Daratumumab for relapsed or refractory AL amyloidosis with high plasma cell burden

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Abstract
Daratumumab, an anti-CD38 antibody, is effective in AL amyloidosis with low tumor burden. Data of daratumumab treatment in patients with AL amyloidosis but high tumor burden (≥10% bone marrow plasma cells) are limited. We report retrospective data of 10 consecutive patients with high tumor burden treated with daratumumab for relapsed/refractory AL amyloidosis. The median age at diagnosis was 62.3 years; all patients had cardiac involvement, and six (60%) patients had renal involvement. Median bone marrow plasma cell infiltration was 15% (range 10%-40%), and the median difference between involved and noninvolved free light-chains (dFLC) was 446 mg/L (range 102-1392 mg/L). Patients had a median of three prior lines of therapy, including bortezomib in all patients and lenalidomide in seven (70%) patients. The median time to first hematological response was 14 days (range 7-28 days), and the median time to best hematological response was 64 days (range 7-301 days). The hematological overall response was 90%, with high-quality response (≥ very good partial remission [VGPR]) in 70% of the patients. Fifty percent of the patients had a cardiac response after a median of 3.8 months (range 0.7-9.1). Infusion-related adverse events ≤ grade 2 occurred in seven (70%) patients and grade 3 adverse events in one patient. After a median follow-up time of 10 months, eight (80%) patients continued to receive daratumumab. We conclude that daratumumab is a very effective and safe treatment option in AL patients with relapsed/refractory disease and high disease burden at diagnosis. Daratumumab leads to rapid disease control and improvement of organ function.

KEYWORDS
AL, amyloidosis, daratumumab, light chain, organ, plasma cell, response
1 | INTRODUCTION

Light-chain amyloidosis (AL) is the most common form of systemic amyloidosis. Its clinical course largely depends on the type and severity of organ involvement. Patients with advanced cardiac involvement and high tumor burden have the poorest outcome. For decades, the standard of care for AL amyloidosis patients has been oral melphalan with high-dose dexamethasone or high-dose melphalan followed by autologous stem cell transplantation (ASCT). The prognosis of AL amyloidosis patients in relapsed or refractory disease has been poor and limited by the lack of treatment options. In recent years, a trend to longer survival has been observed, most likely explained by a more conscious patient selection for ASCT and, more importantly, by the introduction of novel plasma cell (PC)-directed therapies. Nevertheless, treatment of patients with relapsed or refractory AL amyloidosis remains challenging, as resistance to first-line treatment is difficult to overcome, and as the treatment tolerability may be hampered by concomitant organ dysfunction and comorbidities. Rapidly acting and well-tolerated PC-directed treatments are needed. Daratumumab, a humanized anti-CD38 antibody, has the potential to induce rapid responses with excellent tolerability as shown in case series of patients with AL amyloidosis and low PC burden. However, patients with a bone marrow PC count of ≥10% have a worse outcome when compared with patients with a lower tumor burden, and more data for this especially challenging patient population are needed. We here present data of 10 consecutive patients from the Swiss Amyloidosis Registry with a bone marrow PC burden of ≥10% who received daratumumab for relapsed or refractory AL amyloidosis.

2 | MATERIALS AND METHODS

In this observational multicenter research project involving the Centers of the Swiss Collaborative Amyloidosis Network, consecutive patients >18 years with relapsed or refractory AL amyloidosis and a bone marrow PC count of ≥10% were enrolled between August 2017 and October 2018. Data have been extracted from the Amyloidosis Registry, which is a prospective, longitudinal collection of data from all patients of the Swiss Collaborative Amyloidosis Network. All patients provided written consent prior to inclusion in the Amyloidosis Registry, which was approved by the Local Ethical Committees, Switzerland (KEK-ZH-Nr. 2014-0490). Diagnosis of systemic AL amyloidosis required biopsy proven light-chain amyloid deposits with typical green birefringence under cross-polarized light following Congo red staining and positive immunohistochemistry. Baseline data were captured at the time of diagnosis. Organ involvement was defined as biopsy proven amyloid deposit of the concerning organ (or tissue) and/or typical organ alterations as defined for AL amyloidosis. Hematological response and organ response were recorded according to the currently accepted response criteria. Organ function and hematological parameters at diagnosis served as the reference values.

2.1 | Treatment regimen

Daratumumab was administered intravenously at 16 mg/kg weekly for 8 weeks, followed by an infusion every 2 weeks for eight doses, and a maintenance dose every 4 weeks. Dexamethasone in a dose of 20 to 40 mg at the day of daratumumab treatment could be added upon treating physician’s choice. The first daratumumab dose was administered slowly over eight hours in 500-mL intravenous fluids but could also be split in half and given on two consecutive days. If the first dose was well tolerated, subsequent doses could be administered over 4 hours. Some patients received prehydration of 250- to 500-mL intravenous fluids; premedication included paracetamol, antihistamines, montelukast, and corticosteroids.

