

# Daratumumab for immune thrombotic thrombocytopenic purpura

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## Key Points

- Treatment of iTTP with daratumumab leads to disappearance of ADAMTS13 inhibitor and restoration of normal ADAMTS13 activity.
- Targeting of plasma cells with daratumumab is a new treatment option in relapsing and refractory iTTP.

Immune thrombotic thrombocytopenic purpura (iTTP) is a life-threatening thrombotic microangiopathy. It is caused by a severe ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motifs, 13) deficiency due to circulating autoantibodies, and is associated with significant morbidity and mortality. Current treatment options include plasma exchange, immunosuppression, and caplacizumab. When remission is achieved, the risk of relapse is high, especially in patients with persistent ADAMTS13 deficiency. We report the eradication of persistent ADAMTS13 inhibitory autoantibodies and restoration of normal ADAMTS13 activity using the anti-CD38 antibody daratumumab in two patients with iTTP. One patient had a frequently relapsing course, and the other a treatment-refractory first episode. There were no relevant adverse drug reactions.

## Introduction

Immune thrombotic thrombocytopenic purpura (iTTP) is a life-threatening thrombotic microangiopathy (TMA) caused by a severe deficiency of ADAMTS13 activity resulting from inhibitory or clearance-enhancing autoantibodies. ADAMTS13 deficiency leads to impaired cleavage of ultralarge von Willebrand factor (VWF) and formation of VWF/platelet-rich microvascular thrombi with thrombocytopenia, microangiopathic hemolytic anemia, and tissue ischemia.<sup>1-3</sup> Before the availability of effective treatment, the mortality rate exceeded 90% and still reaches 10%. Relapse after a first episode occurs in at least 30% of patients.<sup>4</sup>

Current management of iTTP consists of plasma exchange (PE), immunosuppression with corticosteroids, and often administration of rituximab, an anti-CD20 antibody. Caplacizumab, a recently introduced anti-VWF nanobody, contributes to faster remission and reduced morbidity and mortality.<sup>5,6</sup> Anti-CD20 therapy with rituximab reduces the risk of relapse. It is increasingly used upfront but fails to normalize ADAMTS13 activity in ~15% of cases.<sup>7,8</sup> Treatment of relapsing or refractory iTTP remains a challenge. Such patients receive additional cycles of rituximab,<sup>9</sup> second-generation anti-CD20 antibodies,<sup>10</sup> bortezomib,<sup>11</sup> ciclosporin,<sup>12</sup> or cyclophosphamide or undergo splenectomy.<sup>13</sup>

The underlying cause of frequently relapsing or refractory iTTP is the reemergence or continued production of autoantibodies to ADAMTS13 by pathogenic ADAMTS13-specific B cells, possibly plasma blasts and long-lived plasma cells,<sup>14</sup> also implicated in other autoimmune diseases.<sup>15,16</sup> Plasma blasts and plasma cells do not express CD20, thereby escaping CD20-directed therapy. They strongly express CD38, a molecule targeted by daratumumab, a humanized anti-CD38 antibody approved for the treatment of multiple myeloma. Daratumumab has a favorable safety profile<sup>17</sup> and is therefore a promising candidate for treating antibody-mediated autoimmune diseases.

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**Table 1. Patient characteristics and treatment of acute episodes of iTTP that included daratumumab**

	Patient 1	Patient 2
<b>Characteristics</b>		
Sex	Male	Female
Age at presentation, y	32	31
Ethnicity	White	White
BMI, kg/m <sup>2</sup>	32	32
Type of iTTP episode	Relapse	First
N of previous iTTP episodes	3	0
Associated disease	None	Hypothyroidism
<b>Laboratory values at presentation (current iTTP episode)</b>		
ADAMTS13 activity (normal range, >51%, %)	<5	<5
ADAMTS13 inhibitor, BU/mL	>2	>2
Hemoglobin concentration (normal range, 134-170 [men] and 117-153 [women]), g/L	140	108
Platelet count (normal range, 143-400), × 10 <sup>9</sup> /L	6	5
Lactate dehydrogenase (normal range, 240-480), U/L	2000	978
Total bilirubin (normal range, <21), μmol/L	54	39.7
Creatinine (normal range, 62-106), μmol/L	105	54
High-sensitivity troponin	Not elevated	Elevated
<b>Treatment</b>		
PE sessions	7	15
Corticosteroids	Yes	Yes
Caplacizumab, d	32	121
Rituximab, n of doses	4	4
Daratumumab, n of doses	4	6
Follow-up, wk after last dose of daratumumab	14	10

BMI, body mass index; BU, Bethesda units.

Recent reports describe its successful use in patients with autoimmune hemolytic anemia,<sup>18</sup> systemic lupus erythematosus,<sup>19</sup> autoimmune encephalitis,<sup>20</sup> graft rejection,<sup>21</sup> and autoimmune cytopenias following hematopoietic stem cell transplantation.<sup>22,23</sup>

We report the first treatment of iTTP with daratumumab, resulting in rapid and complete ADAMTS13 remission and disappearance of ADAMTS13 inhibitors in 2 patients, 1 with frequently relapsing iTTP and the other with primary refractory iTTP.

