Daratumumab for treatment-refractory acquired idiopathic pure red cell aplasia

by Naseema Gangat, Jonathan Bleeker, Douglas Lynch, Horatiu Olteanu, Louis Letendre, and Ayalew Tefferi

Received: May 11, 2022.
Accepted: June 1, 2022.


Publisher's Disclaimer.
E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication. E-publishing of this PDF file has been approved by the authors. After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors' final approval; the final version of the manuscript will then appear in a regular issue of the journal. All legal disclaimers that apply to the journal also pertain to this production process.
Daratumumab for treatment-refractory acquired idiopathic pure red cell aplasia

Naseema Gangat 1, Jonathan Bleeker 2, Douglas Lynch 2, Horatiu Olteanu 3, Louis Letendre 1, and Ayalew Tefferi 1

1Division of Hematology, Mayo Clinic, Rochester, MN, USA.
2Division of Hematology and Hematopathology, Sanford Health, Sioux Falls, SD, USA.
3Division of Hematopathology, Mayo Clinic, Rochester, MN, USA

Running title: daratumumab in pure red cell aplasia

Key words: red cell aplasia, monoclonal antibody, plasma cells, transfusion

Text: 1048

Figures: 2

References: 9

Disclosures: None

Funding: None

Author contributions: NG wrote the paper. NG, JB, LL, and AT participated in patient care. DL and HO performed review of bone marrow biopsies. All authors reviewed and approved the final draft of the paper.

Data sharing statement: please email corresponding author

Corresponding Author:

Naseema Gangat, MBB, Division of Hematology, Department of Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 5590 Tel- 507-284-2511
E-mail-gangat.naseema@mayo.edu
To the editor,

Acquired pure red cell aplasia (PRCA) is a heterogenous entity, which may present in association with autoimmune diseases, lymphoproliferative disorders including large granular lymphocytic leukemia (LGL) or chronic lymphocytic leukemia (CLL), monoclonal gammopathy of undetermined significance (MGUS), thymoma, viral infections (parvovirus B19), drugs (recombinant erythropoietin), or ABO-incompatible stem cell transplantation.(1) An immune basis involving antibody and cell-mediated responses which inhibit red cell erythropoiesis and is considered a common pathogenetic mechanism. Accordingly, immunosuppressive agents are utilized as first line therapy and cyclosporine in combination with corticosteroids yields high response rates (66-95%).(2) Treatment considerations in refractory cases, include cyclophosphamide, alemtuzumab, antithymocyte globulin, bortezomib, rituximab, and intravenous immunoglobulin (IVIG).(1) Herein, we describe a 74-year-old female with a ten-year history of treatment-refractory idiopathic acquired PRCA with rapid and sustained response to daratumumab.

At initial presentation, she developed symptomatic anemia (hemoglobin 5 g/dl, MCV 98% fl) requiring hospitalization. Anemia workup revealed severe reticulocytopenia, with reticulocyte %, <0.28 and absolute reticulocyte count of 2800. Serology for parvovirus B19, cytomegalovirus, hepatitis B, C, and human immunodeficiency virus were negative. Monoclonal protein studies identified an IgG kappa, 0.5 g/dl with a normal immunoglobulin free light chain ratio. Computed tomography scan of the chest showed no evidence of thymoma. Bone marrow examination revealed maturation arrest in erythroid precursors, few pro-normoblasts were seen, granulopoiesis and megakaryocytes appeared normal, and an increase in plasma cells (5%) was noted. There was no evidence of a lymphoproliferative disorder nor myelodysplastic syndrome. Chromosome analysis and T cell gene rearrangement studies were within normal limits. A diagnosis of idiopathic PRCA was established and patient was initiated on cyclosporine and prednisone 60 mg daily with a 3-month taper. After six months of cyclosporine, given the ongoing transfusion needs, she received rituximab 375 mg/m2 weekly for 4 doses without clinical response. Thereafter, a combination of anti-thymocyte globulin (ATG), cyclosporine and prednisone were administered, and three months later treatment was switched to alemtuzumab, followed by
cyclophosphamide orally for six months which was discontinued due to treatment emergent neutropenia. Next, a trial of bortezomib 2 mg subcutaneously once weekly, two weeks on and one week off for a total of 8 cycles was pursued. Given the lack of clinical benefit with bortezomib, eltrombopag with dose uptitrated to 125 mg daily was prescribed for a total of one year without efficacy, followed by danazol for five months which resulted in masculinization and fluid retention.

