Dear editor,

Systemic amyloid light-chain (AL) amyloidosis is a rare plasma cell disorder caused by the extracellular deposition of misfolded immunoglobulin light chains as protein fibrils in tissues. This leads to vital organ damage. It is incurable and has a relapsing–remitting course. With a lack of approved treatments at relapse, therapies for relapsed multiple myeloma are used in AL amyloidosis. However, this may be challenging due to underlying organ dysfunction, most commonly cardiac and renal impairment. Most data are from the use of immunomodulatory agents and, lately, daratumumab. Options for patients who relapse after daratumumab in AL amyloidosis remain unclear.

Belantamab mafodotin is an antibody–drug conjugate linked to monomethyl auristatin F, which targets B-cell maturation antigen and has been approved for relapsed refractory myeloma. In patients with multiply pre-treated myeloma, the pivotal DREAMM-2 phase II trial reported on 96 patients after greater than three patients with multiply pre-treated myeloma, the pivotal DREAMM-2 phase II trial reported on 96 patients after greater than three months (~4.8 years) with a median of three prior lines of treatment (range 2–5). Prior therapies included immunomodulatory drugs (91%), proteasome inhibitors (100%) and anti-CD38 antibody (82%) treatment. Four patients (36%) had undergone prior melphalan-conditioned autologous stem cell transplantation. At data cut-off, patients have received a median of 6 (range 1–11) doses of belantamab mafodotin. Response rates are shown in Fig. 1. Eight patients (73%) are still on therapy, ORR (partial response [PR] or better) was 64%. CR or very good partial response (VGPR) was reported as per International Society of Amyloidosis consensus criteria [4]. Other adverse events were graded in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

RESULTS AND DISCUSSION

Eleven patients were included (eight male, three female). Baseline characteristics and responses are illustrated in Table 1. The median age at belantamab mafodotin initiation was 65 years (range 42–74) and 3 (27%) patients were aged over 70 years. Eight patients (73%) had λ AL-type and 3 (27%) κ AL-type. At diagnosis, the median involved free light-chain concentration was 534 (range 73–718) mg/l. A median of two organs was involved at baseline (range 1–3): 9 (82%) had renal involvement and 4 (36%) had cardiac involvement. The median eGFR at the time of first belantamab mafodotin dose was 43 ml/min (range 7–120).

The median time from AL amyloidosis diagnosis to first administration of belantamab mafodotin was 58 (range 12–154) months (~4.8 years) with a median of three prior lines of treatment (range 2–5). Prior therapies included immunomodulatory drugs (91%), proteasome inhibitors (100%) and anti-CD38 antibody (82%) treatment. Four patients (36%) had undergone prior melphalan-conditioned autologous stem cell transplantation. At data cut-off, patients have received a median of 6 (range 1–11) doses of belantamab mafodotin. Response rates are shown in Fig. 1. Eight patients (73%) are still on therapy, ORR (partial response [PR] or better) was 64%. CR or very good partial response (VGPR) was achieved in 6 patients (55%). Reasons for treatment discontinuation (n = 1 each, 27% overall) were progressive disease and non-response or toxicity, respectively. At data cut-off, all patients were alive. At a median follow-up of 7.1 months (range 4.5–14.0), progression-free survival was 83% (95% confidence interval 27–97) and the median progression-free survival was not reached.

The most frequent adverse event was keratopathy, in all patients a bilateral microcystic corneal epitheliopathy. This occurred in 8 (73%) patients (grade 1–2: 55%; grade 3: 18%), necessitating dose and schedule modification of the three-weekly delivery in 4 (36%) patients. Ocular adverse events improved after treatment delay (increasing drug intervals to 4–6 weekly) and topical emollients with/without topical corticosteroids. One patient required treatment cessation due to ocular toxicity preventing further dose administration despite achieving PR after just one dose (patient 8).

One patient developed transient grade 1 dyspnoea and asymptomatic liver dysfunction which is similar to the rate reported in DREAMM-2. In our cohort, no patients developed cytopenia, which differed from DREAMM-2, which reported thrombocytopenia in 35% and anaemia in 24% as the most common adverse events after keratopathy. The only other series of reported belantamab mafodotin use in AL amyloidosis described...
thrombocytopenia in 17% (1/6) [2]. In our cohort, no infusion reactions were reported nor infections observed beyond COVID (two patients had mild infections not requiring hospital admission).

