A retrospective study of isatuximab-pomalidomide-dexamethasone in relapsed/refractory systemic AL amyloidosis

Systemic AL amyloidosis (AL) is a multi-system disorder caused by overproduction (by clonal plasma cells or B-cell dyscrasia) and deposition of misfolded immunoglobulin free light chains (FLC) as amyloid fibrils in organs. Outcomes have markedly improved with newer treatments. However, AL remains incurable.[1] Daratumumab-CyBorD became the first licensed treatment for newly diagnosed AL in 2021.[2] Currently, there are no licenced treatments for relapsed AL, and all treatments at relapse are adapted from myeloma therapy.

Isatuximab, an anti-CD38 monoclonal antibody, in combination with pomalidomide, an immunomodulatory drug (IMiD), and dexamethasone (Isa-PD), has shown efficacy in myeloma.[3] Single-agent pomalidomide has shown a modest efficacy in relapsed AL with 3% achieving complete response (CR), 23% very good partial response (VGPR), and 44% at least a partial response (PR).[4] A phase II study using single-agent isatuximab in relapsed AL showed an overall response rate (ORR) of 77.1%.[5] There are currently no published data on Isa-PD in AL amyloidosis. Here, we present the UK experience of Isa-PD in relapsed AL.

We report 28 patients treated with Isa-PD from 2020-2024

Table 1. Baseline characteristics.

Characteristic	Values
Gender, N (%) Male Female	 16 (57.1) 12 (42.9)
Age at diagnosis in years, median (range)	65 (49-79)
ECOG, N (%) 0-2 >2	 28 (100) 0 (0)
Organ involvement, N (%) Heart Renal Liver PNS ANS Soft tissue GI	 20 (71.4) 12 (42.9) 1 (3.6) 4 (14.3) 3 (10.7) 7 (25.0) 2 (7.1)
N of organs involved, median (range)	1 (1-4)
Mayo stage, N (%) 1 2 3A 3B	 6 (21.4) 11 (39.3) 9 (32.1) 2 (7.1)
LVEF %, median (range)	60 (27-77)
LV septum, mm, median (range)	14 (10-19)
NT Pro BNP, ng/L, median (range)	766 (50-10,051)
Troponin, ng/L, median (range)	37 (4-742)
Creatinine, μmol/L, median (range)	103 (44-761)
Albumin, g/L, median (range)	37 (17-47)
Urine ACR, mg/mmol, median (range)	3 (0-430)
dFLC, mg/L, median (range)	74 (3-1,938)
Monoclonal protein, g/L, median (range)	1.5 (0-17)
Bone marrow plasma cell %, median (range)	21 (5-90)
Light-chain isotype, N (%) Lambda Kappa	 24 (85.7) 4 (14.3)
Monoclonal protein isotype, N (%) IgG lambda IgA lambda IgG kappa Kappa Lambda	 12 (44.4) 1 (3.7) 2 (7.4) 2 (7.4) 10 (37)
First-line treatment, N (%) Bortezomib-based Carfilzomib CTD Cyclophosphamide and dexamethasone Lenalidomide	 17 (60.7) 2 (7.1) 7 (25.0) 1 (3.6) 1 (3.6)
Second-line treatment, N (%) Bortezomib-based Daratumumab-based Lenalidomide-based Others	 11 (39.3) 3 (10.7) 10 (35.7) 4 (14.3)
Third-line treatment, N (%) Bortezomib-based Lenalidomide Others	 4 (14.3) 15 (53.6) 9 (32.1)
Median lines of treatment before Isa-PD	3

ANS: autonomic nervous system; CTD: cyclophosphamide, thalidomide, dexamethasone; dFLC: difference in involved and uninvolved free light chains; ECOG: Eastern Cooperative Oncology Group; Isa-PD: isatuximab, pomalidomide, dexamethasone; LV septum: left ventricle septum; GI: gastrointestinal; LVEF: left ventricular ejection fraction; N: number; NTProBNP: N-terminal pro brain natriuretic peptide; PNS: peripheral nervous system; Urine ACR: urine-albumin-creatinine ratio.