We elected to observe off active therapy for three and a half years with continued red cell transfusion support every 3 weeks, and iron overload with peak ferritin of 1194 ng/ml was managed with deferasirox. Monoclonal protein studies were monitored annually; IgG kappa remained stable at 0.5 g/dl. A repeat bone marrow biopsy was obtained which continued to show decreased erythropoiesis and 5-9% CD138-positive plasma cells (Figure 1a). Cytogenetic studies were without clonal abnormality. At that time, treatment with daratumumab, a human IgG1k monoclonal antibody targeting plasma cells, at a dose of 16 mg/kg weekly was initiated. At baseline, patient was transfusion-dependent every 3 weeks and reticulocyte % was <0.28. A week after initiation of therapy, hemoglobin was above 8 g/dl and one and two-month post therapy, hemoglobin values were 9.4 g/dl and 11 g/dl, respectively. Similarly, the reticulocyte % peaked at month 1, at 3.33 (Figure 2). Daratumumab was administered weekly for 8 weeks and given the peak hemoglobin of 11 g/dl, the treatment schedule was changed to bimonthly with hemoglobin consistently remaining above 10 g/dl without transfusion support. Ferritin decreased to 79 ng/ml by two months following initiation of therapy, hence deferasirox was discontinued. At nine months post therapy, a repeat marrow was obtained which demonstrated a normocellular bone marrow with morphologically unremarkable trilineage hematopoiesis, including an adequate number of erythroid precursors, however, clonal plasma cells (up to 10%) remained unchanged (Figure 1b). Daratumumab did not result in any adverse effects., and no infusion-related reactions were noted. Given the sustained hemoglobin > 10 g/dl, but downtrending reticulocytes, she continues to receive daratumumab on a monthly basis. IgG kappa monoclonal gammopathy is still present and measures 0.3 g/dL on last measure. Immunoglobin levels have been closely monitored without major infectious complications other than an upper respiratory tract infection.
The above case highlights the challenges encountered in management of PRCA, specifically in cases without a clear etiology. Treatment recommendations are based on case series and expert opinion.(1) The association of MGUS with PRCA has been previously described and was observed in a quarter, 12 of 51 patients with PRCA that were evaluated at the National Institute of Health (NIH).(3) In addition, three patients were successfully treated with anti-myeloma directed therapy consisting of bortezomib or lenalidomide in combination with dexamethasone.(3) It is to be noted that our patient had previously received bortezomib and rituximab, targeting plasma cells and B cells, respectively. Most recently, successful treatment of PRCA following ABO-incompatible stem cell transplant with daratumumab has been described in a total of ten cases with rapid and prolonged remission achieved after two to four doses of therapy.(4-6) In the aforementioned situation, clinical response was attributed to elimination of the residual recipient plasma cells and reduction in isohemagglutinin titers. In our patient, PRCA was not necessarily associated with MGUS given the lack of therapeutic benefit with bortezomib. Moreover, follow up bone marrow examination after nine months of daratumumab therapy did not demonstrate an appreciable change in the plasma cell clone, in spite of improvements in hemoglobin levels and elimination of transfusion needs.

Although, daratumumab primarily targets high CD38 expressing plasma cells, it is known to have myriad immunomodulatory effects, on CD38-positive T and B cells, including regulatory T cells (Tregs). In addition, an increase in cytotoxic T-cell number, activation, and clonality has been observed following daratumumab in multiple myeloma.(7, 8) A similar effect of daratumumab in modulating CD4 and CD8 T cell responses with reduction in type 1 interferon activity has also been reported in connection with treatment of refractory systemic lupus erythematosus.(9) Based on the above observations, we hypothesize that modulation of T cell-mediated immune responses, although not confirmed by immune profiling, resulted in clinical improvement in our patient. In summary, we describe a patient with idiopathic PRCA refractory to eight prior therapies including rituximab and bortezomib, that achieved a rapid response following daratumumab, suggesting an efficacy signal, which is worthy of further prospective investigation.
References


**Figure Legends**

Title: Bone marrow biopsy findings pre- and post-treatment with daratumumab

Figure 1a. Bone marrow biopsy pre-treatment with daratumumab

Bone marrow aspirate (500x magnification), core biopsy (100x magnification) and immunohistochemical stains (100x magnification) performed on the core biopsy. The findings show decreased erythropoiesis with left shift as demonstrated by scattered E-cadherin-positive pronormoblasts and very rare hemoglobin-positive maturing erythroblasts, a normal number of myelomonocytic elements (positive for myeloperoxidase) and 5-9% CD138-positive plasma cells.

Figure 1b. Bone marrow biopsy post- treatment with daratumumab

Bone marrow aspirate (500x magnification), core biopsy (100x magnification) and clot section (100x magnification). The findings show a normocellular bone marrow for age, with morphologically unremarkable trilineage hematopoiesis, including an adequate number of erythroid precursors. CD138 immunohistochemical stain demonstrates increased plasma cells (up to 10%). Kappa and lambda light chain in situ hybridization demonstrates kappa light chain restriction within the plasma cells.

Figure 2. Pre- and post-daratumumab changes in hemoglobin levels, reticulocyte percentage and monoclonal protein studies
Figure 2.

<table>
<thead>
<tr>
<th></th>
<th>hemoglobin g/dl</th>
<th>reticulocyte %</th>
<th>IgG kappa M spike</th>
<th>Kappa Free light chain</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td>Transfusion-dependent every 3 weeks</td>
<td>&lt;0.031</td>
<td>0.5</td>
<td>2.45</td>
</tr>
<tr>
<td>month 1</td>
<td>9.4</td>
<td>3.33</td>
<td>0.3</td>
<td>1.1</td>
</tr>
<tr>
<td>month 2</td>
<td>11</td>
<td></td>
<td>0.3</td>
<td>0.69</td>
</tr>
<tr>
<td>month 6</td>
<td>10.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>month 9</td>
<td>10.3</td>
<td>0.56</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>month 12</td>
<td>10.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>