

The patient was phlebotomized to a hematocrit less than 42% and started on daily hydroxyurea 500 mg and aspirin 81 mg. Treatment with venesection and hydroxyurea achieved resolution of chorea within 4 weeks.

Neurologic complications have been reported in up to 80% of untreated PV patients.<sup>3</sup> PV-associated chorea (PVC) has been reported as the presenting complaint, primarily in older females, which typically involves the orofaciolingual and appendicular musculature and often resolves with phlebotomy or cytoreductive therapy.<sup>4-6</sup> The exact mechanism underlying PVC is not known and there are no specific neuroimaging abnormalities or pathologic findings.<sup>7,8</sup>

Chorea in this patient represents a possible forme fruste of an MPN in that the patient's clinical features did not allow for a definitive diagnosis of PV even though she was *JAK2V617F*<sup>+</sup>. A similar situation has been documented in patients who present with splanchnic vein thrombosis and are found to be *JAK2V617F*<sup>+</sup>. These patients lack overt signs of an MPN and in some cases have normal BM morphology.<sup>9</sup> More than 50% of such *JAK2V617F*<sup>+</sup> patients with splanchnic vein thrombosis eventually develop clinical features of MPN.<sup>10</sup>

Based on this report, patients over the age of 50 years presenting with chorea should be tested for *JAK2V617F* even if they have a normal hematologic profile. This case highlights the possibility that chorea might represent a forme fruste of an MPN that will be responsive to venesection and cytoreductive therapy. The natural history of an unclassifiable *JAK2V617F*<sup>+</sup> MPN presenting with neurologic complications is not yet known and will require further study.

**Jane Lew**

*Division of Hematology and Medical Oncology, The Tisch Cancer Institute,  
Department of Medicine, Mount Sinai School of Medicine,  
New York, NY*

**Steven J. Frucht**

*Movement Disorders Division, Department of Neurology,  
Mount Sinai School of Medicine,  
New York, NY*

**Marina Kremyanskaya**

*Division of Hematology and Medical Oncology, The Tisch Cancer Institute,  
Department of Medicine, Mount Sinai School of Medicine,  
New York, NY*

**Ronald Hoffman**

*Division of Hematology and Medical Oncology, The Tisch Cancer Institute,  
Department of Medicine, Mount Sinai School of Medicine,  
New York, NY*

**John Mascarenhas**

*Division of Hematology and Medical Oncology, The Tisch Cancer Institute,  
Department of Medicine, Mount Sinai School of Medicine,  
New York, NY*

The online version of this letter contains a data supplement.

**Conflict-of-interest disclosure:** The authors declare no competing financial interests.

**Correspondence:** John Mascarenhas, MD, Myeloproliferative Disorders Program, Tisch Cancer Institute, Division of Hematology/Oncology, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1079, New York, NY 10029; e-mail: john.mascarenhas@mssm.edu.

## References

1. Swerdlow S, Campo E, Harris NL, eds. International Agency for Research on Cancer. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue*. Geneva, Switzerland: World Health Organization; 2008.
2. James C, Ugo V, Le Couëdic JP, et al. A unique clonal *JAK2* mutation leading to constitutive signalling causes polycythaemia vera. *Nature*. 2005;434(7037):1144-1148.
3. Kremyanskaya M, Mascarenhas J, Hoffman R. Why does my patient have erythrocytosis? *Hematol Oncol Clin North Am*. 2012;26(2):267-283.
4. Ashenurst EM. Chorea complicating polycythemia rubra vera. *Can Med Assoc J*. 1972;107(5):434 passim.
5. Midi I, Dib H, Köseoglu M, Afsar N, Günel DI. Hemichorea associated with polycythaemia vera. *Neurol Sci*. 2006;27(6):439-441.
6. Bruyn GW, Padberg G. Chorea and polycythaemia. *Eur Neurol*. 1984;23(1):26-33.
7. Kim W, Kim JS, Lee KS, Kim YI, Park CW, Chung YA. No evidence of perfusion abnormalities in the basal ganglia of a patient with generalized chorea-ballism and polycythaemia vera: analysis using subtraction SPECT co-registered to MRI. *Neurol Sci*. 2008;29(5):351-354.
8. Nazabal ER, Lopez JM, Perez PA, Del Corral PR. Chorea disclosing deterioration of polycythaemia vera. *Postgrad Med J*. 2000;76(900):658-659.
9. Xavier SG, Gadelha T, Pimenta G, et al. *JAK2V617F* mutation in patients with splanchnic vein thrombosis. *Dig Dis Sci*. 2010;55(6):1770-1777.
10. Dentali F, Squizzato A, Brivio L, et al. *JAK2V617F* mutation for the early diagnosis of Ph- myeloproliferative neoplasms in patients with venous thromboembolism: a meta-analysis. *Blood*. 2009;113(22):5617-5623.