## Case description

Patient 1, a 32-year-old man, experienced his first iTTP episode with severe ADAMTS13 deficiency (<5%) resulting from an inhibitory autoantibody in 2014 and was successfully treated with PE and corticosteroids. First and second clinical relapses occurred 20 and 54 months, respectively, after the initial episode. Remission was achieved by PE and corticosteroids. Four doses of rituximab (375 mg/m<sup>2</sup>) were administered after the first relapse, and ADAMTS13 activity was >90% in all 3 controls until his next relapse. The third clinical relapse occurred another 20 months later (Table 1; Figure 1A). In addition to PE and corticosteroids, the patient was treated with caplacizumab and received 4 more doses of rituximab (375 mg/m<sup>2</sup>). Although clinical remission was

achieved, severe ADAMTS13 deficiency and inhibitor persisted during the ensuing 4 months. Considering the high risk of another clinical relapse, we decided to administer 4 once-per-week infusions of daratumumab.

Patient 2, a 31-year-old woman, was diagnosed with acute TMA in the 38th week of her second pregnancy. HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome was suspected and cesarean section performed, but laboratory signs and symptoms of TMA persisted. Detection of severe ADAMTS13 deficiency (<5%) resulting from a functional inhibitor confirmed iTTP (Table 1; Figure 1B). We initiated PE and corticosteroids. The platelet count increased to ~50 × 10<sup>9</sup>/L but did not normalize until caplacizumab was added on day 14 of PE. Like rituximab, it was withheld initially because of the patient's wish to breastfeed. By day 29, 4 doses of rituximab (375 mg/m<sup>2</sup>) had been administered. Although B-cell depletion was documented, ADAMTS13 failed to improve, and caplacizumab had to be continued to prevent a clinical relapse.<sup>24</sup> We then decided to administer 6 once-per-week infusions of daratumumab.

## Methods

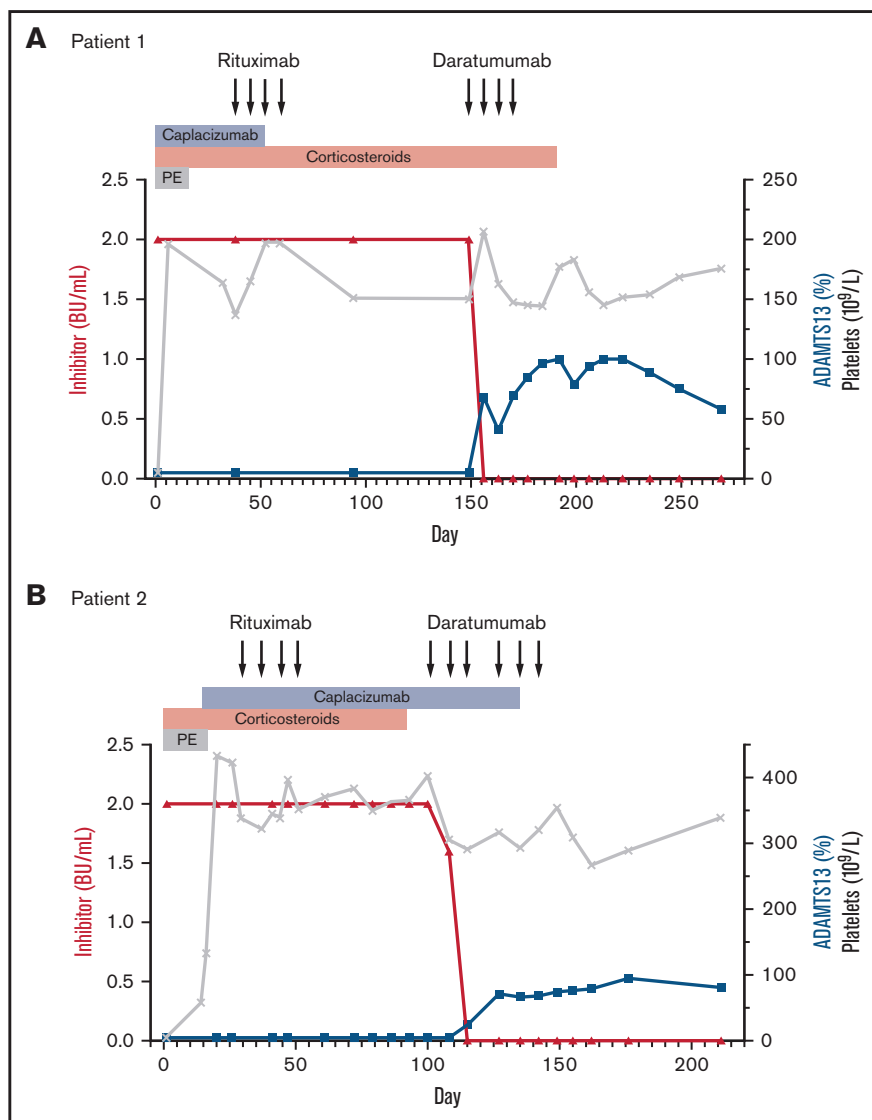
Daratumumab was administered as IV infusions of 16 mg/kg of body weight. The patients were treated at different university hospitals; patient 1 received 4 once-per-week doses based on a report of patients with systemic lupus erythematosus,<sup>19</sup> and patient 2 received 6 once-per-week doses based on an earlier treatment of antibody-mediated graft rejection after kidney transplantation.<sup>21</sup> Methylprednisolone, antihistamines, and paracetamol were administered as premedication to prevent infusion-related adverse reactions.

