bortezomib and dexamethasone; BorRD, bortezomib, lenalidomide and dexamethasone; DaraD, daratumumab and dexamethasone; VenD, venetoclax and dexamethasone; Tec, teclistamab.

were censored at the last follow-up. Overall survival (OS) was defined as the time from the start of treatment to death from any cause. OS and EFS for teclistamab treatment were generated using the Kaplan-Meier method and compared using a 2-sided log-rank test.

Univariate and multivariate logistic regression analyses were conducted to identify factors associated with infection. Variables with a p-value < 0.1 in univariate analysis were subsequently entered into the corresponding multivariate model. Before constructing the multivariate logistic regression model for infections, multicollinearity among the candidate variables was assessed using the variance inflation factor (VIF), with VIF ≥ 5 indicating significant collinearity. Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). A p-value < 0.05 was considered statistically significant.

3. Results

3.1 Baseline Characteristics of the Study Participants

Baseline characteristics at teclistamab initiation of the enrolled 19 patients are summarized in Table 1. Three patients met the SLiM ($\geq$60% clonal bone marrow plasma cells, involved/uninvolved serum FLC ratio $\geq$100, or $>$1 focal lesion on magnetic resonance imaging [MRI]) criteria but lacked CRAB (hypercalcemia, renal impairment, anemia, or bone disease) features [22]. The median age was 66 years (IQR, 55.5–70.0); seven patients were male. The median time from diagnosis to treatment initiation was 17 months (IQR, 7.0–48.5). Cardiac involvement was reported in all patients (19/19, 100%), and renal involvement in 12 (63.2%). Median baseline NT-proBNP was 3410 pg/mL (IQR, 1974.75–9361.75), and median dFLC was 97 mg/L (IQR, 59.47–242.20). Furthermore, hypogammaglobulinemia was observed in seven patients (36.8%).

Patients had received a median of two prior therapy lines (IQR, 1–3). All patients had previously received daratumumab and bortezomib. Regarding the best hematologic response to previous daratumumab-based treatment, seven patients (36.8%) achieved $\geq$hemaVGPR. The median EFS on daratumumab-based treatment was 12.2 months (IQR, 6.5–27.9). Three t(11;14)-positive patients and one t(11;14)-negative patient had received venetoclax, and one patient underwent autologous stem cell transplantation (ASCT). None of the patients had previously used anti-BCMA treatment.

Teclistamab was initiated for hematologic progression in 9 patients (47.4%). One patient started teclistamab at the treating physician's direction after 6 months of daratumumab-based treatment due to achieving hemaVGPR without accompanying organ response. The remaining 9 patients were refractory before treatment. The median EFS of the last-line therapy before teclistamab was 7.7 months (IQR, 5.90–12.95). Six patients (31.6%) received weight-based dosing, whereas 13 patients (68.4%) received fixed-dose teclistamab.