The majority of the cohort required dose reduction either at initiation (patient 4, due to end-stage renal failure and haemodialysis; patient 11, post-renal transplant) or during therapy (5/11; 45%: 3–1.9 mg/kg, 2–1.25 mg/kg). Only one patient remained on the standard dose of 2.5 mg/kg for ≥3 cycles. Four patients had an eGFR <30 ml/min with one patient experiencing grade 1 keratopathy. Two patients (patients 4 and 11) with end-stage renal failure commenced a dose of 1.25 mg/kg and achieved a VGPR and CR, respectively, with no additional toxicity. Patient 11 was treated with belantamab mafodotin after renal transplantation and was taking tacrolimus and mycophenolate mofetil as immunosuppression—we did not see any significant toxicity with a four-weekly dosing schedule and the patient achieved a CR at cycle 3. Patient 3 had a 42% reduction in the involved serum-free light chain after two doses but then had a prolonged gap due to keratopathy and lost the response. There were no treatment-related deaths, hospitalisations due to belantamab mafodotin and cardiac or renal toxicities observed in our cohort.

Belantamab mafodotin demonstrates significant activity in patients with heavily pre-treated AL amyloidosis with an ORR of 64%. Given the low grade underlying clonal dyscrasia in AL amyloidosis, these response rates appear to compare favourably

---

**Table 1. Baseline characteristics and responses.**

| Patient number | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  | 11  |
|----------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Age, gender   | 60, F | 72, M | 42, F | 65, F | 64, M | 74, M | 63, M | 73, M | 66, M | 67, M | 58, M |
| iFLC at diagnosis, mg/l | 2368 | 97 | 1069 | 73 | 499 | 7181 | 2330 | 1940 | 534 | 495 | 235 |
| Cardiac       | ✓   | x   | ✓   | x   | ✓   | x   | ✓   | x   | x   | x   | x   |
| Renal         | ✓   | ✓   | ✓   | ✓   | ✓   | x   | ✓   | x   | x   | x   | x   |
| Liver         | x   | ✓   | x   | ✓   | x   | x   | x   | x   | ✓   | x   | x   |
| Soft tissue   | ✓   | ✓   | x   | x   | ✓   | x   | x   | ✓   | x   | ✓   | x   |
| Prior lines of therapy | 4 | 2 | 3 | 4 | 3 | 3 | 4 | 4 | 3 | 5 | 3 |
| Prior therapy | Immunomodulatory drug | ✓ | x | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Proteasome inhibitor | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Anti-CD38 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Melphalan ASCT | x | x | x | x | x | x | ✓ | ✓ | ✓ | ✓ | x |
| iFLC at belantamab mafodotin initiation, mg/l | 267 | 31 | 194 | 172 | 57 | 341 | 109 | 453 | 89 | 133 | 45 |
| Doses delivered | 11 | 4 | 6 | 4 | 6 | 6 | 8 | 1 | 7 | 6 | 4 |
| Dose reduction | ✓ | ✓ | x | ✓ | ✓ | ✓ | x | ✓ | x | ✓ | ✓ |
| Toxicity | Keratopathy, grade | 1 | 1 | 2 | — | 3 | — | 2 | 3 | 2 | 1 | — |
| Dyspnoea, grade | — | 1 | — | — | — | — | — | — | — | — | — |
| Liver dysfunction, grade | — | 1 | — | — | — | — | — | — | — | — | — |

*iFLC* involved free light chain, *ASCT* autologous stem cell transplant.

---

![Fig. 1](image_url)  
**Fig. 1  Treatment response rates.**  
(a) Overall response rates; (b) Time to treatment response; Key: CR complete response, VGPR very good partial response, NR no response, ORR overall response rate.
with trial and real-world data of 30% achieving responses in relapsed myeloma. Effective novel therapies in multiply relapsed refractory AL amyloidosis are welcomed as data in this setting is scant. We recently reported real-world longitudinal data showing good outcomes and that responses do not significantly worsen with subsequent relapses in AL amyloidosis with 40–50% achieving at least a VGPR [6]. In the current cohort, apart from reversible keratopathy requiring dose modification and one treatment cessation, no other substantial toxicity was observed. Crucially, the common problems with AL amyloidosis treatment, often caused by steroids, like fluid retention and fatigue were not seen with belantamab mafodotin. Corneal toxicity was not unexpected; baseline and sequential ophthalmic examinations between belantamab mafodotin treatments allow monitoring for keratopathy. Of the current cohort, five patients would have been trial ineligible for the current prospective phase II trial (four due to renal impairment and one due to cardiac biomarkers). Two patients with severe renal impairment (stage V CKD) and one patient post-renal transplant tolerated treatment without additional toxicity and had good responses.