Anti-infectious prophylaxis with valacyclovir for HSV and VZV, as well as trimethoprim/sulfamethoxazole for Pneumocystis jirovecii pneumonia prophylaxis, was recommended. Intravenous immunoglobulin replacement was considered in patients with severe secondary hypogammaglobulinemia at high risk for infections.

3 | RESULTS

3.1 | Patient characteristics at diagnosis

Ten patients were included in the analysis (Table 1). The median age at diagnosis was 62.3 years; 20% of the patients were female. Risk stratification according to Mayo 2004 staging system was stage II for all 10 patients, while the Revised 2012 Mayo staging system revealed stages I, II, III, and IV disease in 0 (0%), 3 (30%), 5 (50%), and 2 (20%) of the patients, respectively. Median bone marrow infiltration by clonal PCs was 15% (range 10%-40%), and the median difference between involved and noninvolved free light-chains (dFLC) was 446 mg/L (range 102-1392 mg/L). High-risk cytogenetics defined as the presence of del17p, t(4;14), or t(14;16) was present in one (10%) patient and t(11;14) in four (40%) patients. All patients had cardiac involvement at diagnosis, and the median NT-proBNP was 1291 pg/mL (range 419-7021 pg/mL). Renal involvement occurred in 6 (60%) of patients, and the median estimated glomerular filtration rate (eGFR) was 73 mL/min/1.73 m² (range 25-108) according to the CKD-EPI equation. Other organs involved were the peripheral nervous system (n = 2, 20%), soft tissue (n = 7, 70%), and gastrointestinal system (n = 2, 20%).

Patients received a median of 3 (range 1-5) prior lines of therapy including bortezomib in all patients and lenalidomide in 7 (70%) patients. Oral melphalan plus dexamethasone, carfilzomib, and pomalidomide were treatment regimens for 2 (20%), 2 (20%), and 2 (20%) of the patients, respectively. Three (30%) patients were treated with high-dose melphalan and ASCT, whereas one patient received prior allogeneic stem cell transplantation. Median time from diagnosis to daratumumab therapy was 11.9 months (range 2.8-124.3). Median dFLC burden at daratumumab treatment initiation was 191 mg/L (range 40-1382).
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Diagnosis</th>
<th>Sex</th>
<th>Bone Marrow PC Infiltration, %/Clonality</th>
<th>dFLC mg/L</th>
<th>iFISH</th>
<th>Mayo Risk Stage 2004/Revised Mayo Risk Stage</th>
<th>Organ involvement</th>
<th>Prior Lines of Therapy</th>
<th>CRAB</th>
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<td>1392</td>
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<td>II/III</td>
<td>Heart, kidneys, soft tissue, PNS</td>
<td>Td, Rd/HDM-ASCT/Vd, Rd, AlloSCT, Rd</td>
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<td>70.1</td>
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<td>50/κ</td>
<td>386</td>
<td>t(11;14)</td>
<td>II/II</td>
<td>Heart, kidneys</td>
<td>VCD, Md, Pd</td>
<td>-/-/-/B</td>
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<td>3</td>
<td>68.5</td>
<td>Female</td>
<td>10/κ</td>
<td>190</td>
<td>t(11;14)</td>
<td>II/II</td>
<td>Heart, kidneys, GI, soft tissue</td>
<td>VCD, Md, Rd</td>
<td>-/-/-/B</td>
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<td>4</td>
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<td>Male</td>
<td>15/λ</td>
<td>506</td>
<td>Normal</td>
<td>II/III</td>
<td>Heart, kidneys, PNS</td>
<td>VCD, Rd, Kd</td>
<td>-/-/-/B</td>
</tr>
<tr>
<td>5</td>
<td>63.8</td>
<td>Male</td>
<td>15/λ</td>
<td>102</td>
<td>1q, del17p, del13q, t(11;14)</td>
<td>II/III</td>
<td>Heart, soft tissue</td>
<td>Vd</td>
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<td>6</td>
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<td>Male</td>
<td>15/λ</td>
<td>138</td>
<td>Not known</td>
<td>II/III</td>
<td>Heart, kidneys, soft tissue</td>
<td>VCD, Rd</td>
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<td>7</td>
<td>66.2</td>
<td>Female</td>
<td>25/λ</td>
<td>1370</td>
<td>Hyperdiploid</td>
<td>II/IV</td>
<td>Heart, soft tissue</td>
<td>Vd, Rd</td>
<td>-/-/-/B</td>
</tr>
</tbody>
</table>
| 8       | 61.0             | Male | 40/κ                                   | 550    | del13, +7, +9, +15 | II/III | Heart, soft tissue                         | Vd, HDM-ASCT, RCd | -/R/-/-
| 9       | 73.2             | Male | 10/λ                                   | 178    | IGH rearrangement, unknown partner gene | II/III | Heart, kidneys                            | V, Md             | -/-/-/B |
| 10      | 39.7             | Male | 25/κ                                   | 871    | t(11;14), del16q | II/IV | Heart, GI, soft tissue                    | VCD/HDMel, Rd | -/R/-/-