## To the editor:

### No cross-resistance after sequential use of romiplostim and eltrombopag in chronic immune thrombocytopenic purpura

Romiplostim and eltrombopag (a synthetic fusion peptibody and a nonpeptide molecule, respectively) are second-generation thrombopoietin mimetics/agonists that are structurally dissimilar to thrombopoietin and do not induce the formation of autoantibodies.<sup>1-3</sup> They have been recently approved for the treatment of relapsed/resistant immune thrombocytopenia (ITP) and both are able to improve the production of new platelets, which, in this disease, are reduced by binding of antiplatelet antibodies to BM megakaryocytes.<sup>4</sup> What is still not completely clear is whether these agents are cross-resistant. We describe herein 2 ITP patients who received eltrombopag as salvage therapy after they had become resistant to romiplostim.

A 58-year-old man was diagnosed in November 2007 with recurrent ITP after several lines of treatment, including steroids, high-dose immunoglobulins, cyclosporine, and rituximab. All of these therapies had induced significant responses but these were of brief duration. In June 2010, the patient's platelet count dropped to 6000/ $\mu$ L and he was started on weekly subcutaneous administrations of romiplostim progressively increased from 1-4  $\mu$ g/kg of body weight (Figure 1A). A complete response was achieved. However, 8 weeks later, a rapid decline of the platelet count occurred and further increasing romiplostim up to 10  $\mu$ g/kg was not effective. After an episode of subdural bleeding, the patient underwent splenectomy, initially refused, in October 2010. A

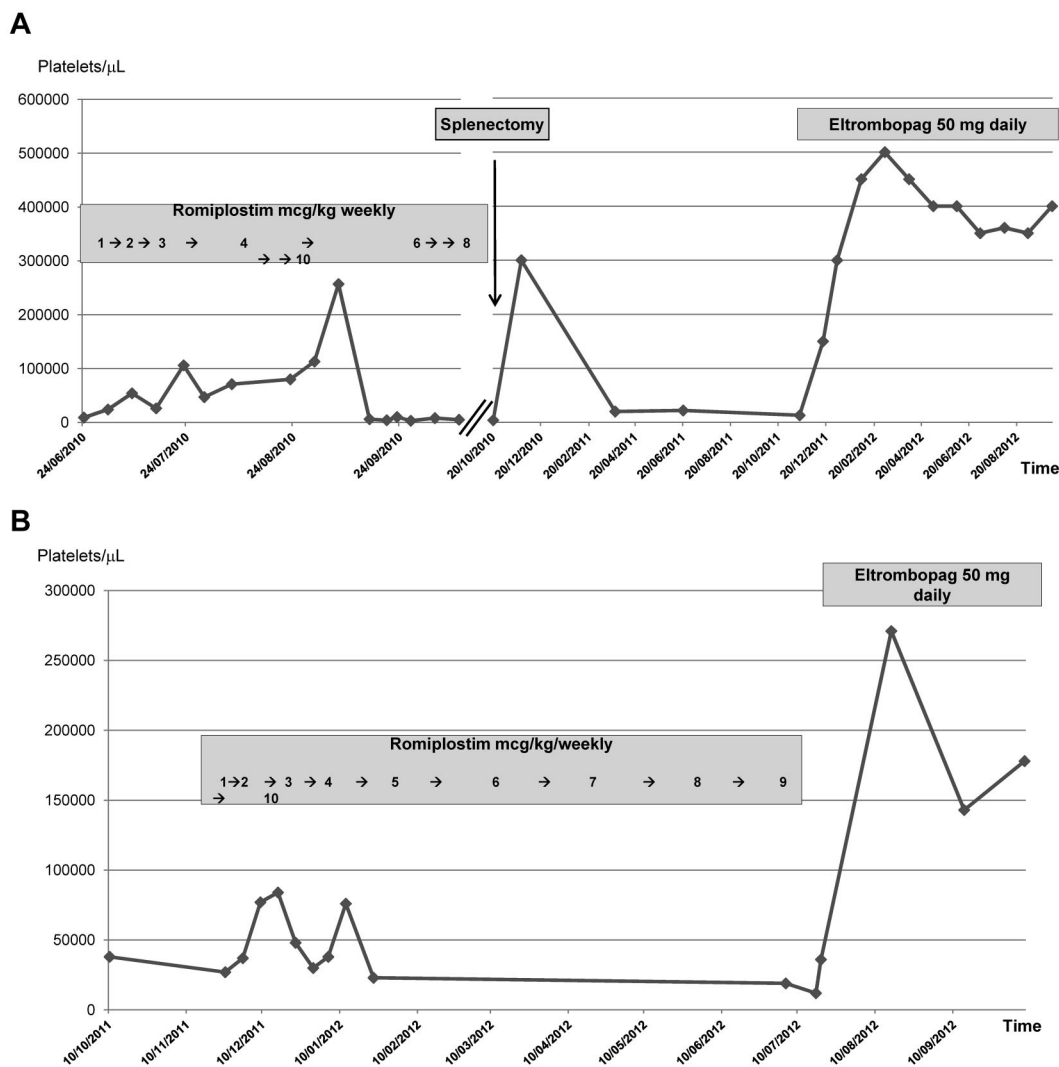


Figure 1. Romiplostim and eltrombopag sequential administration and platelet count in 2 different patients (A and B) with chronic, pretreated ITP.

