Effectiveness of Thrombopoietin-receptor Agonists in the Treatment of Refractory Immune Thrombocytopenia Associated to Systemic Lupus Erythematosus

To the Editor:

Thrombocytopenia is frequent in patients with systemic lupus erythematosus (SLE), occurring in 7% to 30% of patients. Less than 5% present a platelet count of < 50,000/mm³ and they usually respond to first- or second-line therapy [corticosteroids, immunosuppressive agents, intravenous immunoglobulin (IVIG), rituximab, or splenectomy]. However, a significant number of patients will not respond to these treatments or will relapse afterward¹.

Romiplostim and eltrombopag are 2 thrombopoietin-receptor agonist drugs that were approved in 2008 by the US Food and Drug Administration (FDA) to treat patients with chronic idiopathic thrombocytopenic purpura and other clinical manifestations of SLE flare. White blood cell count and hemoglobin were normal, and C3 and C4 levels were low [0.83 g/l (normal range 0.870–1.700) and 0.094 g/l (normal range 0.110–0.540), respectively]. Methylprednisolone (250 mg/6 h for 3 days, this being the standard regimen in our department to minimize adverse effects) was instituted with poor response (platelet count of 3000/mm³ 24 h after initiation of treatment). Therefore, IVIG (400 mg/kg/day for 5 days) was administered, achieving a partial response (71,000/mm³). The patient was discharged with prednisone at 1 mg/kg/day, azathioprine (100 mg/day), and hydroxychloroquine (200 mg/day). Rituximab was readministered in July 2008 and in August 2010, achieved a partial response (platelet count between 45,000/mm³ and 60,000/mm³; Table 1). Nevertheless, in January 2012, she relapsed again. Romiplostim was started and an initial complete response was achieved with a dose of 2 µg/kg/week. During the following weeks, the patient required subsequent increases in romiplostim dose to maintain the platelet count above 100,000/mm³, up to a maximum dose of 7 µg/kg/week. A platelet level above the threshold was sustained for more than 15 months, with excellent tolerance.

We describe 2 patients with immune thrombocytopenia associated with SLE refractory to first- and second-line therapy, which presented complete remission after treatment with thrombopoietin-receptor agonists (eltrombopag and romiplostim). In addition, a low dose of prednisone (7.5 mg/day) has been continued in both patients, and azathioprine could be definitively stopped in patient #2.

Both thrombopoietin agonists are currently available in many countries since the approval in 2008 by the main regulatory agents, FDA and European Medicines Agency, for the treatment of thrombocytopenia in patients with chronic immune thrombocytopenia and with an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Eltrombopag is a nonpeptide thrombopoietin agonist that binds to the transmembrane domain of the thrombopoietin receptor and stimulates the proliferation and differentiation of megakaryocytes in bone marrow²⁻⁴. It is admin-

Table 1. Characteristics of the patients with SLE-associated refractory immune thrombocytopenia who were treated with thrombopoietin-receptor agonists.

<table>
<thead>
<tr>
<th>Case (ref)</th>
<th>Age, yrs</th>
<th>Sex</th>
<th>Previous Treatments</th>
<th>Thrombopoietin-receptor Agonist</th>
<th>Dose</th>
<th>Response</th>
<th>Time to Response</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 (PC)</td>
<td>69</td>
<td>F</td>
<td>CS, IVIG, splenectomy, RTX</td>
<td>Eltrombopag</td>
<td>25 mg/day</td>
<td>Yes</td>
<td>2 weeks</td>
<td>No</td>
</tr>
<tr>
<td>#2 (PC)</td>
<td>39</td>
<td>F</td>
<td>CS, IVIG, CYC, azathioprine, RTX</td>
<td>Romiplostim</td>
<td>2 mcg/kg/week, further increased to 7 µg/kg/week</td>
<td>Yes</td>
<td>2 weeks</td>
<td>No</td>
</tr>
<tr>
<td>#3 (6)</td>
<td>44</td>
<td>M</td>
<td>CS, IVIG, azathioprine, RTX, CYC</td>
<td>Romiplostim</td>
<td>2 mcg/kg/week</td>
<td>Yes</td>
<td>3 weeks</td>
<td>No</td>
</tr>
<tr>
<td>#4 (7)</td>
<td>34</td>
<td>F</td>
<td>CS, IVIG, RTX, CYC</td>
<td>Romiplostim (previously eltrombopag without response)</td>
<td>3 mcg/kg/week</td>
<td>Yes</td>
<td>6 days</td>
<td>No</td>
</tr>
<tr>
<td>#5 (8)</td>
<td>19</td>
<td>F</td>
<td>CS, IVIG, RTX</td>
<td>Romiplostim</td>
<td>NS</td>
<td>Yes</td>
<td>NS</td>
<td>Kidney-limited thrombotic microangiopathy</td>
</tr>
<tr>
<td>#6 (9)</td>
<td>55</td>
<td>F</td>
<td>CS, RTX, CSA</td>
<td>Eltrombopag</td>
<td>50 mg/day</td>
<td>Yes</td>
<td>2 weeks</td>
<td>No</td>
</tr>
<tr>
<td>#7 (10)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>Eltrombopag</td>
<td>NS</td>
<td>Yes</td>
<td>NS</td>
<td>No</td>
</tr>
</tbody>
</table>

PC: present case; CS: corticosteroids; IVIG: intravenous immunoglobulin; RTX: rituximab; CYC: cyclophosphamide; CSA: cyclosporine; NS: not specified.

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istered orally once daily in doses ranging from 25 mg to 75 mg. Romiplostim is a synthetic peptide capable of binding to the thrombopoietin receptor myeloproliferative leukemia virus oncogene, which is administered as subcutaneous injections once weekly in doses ranging from 1 µg/kg to 10 µg/kg.

In SLE-associated thrombocytopenia, 2 types of antibodies have been described: those directed against thrombopoietin receptor (TPO-R), and those directed against the glycoprotein GPIIb/IIIa. Both antibodies are associated with different phenotypes of thrombocytopenia and different therapeutic responses. In fact, patients with antibodies against TPO-R tend to have more frequent megakaryocytic hypoplasia and poor response to treatment with corticosteroids and IVIG. Therefore, thrombopoietin analogs represent an exceptional therapeutic target in these patients. Bone marrow examination performed in both patients revealed the presence of a normal–high number of megakaryocytes, without signs of megakaryocytic hypoplasia that could suggest the presence of TPO-R antibodies.

Positive results in terms of effectiveness and tolerance of these drugs have been reported in the treatment of chronic immune thrombocytopenia. To date, only 4 cases of refractory SLE-associated thrombocytopenia successfully treated with thrombopoietin-receptor agonists have been reported (Table 1). One patient presented thrombocytopenia in the context of Evans syndrome and a pregnant woman with thrombocytopenia associated with different phenotypes of thrombocytopenia and different therapeutic analogs. Bone marrow examination performed in both patients revealed the presence of a normal–high number of megakaryocytes, without signs of megakaryocytic hypoplasia that could suggest the presence of TPO-R antibodies.

Both eltrombopag and romiplostim represent good and safe options for SLE-associated thrombocytopenia refractory to conventional immunosuppressive agents and even splenectomy.

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REFERENCES


8. Tomov S, Lazarchick J, Self SE, Bruner ET, Budisavljevic MN, Kidney-limited thrombotic microangiopathy with hypoplasia that could suggest the presence of TPO-R antibodies.

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