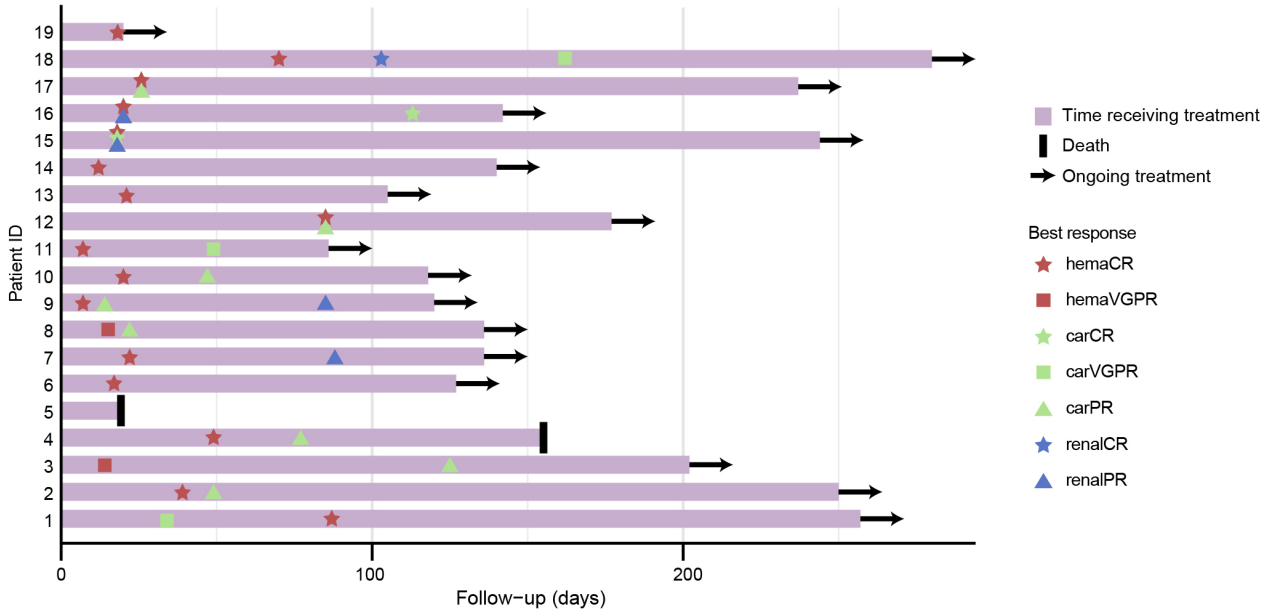


Fig. 2. Swimmer plot showing the trajectory of individual patients upon treatment with teclistamab. The purple bar represents time while receiving treatment with teclistamab. Black arrow at the end of each bar indicates that the patient was alive and remained on teclistamab therapy at data cutoff, while the black vertical segment represents the death of the patient (Software: R version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria). Best response assessment: red pentagram, hematologic complete response (hemaCR); red square, hematologic very good partial response (hemaVGPR); green pentagram, cardiac complete response (carCR); green square, cardiac very good partial response (carVGPR); green triangle, cardiac partial response (carPR); blue pentagram, renal complete response (renalCR); blue triangle, renal partial response (renalPR).

3.2 Assessment of Treatment Efficacy

At a median follow-up of 4.0 months (IQR, 3–8), patients had received a median of 4 teclistamab cycles (IQR, 3–6). Except patient 5, who had stage IIIb disease and died within one month of teclistamab initiation, the remaining 18 patients (94.7%) achieved a stringent dFLC response, regardless of t(11;14) status or 1q21 amplification. The median time to a stringent dFLC response was 18.5 days (IQR, 14.25–20.75), and 14 patients (73.7%) achieved this outcome within the first month (Fig. 1).

To assess the impact of baseline disease burden on treatment efficacy, a sensitivity analysis was conducted stratifying patients by pre-treatment dFLC. There was no significant difference in the time to stringent dFLC response between the patients with pre-treatment dFLC $\geq$180 mg/L (n = 7) and those with dFLC $<$180 mg/L (n = 11) (median 18 days [IQR, 16.0–26.5] vs 20 days [IQR, 13.0–23.5], p = 0.860).

Similarly, a sensitivity analysis was performed to evaluate the influence of the varying interval from initial diagnosis to treatment. Patients were stratified by the median time from diagnosis to teclistamab initiation (17 months). Time to stringent dFLC response was comparable between patients with a longer time to treatment ($>$17 months; n = 9) and those treated earlier ($\leq$17 months; n = 9) (median 18 days [IQR, 8–20] vs 20 days [IQR, 17–34], p = 0.222). Furthermore, no substantial difference was observed between evaluable patients receiving weight-based dosing (n = 6) and those receiving fixed-dose dosing (n = 12) (median 20.5 days [IQR, 18–26] vs 17.5 days [IQR, 11–27], p = 0.385). No baseline indicators were related to achieving an early, high-quality hematologic response (**Supplementary Table 2**).

Overall, 16 patients (84.2%) achieved hemaCR, with a median time to hemaCR of 20.5 days (IQR, 17.75–29.25), while two patients (10.5%) had hemaVGPR as their best hematologic response. MRD was assessed in four patients, all of whom were MRD-negative at the first evaluation (median 94 days, IQR, 80.75–103).

Regarding the best cardiac responses, two patients (10.5%) achieved carCR, three (15.8%) achieved carVGPR, and eight (42.1%) achieved carPR, with a median time to best cardiac response of 49 days (IQR, 26–85). Time to best cardiac response did not differ substantially between the weight-based group (n = 4) and the fixed-dose group (n = 8) (median, 69.5 days [IQR, 22.0–137.5] vs 49 days [IQR, 34–77], p = 0.825).

Moreover, among the 12 patients with renal involvement, one (8.3%) achieved renalCR and four (33.3%) achieved renalPR as the best renal response, with a median time to best renal response of 85 days (IQR, 20.00–87.25, Fig. 2). Patient 5 was the only one with hepatic involvement and was categorized as having hepaNR due to death within one month of treatment initiation.