Abbreviations: PC, plasma cells; κ, kappa; λ, lambda; dFLC, difference between involved and noninvolved free light-chains; iFISH, interphase fluorescent in situ hybridization; PNS, peripheral nervous system; GI, gastrointestinal; Td, thalidomide-dexamethasone; Rd, lenalidomide-dexamethasone; HDM-ASCT, high-dose melphalan followed by autologous stem cell transplantation; Vd, bortezomib-dexamethasone; AlloSCT, allogenic stem cell transplantation; Pd, pomalidomide-dexamethasone; VCD, bortezomib-cyclophosphamide-dexamethasone; Md, melphalan-dexamethasone; Kd, carfilzomib-dexamethasone; RCd, lenalidomide-cyclophosphamide-dexamethasone; V, bortezomib monotherapy. CRAB features, end organ damage that can be attributed to multiple myeloma (C, hypercalcemia; R, renal insufficiency; A, anemia; B, bone lesions).
3.2 | Daratumumab treatment

All patients initiated daratumumab either in mono-therapy or in combination with dexamethasone (Table 2). After a median follow-up time of 9 months (range 2-13), eight patients (80%) were still receiving daratumumab. Treatment was intensified in two patients: patient 3 lost hematological very good partial remission (VGPR) during the maintenance phase, and venetoclax was added 5.8 months after daratumumab initiation. Patient 1 had stable disease with daratumumab mono-therapy, and lenalidomide plus dexamethasone was added 3.5 months after daratumumab initiation. Daratumumab was stopped in two patients: patient 9 achieved a CR and decided to stop treatment for personal reasons. Patient 4 achieved a VGPR after two daratumumab administrations, when the treating physician decided to suspend the therapy. Despite treatment cessation, the hematological response was maintained in both patients at time of last follow-up.

3.3 | Hematological response

Overall hematological response rate was 90% (Figure 1). Complete remission (CR) was observed in 40% (n = 4) of patients, VGPR in 30% (n=3), and partial remission (PR) in 2 (20%). One (10%) patient had no measurable hematological response (NR). Hematological response was observed after a median of 14 days (range 7-28) (Figure 2). The first hematological response assessment of patient 10 was performed 28 days after treatment initiation, and it is not known whether a response might have been detected at an earlier time point. The best hematological response was reached after a median of 73 days (range 7-301).

3.4 | Organ response

Five (50%) patients had an organ response at the end of follow-up. All five patients had a cardiac response, four (80%) based on an improved

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**TABLE 2** Response to treatment

<table>
<thead>
<tr>
<th>Patient</th>
<th>Baseline Remission Status</th>
<th>Time from Diagnosis to Daratumumab, mo</th>
<th>Time to First Hematological Response, d/Response</th>
<th>Treatment Scheme</th>
<th>Time to Best Hematological Response, d/Response</th>
<th>Organ Response</th>
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<tbody>
<tr>
<td>1</td>
<td>PR</td>
<td>124.3</td>
<td>NA/SD</td>
<td>NA/SD</td>
<td>NA/SD</td>
<td>Cardiac response</td>
</tr>
<tr>
<td>2</td>
<td>SD</td>
<td>11.9</td>
<td>7/PR</td>
<td>D</td>
<td>7/PR</td>
<td>Cardiac response</td>
</tr>
<tr>
<td>3</td>
<td>SD</td>
<td>10.1</td>
<td>7/PR</td>
<td>D</td>
<td>7/PR</td>
<td>Cardiac response</td>
</tr>
<tr>
<td>4</td>
<td>PR</td>
<td>32.9</td>
<td>16/VGPR</td>
<td>D</td>
<td>10/CR</td>
<td>Cardiac response</td>
</tr>
<tr>
<td>5</td>
<td>SD</td>
<td>2.8</td>
<td>5.6</td>
<td>D</td>
<td>10/CR</td>
<td>Cardiac response</td>
</tr>
<tr>
<td>6</td>
<td>SD</td>
<td>7.3</td>
<td>15/VGPR</td>
<td>D</td>
<td>10/CR</td>
<td>Cardiac response</td>
</tr>
<tr>
<td>7</td>
<td>SD</td>
<td>7.5</td>
<td>15/VGPR</td>
<td>D</td>
<td>10/CR</td>
<td>Cardiac response</td>
</tr>
<tr>
<td>8</td>
<td>SD</td>
<td>8.6</td>
<td>14/PR</td>
<td>D</td>
<td>10/CR</td>
<td>Cardiac response</td>
</tr>
<tr>
<td>9</td>
<td>PD</td>
<td>6.8</td>
<td>14/PR</td>
<td>D</td>
<td>14/PR</td>
<td>Cardiac response</td>
</tr>
<tr>
<td>10</td>
<td>PR</td>
<td>15.9</td>
<td>28/CR</td>
<td>D</td>
<td>28/CR</td>
<td>Cardiac response</td>
</tr>
</tbody>
</table>