at the UK National Amyloidosis Centre (UK-NAC). Diagnosis, organ involvement,[6,7] hematologic response (at 3, 6, and 12 months),[8] and organ response (at 12 months)[8] was as per standard criteria. The suggested regimen was: intravenous (IV) isatuximab, 10 mg/kg weekly for the 1st month; then, alternate weeks in a 28-day cycle; oral pomalidomide 4 mg daily on days 1-21; and dexamethasone 20 mg weekly. Patients received paracetamol, chlorphenamine, and dexamethasone before isatuximab. Montelukast was used for the first three cycles. Hematologic response was the primary endpoint.[8] Toxicity, overall survival (OS), and event-free survival (EFS) were secondary endpoints. OS and EFS were calculated from the initiation of Isa-PD to death from any cause and to next treatment or death, respectively. The study was approved by the UK National Health Service (NHS) ethics board and patients provided informed consent.

Table I shows the pre-treatment characteristics. The median age at diagnosis was 65 years. 42.9%, 46.4% and 10.7% of patients received Isa-PD for inadequate response, hematologic progression, and organ progression, respectively. Twenty out of 28 (71.4%) had cardiac involvement and 12/28 (42.9%) had renal involvement. Eleven out of 28 (39.3%) had ≥Mayo stage 3 disease. The median pre-treatment dFLC, N-terminal pro brain natriuretic peptide (NT-proBNP), and creatinine were 74 mg/L, 766 ng/L, and 103 µmol/L, respectively. All patients had received three prior lines of treatment before receiving Isa-PD. The median time from diagnosis to start of Isa-PD was 77 months. Patients received a median of 24 cycles. Of the 28 patients, 2 patients progressed and received a further, different treatment, one patient progressed and died, 6 patients died whilst on treatment, and 19 remain on treatment at the time of this analysis.

Hematologic responses were assessed on an intention to treat basis (ITT). Response data were not available in 4/28, 3/28, and 4/28 patients at 3, 6, and 12 months, respectively; these patients were excluded from the response analysis at those time points. One patient progressed between 3-6 months and 2 progressed between 6-12 months. One patient died between 3-6 months of treatment.

The overall hematologic response at 3, 6, and 12 months was 22/24 (91.7%), 23/25 (92%), and 21/24 (87.5%). 15/24 (62.5%), 15/25 (60%), and 15/24 (62.5%) patients achieved ≥VGPR at 3, 6, and 12 months, respectively. The best hematologic responses at any point were: CR - 18 (64.2%), VGPR - 6 (21.4%), PR - 2 (7.1%). Five out of 6 patients in VGPR had achieved a free light chain CR (FLC-CR). 66%