Among the six patients with Mayo 2004, stage IIIa and IIIb disease, four achieved hemaCR, and one hemaVGPR; while four achieved carPR. However, two patients died during the treatment process, whereas all other patients remained on teclistamab at the time of analysis. At this point, the EFS curve overlapped the OS curve because no non-fatal events had occurred. OS and EFS did not differ significantly between the weight-based and fixed-dose groups (log-rank $p = 0.300$; Fig. 3).

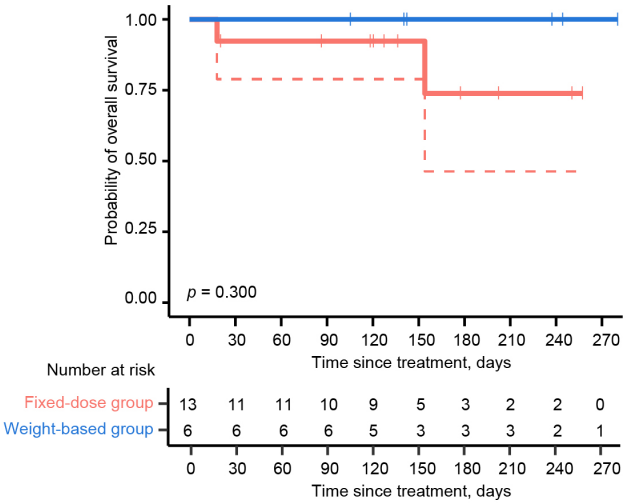


Fig. 3. Overall survival of the patient after receiving treatment. Overall survival (OS) stratified by weight-based group and fixed-dose group. The dotted line represents the 95% CI (confidence interval).

Patient 5, who had stage IIIb disease at the time of teclistamab treatment, died early within one month from sudden cardiac death. The remaining three Mayo 2004 Phase IIIb patients were alive at the time of data cutoff. Patient 4 achieved a stringent dFLC response by day 14 and carPR by day 77 but died from a pulmonary infection on day 154.

3.3 Evaluation of Treatment Safety Profile

Ten patients (52.6%) experienced ten CRS events; eight had grade 1, and two had grade 2 events. Two patients were treated with dexamethasone, five with tocilizumab and the others with nonsteroidal anti-inflammatory drugs (NSAIDs). Symptoms improved significantly within 24 hours in all cases. Patient 1 also developed grade 1 ICANS on day 3 of dose escalation, manifested as decreased ability to produce complete sentences and impaired numeracy. The patient received dexamethasone, and symptoms resolved within 3 days without recurrence.

Furthermore, ten infection events were documented in nine patients (47.4%), including one grade 1, five grade 2, three grade 3, and one grade 5, all confirmed microbiologically or radiographically. The grade 5 event occurred in patient 4, who developed pneumonia that led to death. Grade 3 infections included pulmonary infection, appendicitis, and a respiratory tract infection in patients 1, 3 and 16, respectively. Notably, COVID-19 infection was observed in three patients (15.8%). However, the incidence of infection did not differ significantly between the weight-based and fixed-dose groups (33.3% vs 53.8%, $\chi^2 = 0.114$, $p = 0.735$). No baseline variables, including age $\geq$65 years, hypogammaglobulinemia, or number of prior therapy lines at teclistamab initiation, were substantially associated with infection risk (**Supplementary Tables 3,4**). Notably, "Triple class refractory" status showed a potential association in univariate analysis (odds ratio [OR] 0.122; 95% confidence interval [CI] 0.015–0.974; $p = 0.047$), but this association was not sustained after multivariate adjustment (OR 0.122; 95% CI 0.012–1.269; $p = 0.078$). Therefore, future studies with larger sample sizes are needed to elucidate these potential risk factors.

4. Discussion

We report real-world data on the safety and efficacy of teclistamab in patients with daratumumab-RRAL amyloidosis without concurrent MM and highlight three key findings. First, teclistamab induces rapid, high-quality hematologic responses and early cardiac improvement in RRAL amyloidosis. Second, teclistamab was tolerable in this setting, with no CRS event of grade $\geq$3 and four infections of grade $\geq$3. Third, the fixed-dose (60 mg) regimen showed efficacy consistent with the weight-based regimen (1.5 mg/kg).

