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Daratumumab, an original approach for treating multi-refractory autoimmune cytopenia

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Authorship contributions

EC and MMa designed the study and analyzed the data. EC, SA, AR, TC, DB, MC, EO, MMi, BG and MMa wrote the manuscript and included patients in the study.

Conflict of Interest Disclosures

The authors have no conflict of interest to declare.

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To the editor,

Immune thrombocytopenia (ITP) and warm autoimmune hemolytic anemia (wAIHA) are antibody-mediated autoimmune diseases in which plasma cells (PCs) secrete pathogenic antibodies directed against platelet and red blood cell antigens. Some patients show no response to first- or second-line treatments, including corticosteroids, rituximab, immunosuppressive drugs, splenectomy and in the case of ITP, thrombopoietin receptor agonists, a situation that increases the risk of morbidity and mortality. In these refractory cases, persistent autoreactive long-lived PCs in bone marrow could explain treatment failure.

Daratumumab, an anti-CD38 monoclonal antibody developed to target tumoral PCs in multiple myeloma, was recently found effective in antibody-mediated diseases, such as autoimmune cytopenia following hematopoietic stem cell transplantation and systemic lupus. Here we report the characteristics and outcome of patients who received daratumumab “off label” (compassionate use) for severe refractory ITP or wAIHA.

We conducted an observational, retrospective study including patients >18 years and treated by daratumumab for ITP and/or wAIHA (primary or secondary) according to international criteria and identified through the French National Reference Center for Adult's Immune Cytopenia network from November 2019 to November 2021. Exclusion criteria was patient opposition to data collection. All patients were informed and gave consent for “off label” use of daratumumab. The initial treatment regimen was extrapolated from the one commonly used in myeloma (i.e., at least 4 daratumumab infusions at 16 mg/kg per week combined with oral dexamethasone 20 mg before each infusion). For ITP, complete response (CR) was defined as platelet count >100 x10⁹/L and response (R) as platelet count between 30 and 100 x10⁹/L with at least a 2-fold increase from baseline. For wAIHA, CR was defined as hemoglobin level ≥ 12 g/dL in the absence of recent transfusion and R as hemoglobin level ≥ 10 g/dL with at least a 2-g/dL increase from the pre-treatment level in the
absence of recent transfusion (< 1 month). Patients who required any other treatment for autoimmune cytopenia including rescue therapy >6 weeks after first daratumumab infusion were considered non-responders regardless of platelet or hemoglobin levels. The first daratumumab infusion was considered day 0 for subsequent time points. Clinical and biological data were collected with a standardized form. The study received IRB approval (00011558, UPEC University, AP-HP).

Eight patients (5 females [62.5%]; median age 45 years [range 34–70]) from 6 participating centers received daratumumab for refractory ITP (n=5), acquired Glanzmann syndrome with former ITP and normal platelet count (n=1) or wAIHA (n=2). Six had secondary ITP or wAIHA, 5 had Evans syndrome with no underlying immunodeficiency (including one patient with primary anti-phospholipid syndrome) and one patient had a history of Hodgkin lymphoma that was cured (#5) 9 years before the onset of ITP/Glanzmann syndrome (Table 1). At the time of daratumumab initiation, median disease duration was 84.5 months [range 18–174]. The median number of previous therapies was 6 [6-11]. All patients showed no response to their last course of rituximab (except one patient with relapse at 3 months) and 5 underwent splenectomy (Table 1).

For the 5 patients with ITP, the median platelet count was 11 x10⁹/L [range 0–21], and all patients had skin and/or mucosal bleeding within the month before daratumumab. Two patients (#1, #2) achieved CR at 4 weeks (Figure 1). Patient #1 had a history of arterial and venous antiphospholipid syndrome, with strong positivity of lupus anticoagulant and IgM anti-beta2GP1 antibodies without IgG or anticardiolipin antibodies. Nine months after daratumumab, the patient had no remaining IgM anti-beta2GP1 antibodies, and lupus anticoagulant was barely detectable. He had no recurrence of thrombosis during follow-up with ongoing vitamin K antagonist treatment.
Patient #3 was dependent on corticosteroids and had no response at 4 weeks, which resulted in a transient increase in corticosteroid doses. However, he achieved long-lasting CR even after corticosteroids discontinuation 24 weeks after daratumumab, suggesting a delayed effect of anti-CD38 treatment. The two remaining patients (#4, #6) showed no response after daratumumab.