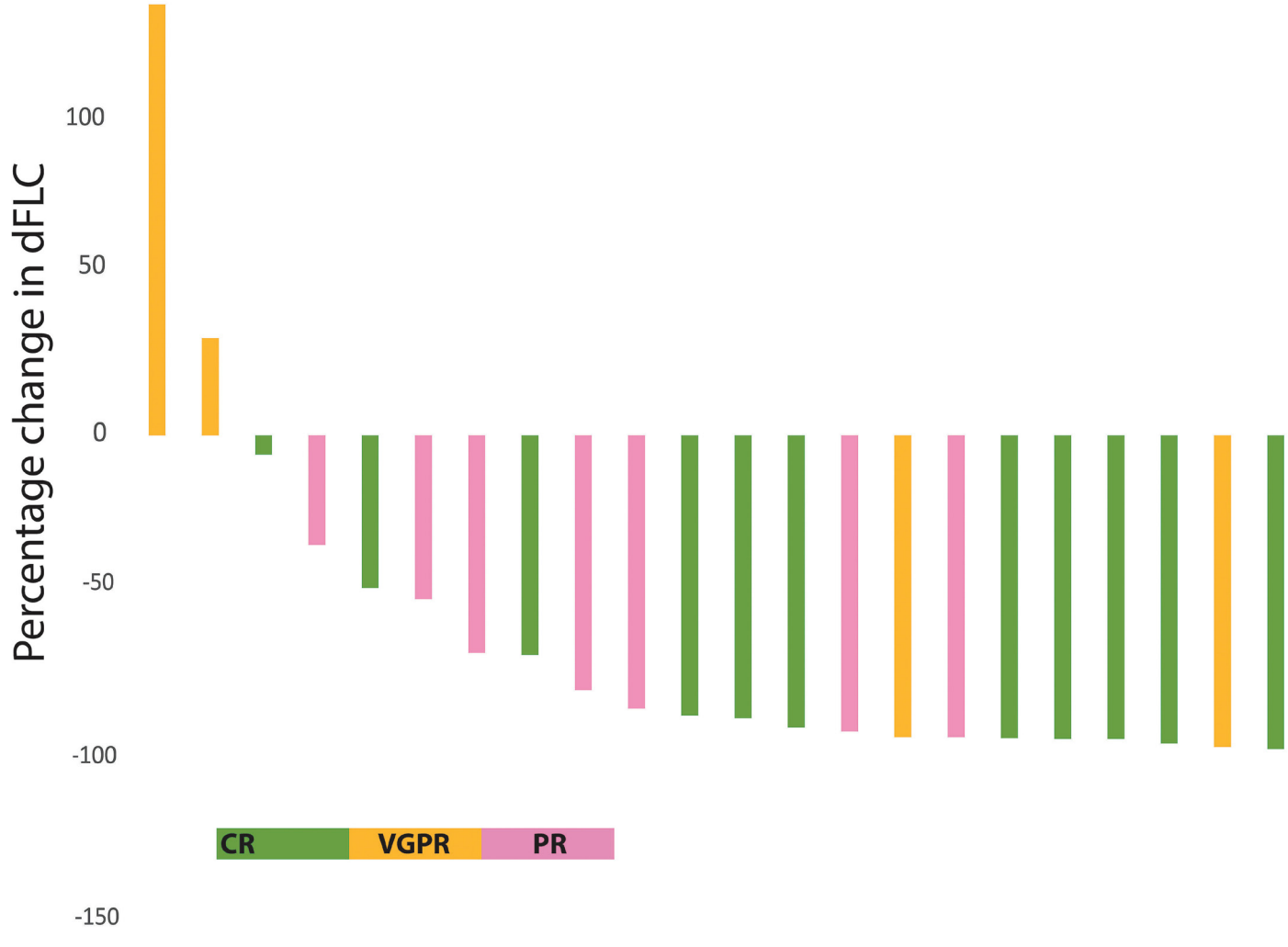

Figure 1. Waterfall plot showing the percentage change in difference between involved and uninvolved light chains six months after starting combined isatuximab, pomalidomide, dexamethasone. Median decrease in involved and uninvolved light-chain (dFLC) levels at six months was 87.8%. Amongst these patients, 11 achieved a complete response (CR), 4 showed a very good partial response (VGPR), and 7 exhibited a partial response (PR). Isa-PD.

patients achieved their best response within three months. Figure 1 shows the change in dFLC at six months after starting Isa-PD for each patient. Three patients previously treated with daratumumab received Isa-PD at 14, 20, and 36 months post daratumumab. One patient achieved CR, one achieved VGPR, and one achieved PR.

Eight patients deepened their hematologic response with continuing treatment (Figure 2). Six out of 8 (75%) with <VGPR at three months improved to ≥VGPR with continuing treatment. Two patients with VGPR improved to CR with continued treatment.

Nine out of 20 (45%) patients were excluded from the organ response analysis as their pre-treatment NT-proBNP was <650 ng/L. Two out of 11 (18%) evaluable patients had a cardiac response. Renal responses were not evaluable due to inadequate data.

The median OS and EFS were 53 months (*Online Supplementary Figure S1A)*, and 41 months, respectively. The depth of hematologic response did not significantly affect the OS or EFS (*Online Supplementary Figures S2, S3*). There was no statistically significant difference in OS based on cardiac involvement (P=0.167).

A total of 76 adverse events were reported. Fatigue (11.8%), arrhythmias (10.5%), infections (9.2%), dizziness (6.6%), nausea (5.3%), fluid retention (5.3%), dyspnea (5.3%), diarrhea (3.9%), and hypotension (3.9%) were experienced by ≥3 patients. Grade 2 neutropenia, grade 2 thrombocytopenia, and grade 4 infection were noted in one, one, and 4 patients, respectively. There were no cytopenia over grade 2. No grade 3 or greater infusion-related reactions were reported.

