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/mm^3 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 afterward[1].

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 who have an insufficient response to conventional therapy[2,3,4,5]. To date, there are only 4 published cases of patients with SLE and immune thrombocytopenia successfully treated with these agents[6,7,8,9] and 1 case in whom this treatment was not effective[10]. We describe 2 additional cases of patients with SLE and refractory immune thrombocytopenia who responded to thrombopoietin-receptor agonists.

Case 1. A 69-year-old woman was diagnosed with SLE in 1992 because of anemia, thrombocytopenia, positive antinuclear antibody (ANA), anti-dsDNA, anti-Sm antibodies, lupus anticoagulant, and hypocomplementemia. In 1999, a laparoscopic splenectomy was performed because of severe immune thrombocytopenia (< 10,000/mm^3) that was refractory to high-dose prednisone and IVIG. She maintained a normal platelet count until March 2013 when she presented with mild epistaxis, ecchymosis, and thrombocytopenia of 22,000/mm^3 without 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/mm^3 24 h after initiation of treatment). Therefore, IVIG (400 mg/kg/day for 5 days) was administered, achieving a partial response (71,000/mm^3). The patient was discharged with prednisone at 1 mg/kg/day, but after a week, platelet count decreased to < 10,000/mm^3. Rituximab (2 doses of 1 g fortnightly) was initiated. Despite appropriate checked lymphocytic depletion (CD19 cell count < 0.5% 1 month after last dose), the patient persisted with severe thrombocytopenia (< 10,000/mm^3) with epistaxis and ecchymosis. All the agents previously used for treatment of immune thrombocytopenia are listed in Table 1. Eltrombopag (25 mg/day) was initiated, achieving a complete response (> 100,000/mm^3) in 2 weeks that continued after 5 months of treatment.

Case 2. A 39-year-old woman was diagnosed with SLE in November 1998 because of photosensitivity, arthritis, thrombocytopenia (2000/mm^3), positive ANA, anti-dsDNA, anti-Sm antibodies, and hypocomplementemia. Antiphospholipid antibodies were negative. She started treatment with hydroxychloroquine (200 mg/day) and prednisone (1 mg/kg/day) with normalization of platelet count, and subsequently a tapering dose of corticosteroids. In April 2006, she relapsed with severe immune thrombocytopenia (< 10,000/mm^3), mild leukopenia (3.7 × 10^9/l), hemoglobin of 15 g/l, and hypocomplementemia (C3 0.58 g/l and C4 < 0.007 g/l). Additional systemic manifestations of SLE were absent. The patient was refractory to a high dose of corticosteroids and IVIG, so she received rituximab (375 mg/m^2/week for 4 weeks). The platelet count remained persistently below 30,000/mm^3 despite combined therapy with maintenance doses of prednisone (25 mg/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/mm^3 and 60,000/mm^3; 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/mm^3, 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 marrow[11]. It is admin-

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

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

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

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[11], 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[12]. 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[2,3,4,5]. To date, only 4 cases of refractory SLE-associated thrombocytopenia successfully treated with thrombopoietin-receptor agonists have been reported[6,7,8,9] (Table 1). One patient presented thrombocytopenia in the context of Evans syndrome[6] and a pregnant woman with SLE had at 27 weeks of gestation thrombocytopenia refractory to corticosteroids, IVIG, rituximab, IV cyclophosphamide, and eltrombopag. She responded to romiplostim, which enabled her to deliver safely at 34 weeks of gestation[7]. Of note, the third patient presented renal thrombotic microangiopathy shortly after treatment with romiplostim[8]. In fact, venous and arterial thrombotic events have been described in patients treated with romiplostim. However, the incidence of these events did not differ from that of patients receiving placebo in a pooled analysis of all studies[13]. The fourth patient developed acquired amegakaryocytic thrombocytopenia about 14 years after initial diagnosis of SLE. She experienced an excellent response to eltrombopag after failing to respond to corticosteroids and rituximab, and being intolerant of cyclosporine[9]. Finally, an additional patient with a refractory SLE-associated thrombocytopenia was reported in a Danish case, although this patient did not achieve a significant response to thrombopoietin-receptor agonists[10].

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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J Rheumatol 2014;41:9; doi:10.3899/jrheum.140080