The efficacy observed in this study is comparable to prior RRAL amyloidosis reports. Our study showed both $\geq$hemaVGPR and stringent dFLC response rates of 94.7%, including three patients with 1q21 amplification. Two previous teclistamab-treated RRAL cohorts (7 and 17 patients) reported $\geq$hemaVGPR rates of 100% and 88%, respectively [8,9]. Another cohort of nine RRAL patients treated with teclistamab reported a $\geq$hemaVGPR rate of 89% [23]. Regarding organ responses, teclistamab achieved a cardiac response rate of 68.4% in our study, with a median time to best cardiac response of 49 days, relative to the reported rates of 75%, 23.5%, and 55.6% in three other studies [8,9,23]. Despite substantial heterogeneity in baseline disease burden, including a wide range of dFLC levels, sensitivity analysis confirmed that the time to achieve a deep hematologic response was equally rapid in patients with both high and low baseline dFLC. These observations support the potential utility of teclistamab across a diverse spectrum of RRAL amyloidosis patients in routine clinical practice.

The rapid and profound responses observed with teclistamab in this study, including a hemaCR rate of 84.2% with a median time to hemaCR of 20.5 days, are encouraging in the context of historical data. For comparison, the Dara-CyBorD regimen in newly diagnosed patients

achieved a hemaCR rate of 53.3%, with a median time to response of 60 days [24]. Furthermore, the ≥hemaVGPR and cardiac response rates of 83.3% and 66.7% observed in our high-risk (stage IIIa/IIIb) subgroup appear favorable compared to outcomes reported in a comparable risk group treated with daratumumab-based regimens [25].

Although these indirect comparisons are limited by differences in patient selection and study design, the data suggest that the depth and speed of response with teclistamab warrant direct evaluation in higher-risk cohorts. It is crucial to note that, despite some patients having previously achieved deep hematologic responses on daratumumab-based therapy, all patients had subsequently relapsed or become refractory and had measurable hematologic disease at the baseline of teclistamab initiation. Therefore, the significant and rapid hematological response observed in this study can be attributed primarily to teclistamab, with a limited likelihood of substantial residual benefit from previous treatment history.

The efficacy of teclistamab observed in our RRAL amyloidosis cohort is biologically supported by the shared clonal plasma cell origin with MM. While MM is characterized by malignant plasma cell proliferation, and AL amyloidosis by the production of misfolded light chains, both are generated by the same pathogenic plasma cell clone, rationalizing the use of plasma cell-directed therapies such as daratumumab and BCMA-targeting agents. The profound responses to teclistamab in RRMM further validate its potency against this compartment [26]. We propose that the rapid and profound hematologic responses observed in RRAL amyloidosis may be attributed to its typically lower tumor burden compared with RRMM, a less complex cytogenetic landscape, and the relatively short half-life of FLCs in amyloidosis [27,28,29]. Collectively, these features may enable teclistamab to achieve more rapid and complete clonal eradication, resulting in a swift reduction of toxic light chains and thereby supporting earlier organ improvement.

Regarding safety, CRS occurred in 52.6% of patients and ICANS in 5.3%, and both toxicities were manageable even in those with stage IIIa/IIIb disease. Previous comparative studies reported CRS rates of 57.1%, 53%, and 85.7% (all resolving rapidly), and ICANS rates of 0%, 5.9%, and 11.1%, respectively [8,9,23]. Prophylactic tocilizumab may further reduce CRS incidence and should be considered when developing future treatment plans [30]. However, compared to CRS and ICANS, the burden of infectious complications with teclistamab remains substantial in real-world settings, likely reflecting treatment-induced immunosuppression and high baseline tumor burden. Identifying factors associated with infection is therefore crucial for early preventive approaches. In RRMM, IVIG prophylaxis (hazard ratio [HR] 0.33; 95% CI 0.17–0.64; $p = 0.001$) and a history of teclistamab-associated infections (HR 1.39; 95% CI 1.11–1.74; $p = 0.004$) have been reported to predict infection risk independently [13]. Despite routine IVIG prophylaxis in our study, infection rates remained high. Extended follow-up and longer studies are warranted to assess cumulative infection risk and explore associated risk factors for better supportive care.

Consequently, there is increasing interest in strategies that minimize drug exposure while maintaining efficacy, aiming to reduce long-term toxicities such as T-cell exhaustion and infectious complications. Exploratory efforts in MM indicate that lowering the dose or administration frequency of teclistamab can maintain response durability while minimizing adverse event rates [31]. The MajesTEC-7 and MajesTEC-5 trials are investigating teclistamab-based combination therapies with reduced monthly dosing frequency in newly diagnosed MM, demonstrating manageable safety profiles and significantly high MRD negativity rates [32,33]. In our study, the fixed-dose group demonstrated rapid hematologic and organ response comparable to the weight-based group. However, due to the relatively short follow-up period, no significant difference in infection rates was observed between the dosing approaches. Validation of the comparative efficacy and safety of the two approaches will need larger cohorts and a longer follow-up observation.