Systemic AL amyloidosis is an incurable disease; relapse and further treatment is inevitable. There are no licensed or standardized treatments for relapsed AL. IMiD-based doublets have shown modest efficacy in relapsed AL.[9] Pomalidomide-dexamethasone induced an ORR of 50% in a prospective study in relapsed AL and 77% in a larger multicenter retrospective analysis but with a limited number of CR.[4,10] We reported the efficacy of a triplet ixazomib, lenalidomide and dexamethasone.[11] Venetoclax is an excellent option for patients with t(11;14), but there is limited global access. Single agent daratumumab in relapsed AL showed excellent response rates in a number of studies.[12] Isatuximab targets a different epitope of the CD38 molecule. A recent phase ll study of single-agent isatuximab showed a good ORR (77%) in relapsed AL with VGPR in 51%, but CR only in 6%.[5] Lately, with the upfront use of daratumumab, the role for single agent anti-CD 38 in the relapsed setting has been limited. Hence, triplet combinations are of interest. Isa-PD is licensed for the treatment of relapsed myeloma. There are limited data on its efficacy or toxicity in AL. Results of a multicenter, phase II study of Isa-PD in relapsed AL were reported at the 2024 American Society of Haematology Meeting. Here, 51% and 80% of patients had achieved a CR or ≥VGPR after six cycles. This study excluded patients refractory to daratumumab with only 2 patients exposed to this drug – our current study had 3 daratumumab-exposed (but not refractory) patients with responses in 2/3 cases.

In this study, deep/rapid clonal responses were achieved within the first few weeks.[12] These results are concordant with our report (≥VGPR in 85.7% patients). 66% of our patients achieved their best response within three months. We found that responses deepen (8/23) with continuing thera-