One 35-year-old patient (#5) had chronic ITP, and after splenectomy, acquired Glanzmann’s thrombasthenia developed with bleeding despite normal platelet counts. She had anti-GPIIbIIIa antibodies, and platelet aggregation studies showed no aggregation with adenosine diphosphate, epinepherin, or arachidonic acid, with reverse ristocetin agglutination. She showed no response to intravenous immunoglobulin, corticosteroids or mycophenolate mofetil and was given daratumumab, with no response for hemorrhagic symptoms. She eventually had ITP relapse 24 weeks after daratumumab.

For the 2 patients with wAIHA, the median baseline hemoglobin level was 9.4 g/dL [range 8.2–10.7], median reticulocyte count 174 x 10^9/L [124–225], and median bilirubin level 27 μmol/l [range 24–30]. For both patients, the haptoglobin level was < 0.1 mg/L, and the median lactate dehydrogenase level was 2.8 times the normal range [range 1.34–4.2]. Both had a history of ITP but normal platelets at first daratumumab infusion. One patient achieved CR after 4 cycles of daratumumab but relapsed after 9 months, and one had no response after 11 cycles, despite a progressive decrease in transfusion requirement after 3 months.

After a median follow-up of 24 weeks [range 24–36] from the first infusion of daratumumab, 5 patients experienced at least one moderate adverse event. Three (#3, #7 and #8) had a minor reaction at the first daratumumab infusion. No further infusion-related reactions occurred afterwards. Two patients had infectious events: patient #5 had bacterial pneumonia requiring hospitalization at 4 weeks and patient #8 had COVID-19 pneumonia.
requiring hospitalization and convalescent plasma therapy because of persistent symptoms at 20 weeks (chronic viremia without seroconversion). Median gammaglobulin level decreased from 7.1g/L [4.8–16.2] before treatment to 4.2g/L [3.5–7.6] at week 12 and 6.1g/L [6–15.5] at week 36 (Figure 2). Hypogammaglobulinemia (i.e., gammaglobulin level <6g/L) was observed in 5 out of 6 patients at 12 weeks (after exclusion of 2 patients that had received intravenous immunoglobulin in the 3 weeks before dosage).

Although this study has some limitations, including its uncontrolled design and the heterogeneity of the patients, our results suggest that daratumumab may be effective for some patients with refractory ITP and/or wAIHA, two conditions associated with high mortality rate. Three of 8 patients achieved CR and 1 patient a delayed response despite previous failure to respond to several treatment lines including rituximab, splenectomy and at least one immunosuppressant. One patient showed complete disappearance of antiphospholipid antibodies. Whether depletion of CD38+ cells correlates with response and/or relapses remains an open question that should be addressed in future studies.

We observed rapid response (within 1 month) among responders, suggesting that 4 daratumumab infusions are sufficient to induce remission in responders. However, the optimal number of infusions remains to be determined. Importantly, two patients with an initial CR eventually relapsed at 3 and 9 months, suggesting that PC reconstitution had occurred. In these patients, the ongoing auto-immune B-cell response may not be affected by daratumumab, which targets PCs and spares CD38− B cells. Thus, combining B-cell depletion with an anti-CD20 antibody and daratumumab may impair the generation of newly formed autoreactive PCs and prevent relapse.

In this particular group of immunocompromised patients, the risk of severe infection was a main concern. All but one experienced profound although transient hypogammaglobulinemia, and two had a symptomatic infection. Therefore, the risk/benefit
balance of such therapy should be carefully discussed according to the patient's clinical history.

In conclusion, daratumumab may provide clinical benefit in a subset of patients with ITP or wAIHA refractory to standard therapy. However, the efficacy seems relatively modest and hypogammaglobulinemia exposes to risk of infection. Future prospective trials will evaluate the use of CD38 directed monoclonal antibodies for the management of patients with immune cytopenias, such as daratumumab in ITP (NCT04703621) or isatuximab in wAIHA (NCT04661033).