Future research may proceed along several lines: First, in the contexts of clinical application, given that teclistamab induced rapid, deep hematologic and organ responses regardless of Mayo 2004 stage or 1q21 amplification, it could be assessed as consolidation therapy in patients who do not achieve hemaCR or MRD negativity after frontline daratumumab, and potentially as a candidate to replace daratumumab in first-line treatment of AL amyloidosis. Second, in the context of treatment regimen optimization, we suggest that future studies should not only define the efficacy and safety of teclistamab in RRAL amyloidosis but on exploring dose-reduction approaches and extend dosing intervals to reduce toxicity, particularly infectious events and T-cell dysfunction. Third, in resistance mechanisms, we propose that many patients who initially respond to daratumumab ultimately develop resistance, driven by mechanisms such as CD38 downregulation, clonal evolution, expansion of pre-existing subclones, and $CD8^+$ T-cell exhaustion [34]. Moreover, following BCMA-targeted chimeric antigen receptor-modified T (CAR-T) cell therapy, approximately 45% of RRMM patients relapse, primarily due to BCMA loss or low expression [35,36]. It is therefore conceivable that resistance to teclistamab will emerge as a significant concern. Concurrent mechanistic studies are required to elucidate resistance pathways, reduce their incidence, and enable a more durable response.

Despite many encouraging findings, we acknowledge several limitations to this study. First, the small sample size reduced the power to identify differential therapeutic effects and robust predictors of infection. Furthermore, the relatively short follow-up period limited full evaluation

of organ responses, and survival estimates remain preliminary due to the limited observed events. Ongoing longitudinal follow-up is underway and will enable more mature EFS and OS analyses in future data. Second, the assessment of MRD was performed in a subset of only four patients, limiting the generalizability of these findings. This was largely due to the real-world, retrospective, multiple-centers study design, in which standardized MRD monitoring protocols were not uniformly applied. Future prospective studies should prioritize systematic MRD evaluation to validate its role as a predictive biomarker for treatment response and durability in AL amyloidosis treated with teclistamab. Third, dosing frequency in the weight-based group was not strictly standardized, which could lead to heterogeneity in exposure. Fourth, there was significant baseline heterogeneity within the study cohort, which reflects the characteristics of the real-world patient population. Although sensitivity analyses reveal that this variability did not hinder the achievement of significant efficacy signals, validation in larger prospective cohorts is warranted. Finally, due to the real-world study design, bone marrow plasma cell burden was assessed at initial diagnosis. It was not systematically re-evaluated immediately before teclistamab initiation, limiting accurate characterization of the baseline plasma cell clone at the time treatment was initiated.

5. Conclusion

In summary, teclistamab induces rapid, high-quality hematologic responses and early cardiac improvement in RRAL amyloidosis. It may be particularly suitable for treating patients with high FLC levels, significantly high bone marrow plasma cell burden, or Mayo 2004 stage IIIb disease, provided that rigorous early infection prevention and strict clinical management are implemented. In real-world practice, a fixed-dose strategy and timely reduction of dosing frequency guided by treatment response appear to be practical and feasible approaches.

Key Points

• This was a multicenter trial to evaluate the efficacy and safety of teclistamab in daratumumab-related relapsed/refractory AL amyloidosis without concurrent symptomatic MM.

• Teclistamab demonstrated profound and rapid hematologic responses and a notable organ improvement in patients with RRAL amyloidosis, including those who were refractory to daratumumab.

• Fixed-dose regimens and reduced dosing frequency were feasible, offering a practical, real-world strategy to decrease treatment burden and potentially lower risks of long-term toxicity.

Availability of Data and Materials

The datasets generated during and/or analyzed during the current study are available from the corresponding authors on reasonable request.

Author Contributions

Conceptualization, KNS and JL; methodology, CYX; software, CYX; validation, LYZ and PLL; formal analysis, CYX; investigation, LYZ, CYS and PLL; resources, CYS; data curation, DHH, AG and YX; writing—original draft preparation, CYX; writing—review and editing, KNS and JL; visualization, CYX; supervision, AG and YX; project administration, KNS and JL; funding acquisition, KNS and JL. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by the ethics committees of Peking Union Medical College Hospital (approval number: I-25PJ0813). The research was performed in compliance with the terms of the Declaration of Helsinki. All patients signed informed consent forms prior to treatment.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/BJHM62006.

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