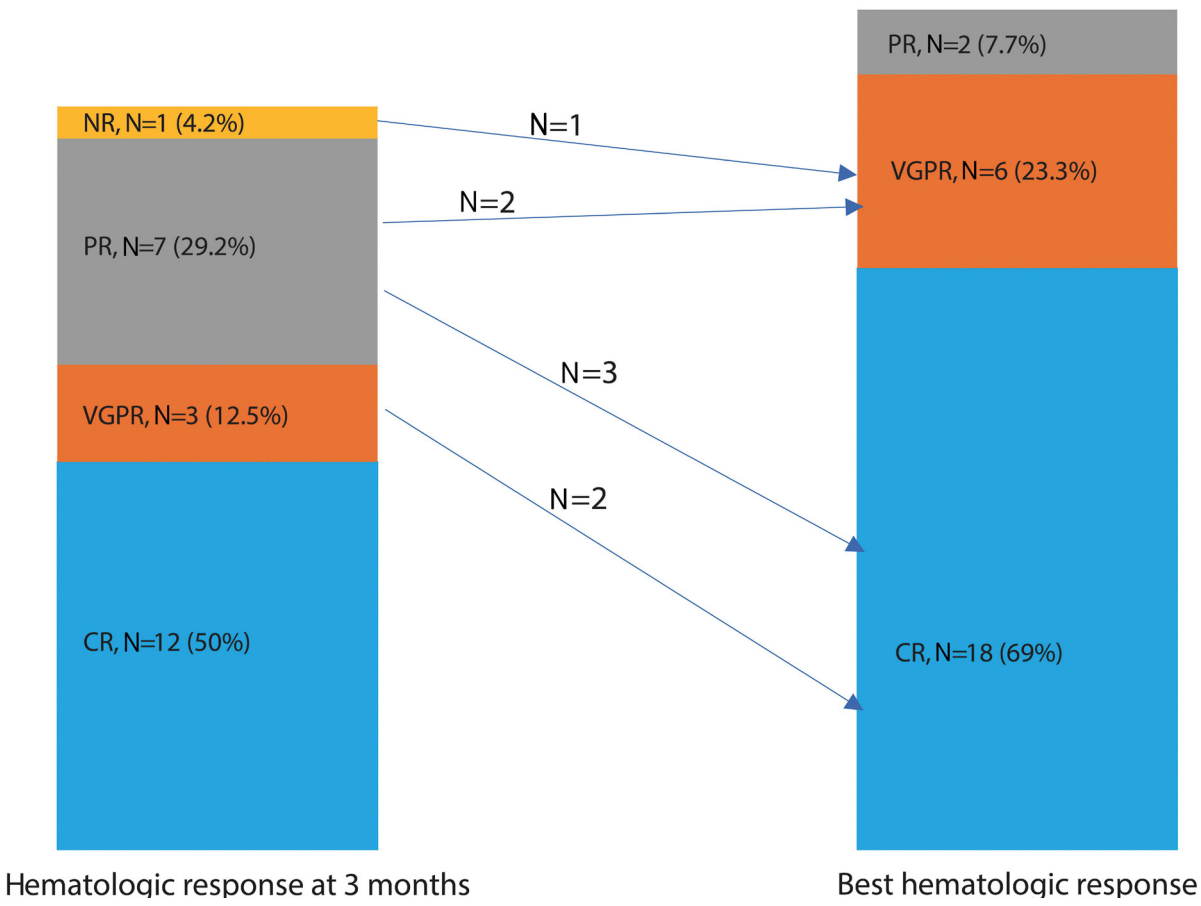

Figure 2. Deepening hematologic response with continued treatment. Eight patients improved their hematologic response with continued treatment. Six out of 8 (75%) patients with a less than very good partial response (VGPR) at three months improved their response to a VGPR or better with continued treatment. Two patients with VGPR improved their response to complete response with continued treatment. CR: complete response; N: number; NR: no response; PR: partial response.

py, even in non-responders. This indicates that, tolerability permitting, it is worth persisting with Isa-PD beyond three months. We had very few progressions, with the majority of patients continuing treatment.

There was a transient rise in NT-proBNP in the phase II multicenter study, a likely pomalidomide effect, and this does not suggest cardiac deterioration. The lack of cardiac responses in our cohort (only 2/11 evaluable patients), despite a good proportion of deep hematologic response, may be partly explained by this phenomenon. At the UK-NAC, cardiac biomarker measurements are typically obtained at 6- to 12-month intervals. As a result, we are unable to evaluate changes in these biomarkers on a monthly basis, thus limiting detailed evaluation of a paradoxical increase in biomarkers with pomalidomide. 80.5% patients in the phase II study showed greater than grade 2 adverse effects (AE); infections and cytopenias were common.[13] No patient discontinued treatment due to toxicity in our cohort, and we report a lower AE burden. Ours is a retrospective cohort and we acknowledge that AE may be under-reported.

The OS and EFS in this cohort were excellent at 53 and 41 months, respectively. We did not find any significant difference in survival based on the best hematologic response.[14] This may be due to 5/6 patients in VGPR achieving an FLC-CR (thus likely to have outcomes not dissimilar to patients in a true CR) and to the overall small size of the cohort. Moreover, this is a selected group of patients with good prognosis, as documented by more than six years of median survival before starting IPD. A much longer period of follow-up is likely to be required to show the impact on survival. We also lack bone marrow data at response (minimal residual disease or otherwise) which may help stratify patients better for EFS/OS outcomes.

We acknowledge some additional limitations of our cohort. Bone marrow plasma cell burden at diagnosis/relapse is only known for a minority of patients. We lack data on dose intensity/modifications. Mild grade 1-2 reactions might not have been documented. As part of the NHS requirement for eligibility for Isa-PD, patients could not have been refractory to daratumumab. Hence, we lack data on the impact of this regime in patients refractory to daratumumab.

In summary, we show that Isa-PD achieves high, rapid, and deep responses and excellent OS and EFS in relapsed AL. It is well tolerated and no patient discontinued treatment due to toxicity. Availability of subcutaneous isatuximab will make the delivery of this combination easier. Isa-PD is a useful treatment option in relapsed AL amyloidosis.

Authors

Sargam Rachit Vohra, Sriram Ravichandran, Darren Foard, Ana Martinez-Naharro, Lucia Venneri, Marianna Fontana, Carol J. Whelan, Philip N. Hawkins, Julian Gillmore, Helen J. Lachmann, Shameem Mahmood and Ashutosh D. Wechalekar

National Amyloidosis Centre, UCL (Royal Free Campus), London, UK

Correspondence:
A. WECHALEKAR - a.wechalekar@ucl.ac.uk

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Disclosures

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Contributions

SRV and AW designed the study, collected and analyzed the data, and wrote and approved the manuscript. SR analyzed the data, and wrote and approved the manuscript. DF, AMN, LV, MF, CJW, PNH, JG, HJL and SM reviewed and approved the manuscript.

Data-sharing statement

Data available on request from the corresponding author.

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