Abbreviations: NA, nonapplicable; NR, no response; SD, stable disease; PR, partial remission; VGPR, very good partial remission; CR, complete remission; PD, progressive disease; D, daratumumab mono-therapy; Dd, daratumumab + dexamethasone.

**FIGURE 1** Change in dFLC from baseline
NT-proBNP, and four (80%) had a functional improvement according to the NYHA scale. Median time from daratumumab initiation to organ response was 3.8 months (range 0.7-9.1) (Figure 2). One patient had cardiac progression despite achieving a complete hematological remission. At the end of follow-up, none of the six patients with renal involvement has shown kidney response.

### 3.5 Infusion-related side effects

CTCAE grade 1 and 2 side effects occurred in 7 (70%) of the patients. Fever (n = 2; 20%), hypotension (n = 2; 20%), dyspnea (n = 2; 20%), and cough (n = 2; 20%) were the most common side effects. Only one patient experienced CTCAE grade 3 side effects. Patient 1 with extensive gastrointestinal involvement had to be hospitalized because of vomiting and gastric hemorrhage during the first daratumumab infusion.

### 3.6 Infections and intravenous immunoglobulin therapy

Three (30%) patients had a total of five uncomplicated viral infections of the upper respiratory tract following daratumumab treatment. Infections were caused by influenza A virus, influenza B virus, human parainfluenza virus, and human metapneumo virus. In four (40%) patients, intravenous immunoglobulin therapy was initiated.

### 4 DISCUSSION

In this observational analysis of the Swiss Collaborative Amyloidosis Network, we report the outcome of 10 patients with systemic AL amyloidosis, who were treated with daratumumab for relapsed or refractory disease. All 10 patients presented with cardiac involvement and with a high bone marrow PC burden of at least 10%. The overall hematological response rate of these heavily pretreated patients was 90%, and the majority of patients achieved deep responses of VGPR or better. Even more importantly, half of the patients showed a cardiac response during the still relatively short follow-up. Only one patient experienced progression of cardiac amyloidosis despite achieving a complete hematological response during daratumumab treatment. The clinical course of this particular patient highlights the need for novel treatment approaches for this frail patient population for whom the suppression of the malignant clone alone might not be sufficient. Overall, treatment with daratumumab was well tolerated, and infusion reactions were mostly mild. Only one patient with extensive gastrointestinal amyloidosis experienced > CTCAE grade 2 toxicity during the first daratumumab infusion, with a self-limiting upper GI bleeding caused by vomiting, which led to emergency hospitalization. Treatment was continued as scheduled in this patient, and the further course was uneventful.

Our present analysis adds insights regarding daratumumab treatment in high tumor burden AL amyloidosis patients, for whom data were lacking. The outcome of patients with AL amyloidosis is known to depend on the extent of bone marrow PC infiltration and on the free light-chain production, as patients with ≥10% PC and/or a dFLC >180 g/L generally have an inferior prognosis. Our results on daratumumab monotherapy in this particular patient population are promising, as the hematological response rates are very similar when compared with previous reports, despite a more than two-fold higher dFLC in our patient population. Of note, a hematological response was achieved very quickly following daratumumab initiation, as all responding patients who had weekly dFLC assessment showed a significant dFLC reduction within the first 2 to 3 weeks of therapy.

Our results show that daratumumab in mono-therapy or in combination is an effective treatment option in relapsed or refractory AL amyloidosis patients with cardiac involvement and high tumor burden. Daratumumab leads to a rapid hematological response and organ response. These data need to be confirmed in a prospective trial.

### FUNDING INFORMATION

ABREOC 2016 to BG.
REFERENCES


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