References


Table 1: Characteristics and outcomes of patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age/Sex</th>
<th>Autoimmune cytopenia</th>
<th>Disease duration (months)</th>
<th>Active or past underlying disease</th>
<th>Time from last rituximab infusion</th>
<th>Other previous therapies</th>
<th>Number of daratumumab infusions</th>
<th>Treatments given with daratumumab</th>
<th>Response</th>
<th>Time to response (days)</th>
<th>Duration of response (months)</th>
<th>Relapse</th>
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<tbody>
<tr>
<td>1</td>
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<td>ITP</td>
<td>95</td>
<td>Evans syndrome antiphospholipid syndrome</td>
<td>3</td>
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<td>None</td>
<td>CR</td>
<td>7</td>
<td>12</td>
<td>No</td>
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<td>Evans syndrome</td>
<td>98</td>
<td>No (obesity)</td>
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<td>6</td>
<td>None</td>
<td>CR</td>
<td>35</td>
<td>3</td>
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<tr>
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<td>70/M</td>
<td>ITP</td>
<td>103</td>
<td>Recurrent venous thrombosis ischemic stroke with hemorrhagic transformation</td>
<td>21</td>
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<td>None</td>
<td>Failure</td>
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<td>No</td>
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<tr>
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<td>20/F</td>
<td>ITP</td>
<td>174</td>
<td>Hodgkin disease (9 years before daratumumab)</td>
<td>10</td>
<td>CS (resistant), IV Ig (response), romiplostim (failure), eltrombopag (failure), MMF (failure), disulone (failure)</td>
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<td>High-dose CS and IV Ig</td>
<td>Failure</td>
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<tr>
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<td>35/F</td>
<td>acquired Glanzmann syndrome</td>
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<td>Hodgkin disease</td>
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<td>For ITP: romiplostim (failure), eltrombopag (failure), disulone (failure)</td>
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<td>None</td>
<td>Failure</td>
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<td>NA</td>
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<tr>
<td>6</td>
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<td>12</td>
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<td>CS (response), IV Ig (response), romiplostim (failure), eltrombopag (response then adverse event)</td>
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<td>High-dose CS and IV Ig</td>
<td>Failure</td>
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<td>NA</td>
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<tr>
<td>7</td>
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<td>wAIHA</td>
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<td>CS (response), AZA (failure), CSA (failure), evorolimus (failure), bortezomib (failure)</td>
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<td>High-dose CS with complete weaning at 6 weeks</td>
<td>CR</td>
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<td>9</td>
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<tr>
<td>8</td>
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<td>wAIHA</td>
<td>26</td>
<td>Evans syndrome</td>
<td>5</td>
<td>Yes</td>
<td>CS (response), AZA (failure), CSA (failure), everolimus (failure), bortezomib (failure)</td>
<td>11</td>
<td>None</td>
<td>Failure</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

AGS: acquired Glanzmann syndrome; AZA: azathioprine; CR: complete response; CS: corticosteroids; CSA: ciclosporin; CYC: cyclophosphamide; DAT: direct antiglobulin test; IV Ig: intravenous immunoglobulin; HCQ: hydroxycholoquine; MMF: mycophenolate mofetil; ITP: immune thrombocytopenia; wAIHA: warm autoimmune hemolytic anemia
Figure Legends

Figure 1: Autoimmune cytopenia evolution after daratumumab treatment

(A) Evolution of platelets in patients with Immune thrombocytopenia (ITP) after daratumumab. Patient #5 had acquired Glanzmann syndrome and red stars indicate hemorrhagic symptoms. (B) Evolution of hemoglobin level in warm autoimmune hemolytic anemia (wAIHA) patients after daratumumab. Week 0 corresponds to first daratumumab infusion (orange “D”). CS: corticosteroids, CYC: cyclophosphamide, IVIg: intravenous immunoglobulin, MMF: mycophenolate mofetil, RBC: red blood cell transfusion, SPL: splenectomy. Dotted lines indicate the lower limit of normal values.
Supplementary Figure 1: Serum level of total gammaglobulins and immunoglobulin isotypes after daratumumab treatment

Serum level of total gammaglobulins (A), and immunoglobulin isotypes IgG (B), IgA (C) and IgM (D) evolution at baseline (M0) and 3, 6 and 9 months after daratumumab. Dotted lines indicate the lower limit of normal values. Red triangles indicate measures in patients that had received intravenous immunoglobulin in the past 3 weeks.