Our data has inherent limitations due to its retrospective nature and small sample size; however, we demonstrate good efficacy and tolerability of belantamab mafodotin in multiply relapsed AL amyloidosis including efficacy in patients with renal impairment. In summary, Belantamab mafodotin shows efficacy in our series of patients with multiply relapsed AL amyloidosis including those excluded from clinical trials. Further evaluation in prospective trials including those patients with advanced renal and cardiac disease is welcomed.

Jahanzaib Khwaja1, Joshua Bomsztyk2, Shameem Mahmood2, Brendan Wisniowski2, Raakhee Shah1, Anish Tailor1, Kwee Yong3, Rakesh Popat1, Neil Rabin1, Charalampia Kyriakou1, Jonathan Sive1, Simona Degli Esposti3, Daniel F. P. Larkin3, Sarah Worthington1, Alyse Hart1, Emma Dowling1, Nuno Correia1, Ceri Bygrave4, Andrzej Rydzewski2, Krzysztof Jamrozik4 and Ashutosh D. Wechalekar3

1Department of Haematology, University College London Hospital, London, UK. 2National Amyloidosis Centre, University College London (Royal Free Campus), London, UK. 3Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK. 4Department of Haematology, University Hospital of Wales, Cardiff, UK. 5Department of Internal Medicine, Nephrology and Transplantation Medicine, Central Clinical Hospital of the Ministry of Internal Affairs, Warsaw, Poland. 6Department of Hematology, Transplantation and Internal Medicine, Medical University of Warsaw, Warsaw, Poland. 7email: a.wechalekar@ucl.ac.uk

DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

REFERENCES

1. Lonial S, Lee HC, Badros A, Trudel S, Nooka AK, Chari A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. Lancet Oncol. 2020;21:207–21.

2. Zhang Y, Godara A, Pan S, Toskic D, Fogaren T, Sbrow D, et al. Belantamab mafodotin in patients with relapsed/refractory AL amyloidosis with myeloma. Blood. 2021;138(Suppl 1):1670.

3. Rezk T, Lachmann HJ, Fontana M, Sachchithanantham S, Mahmood S, Petrie A, et al. Prolonged renal survival in light chain amyloidosis: speed and magnitude of light chain reduction is the crucial factor. Kidney Int. 2017;92:1476–83.

4. Palladini G, Schönland SO, Sanchorawala V, Kumar S, Wechalekar A, Hegenbart U, et al. Clarification on the definition of complete haematologic response in light-chain (AL) amyloidosis. Amyl oid. 2021;28:1–2.

5. Farooq AV, Degli Esposti S, Popat R, Thulasi P, Lonial S, Nooka AK, et al. Corneal epithelial findings in patients with multiple myeloma treated with antibody-drug conjugate belantamab mafodotin in the pivotal, randomized, DREAMM-2 study. Ophthalmol Ther. 2020;9:889–911.

6. Ravichandran S, Cohen OC, Law S, Sachchithanantham S, Mahmood S, Foard D, et al. Haematologic responses and survival do not significantly decrease with subsequent lines of therapy in systemic immunoglobulin light chain amyloidosis: results from an analysis of real-world longitudinal data. Br J Haematol. 2021;194:587–97.

AUTHOR CONTRIBUTIONS

ADW, JK and JB designed the study, collected data, analysed data and wrote the paper; all contributors participated in data collection and reviewed the paper.

COMPETING INTERESTS

JK, JB, SM, BW, RS, AT, CK, JS, SDE, DFPL, SW, AH, ED, NC, CB, KJ: no conflict of interest. KY: BMS research funding; Amgen honoraria; GSK honoraria; Takeda honoraria; Janssen honoraria, research funding; Sanofi honoraria, research funding; Autolus research funding; RP: Abbvie, BMS, Janssen, Oncopeptides, and Amgen honoraria; Takeda honoraria; GlaxoSmithKline consultancy, honoraria, research funding; Abbvie, Takeda, Janssen, and Celgene consultancy; Janssen and BMS travel expenses; NR: BMS/Celgene consultancy, honoraria, travel support for meetings; Takeda consultancy, honoraria, travel support for meetings; Janssen: consultancy, honoraria, travel support for meetings; AR: honoraria (for invited lectures) and travel grants Astellas, Fresenius, Sandoz; ADW: Amgen research funding; Alexion, AstraZeneca rare disease consultancy; Caelum Biosciences: clinical trial funding; Janssen consultancy; Takeda honoraria; Celgene honoraria.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Ashutosh D. Wechalekar. 

Reprints and permission information is available at http://www.nature.com/reprints

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2022