ADAMTS13 activity in plasma and functional ADAMTS13 inhibitors were determined as reported.<sup>25</sup> Standard response criteria of iTTP were applied according to consensus definitions.<sup>3</sup> Adverse drug reactions were graded according to Common Terminology Criteria for Adverse Events. The study was conducted in accordance with the Declaration of Helsinki. Both patients provided written consent to off-label treatment with daratumumab and the publication of their cases.

## Results and discussion

The patients described here are representative of iTTP. Patient 1 initially achieved clinical and complete ADAMTS13 remission with standard therapy, later showed a relapsing course, and eventually was nonresponsive with persistence of an ADAMTS13 inhibitor despite repeated anti-CD20 therapy with rituximab. Patient 2 experienced a refractory first iTTP episode. Although treated with PE, corticosteroids, and rituximab, ADAMTS13 deficiency and inhibitor persisted, and we were unable to discontinue caplacizumab.

In both cases, the administration of daratumumab, an anti-CD38 antibody approved for the treatment of multiple myeloma, led to the rapid eradication of ADAMTS13 inhibitors and restoration of normal ADAMTS13 activity (Figure 1). In patient 1, we observed the disappearance of the inhibitor and normalization of ADAMTS13 activity 1 week after the first infusion. Fourteen weeks after completion of daratumumab, he is in ongoing clinical and complete ADAMTS13 remission. In patient 2, partial ADAMTS13 remission (increase to 25%) was noted 1 week after the second infusion, and complete ADAMTS13



**Figure 1. Treatment of iTTP with the anti-CD38 antibody daratumumab.** Clinical course and selected laboratory parameters from hospital admission to the most recent follow-up in 2 patients. Corticosteroids were started at a high dose and then tapered. In patient 2, daily administration of caplacizumab was reduced to every other day after 90 days. (A) Patient 1 with frequently relapsing iTTP; the course of his latest iTTP relapse is shown. (B) Patient 2 with a refractory first iTTP episode. Red line indicates titer of ADAMTS13 inhibitor (Bethesda units [BU] per mL; truncated at 2); blue line indicates ADAMTS13 activity (%); gray line indicates platelet count ( $\times 10^9/L$ ).

remission was observed another 2 weeks later. Caplacizumab was stopped after 121 days. Ten weeks after completion of daratumumab, she is in ongoing clinical and complete ADAMTS13 remission.

Daratumumab was selected as a plasma cell–directed therapy over other options such as bortezomib because of its favorable safety profile. It was indeed well tolerated, with a grade 1 adverse reaction in patient 1 (mild thoracic oppression) and grade 2 reactions in patient 2 (flush, hoarseness, nausea) during the first infusion only.

Despite previous therapy, we hypothesize that this response results from the depletion of pathogenic ADAMTS13 antibody–producing CD38<sup>+</sup> cells, typically plasma cells and most plasma blasts, by

daratumumab and possibly its additional immunomodulatory activity.<sup>18</sup> This is based on the following evidence: severe ADAMTS13 deficiency 30 days after the application of rituximab, as observed in both patients, is predictive of a lack of response later.<sup>7</sup> After his first relapse, patient 1 received rituximab, which at the time was effective. The lack of response to rituximab after his latest relapse is in line with the selection and differentiation of pathogenic B cells into (long-lived) plasma cells that have been documented in rituximab-treated immune thrombocytopenia<sup>15,16</sup> and in the spleen of patients with frequently relapsing iTTP.<sup>14</sup> Rapid response and clearance of autoantibodies following daratumumab have also been observed in patients with other autoimmune diseases<sup>22</sup> and graft rejection.<sup>21</sup> In accordance with trials involving patients with multiple myeloma,<sup>17</sup>

our patients tolerated daratumumab well, and we did not observe infectious complications.

In summary, daratumumab led to rapid normalization of ADAMTS13 activity and disappearance of inhibitors in 2 patients with iTTP, stable now for 14 and 10 weeks after the completion of therapy and without relevant adverse events. We hypothesize that adding daratumumab to standard treatment, thereby targeting inhibitor-producing pathogenic plasma cells, facilitates the clearance of ADAMTS13-inhibitory autoantibodies and recovery of ADAMTS13 activity in relapsing or refractory iTTP. Additional studies are warranted on the long-term efficacy and safety of a plasma cell-directed therapy with daratumumab in patients with iTTP.

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## Authorship

Contribution: J.v.d.B., J.A.K.H., A.H., and J.-D.S. designed the study, collected and analyzed the data, and wrote the manuscript; and C.P., I.H., and G.S. contributed to the collection of data and helped write the manuscript.

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