marked response was obtained, but 2 months later, the patient's platelet count was 3000/ $\mu$ L. Eltrombopag at a daily oral dose of 50 mg was started, with a prompt and sustained response that has been maintained to the present time.

A 49-year-old woman was diagnosed with ITP in September 2009. Because her platelet count was approximately 40 000/ $\mu$ L initially, no therapy was given until August 2011, when the platelet count dropped to 21 000/ $\mu$ L and cutaneous hemorrhagic manifestations appeared. High-dose dexamethasone induced a complete but transient platelet response. In December 2011, the patient's platelet count was 28 000/ $\mu$ L. The patient refused splenectomy and started romiplostim, which was increased weekly from 1-10  $\mu$ g/kg of body weight, with a clinically significant but brief initial response (Figure 1B). In July 2012, the patient's platelet count was 14 000/ $\mu$ L. At that time, eltrombopag was begun orally at the daily dose of 50 mg/kg, achieving a complete and stable response that has been maintained to the present time.

These 2 cases suggest that, at the clinical level, there is probably no cross-resistance between romiplostim and eltrombopag. Both agents were well tolerated, but the quality and duration of response to eltrombopag were better than those previously obtained with romiplostim. A similar outcome was observed in a case that, to the

best of our knowledge, is the only one reported in the literature so far, in which eltrombopag was administered before romiplostim.<sup>5</sup> Our observations provide useful information for the management of ITP patients. These results are not completely unexpected if one takes into account that the 2 molecules bind the same receptor at different levels (romiplostim to the surface thrombopoietin receptor and eltrombopag to the thrombopoietin receptor's transmembrane domain). Confirmation in larger series of patients, including new potential indications currently being investigated (ie, in neoplastic disorders such as myelodysplastic syndromes) is required.

**Giovanni D'Arena**

Department of Onco-Hematology,  
Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS),  
Centro di Riferimento Oncologico della Basilicata,  
Rionero in Vulture, Italy

**Roberto Guariglia**

Department of Onco-Hematology, IRCCS,  
Centro di Riferimento Oncologico della Basilicata,  
Rionero in Vulture, Italy

**Giovanna Mansueto**

Department of Onco-Hematology, IRCCS,  
Centro di Riferimento Oncologico della Basilicata,  
Rionero in Vulture, Italy

**Maria Carmen Martorelli**  
 Department of Onco-Hematology, IRCCS,  
 Centro di Riferimento Oncologico della Basilicata,  
 Rionero in Vulture, Italy

**Giuseppe Pietrantonio**  
 Department of Onco-Hematology, IRCCS,  
 Centro di Riferimento Oncologico della Basilicata,  
 Rionero in Vulture, Italy

**Oreste Villani**  
 Department of Onco-Hematology, IRCCS,  
 Centro di Riferimento Oncologico della Basilicata,  
 Rionero in Vulture, Italy

**Rosa Lerose**  
 Hospital Pharmacy Unit, IRCCS,  
 Centro di Riferimento Oncologico della Basilicata,  
 Rionero in Vulture, Italy

**Pellegrino Musto**  
 Department of Onco-Hematology, IRCCS,  
 Centro di Riferimento Oncologico della Basilicata,  
 Rionero in Vulture, Italy

**Conflict-of-interest disclosure:** The authors declare no competing financial interests.

**Correspondence:** Giovanni D'Arena, MD, Department of Onco-Hematology, IRCCS Centro di Riferimento Oncologico della Basilicata, Via Padre Pio n1, 85028 Rionero in Vulture (Pz), Italy; e-mail: giovannidarena@libero.it.

## References

1. Imbach P, Crowther M. Thrombopoietin-receptor agonists for primary immune thrombocytopenia. *N Engl J Med*. 2011;365(8):734-741.
2. Liebman HA, Pullarkat V. Diagnosis and management of immune thrombocytopenia in the era of thrombopoietin mimetics. *Hematology*. 2011;2011:384-390.
3. Kuter DJ. Biology and chemistry of thrombopoietin. *Semin Hematol*. 2010;47(3):243-248.
4. McMillan R, Wang L, Tomer A, Nichol J, Pistillo J. Suppression of in vitro megakaryocyte production by antiplatelet autoantibodies from adult patients with chronic ITP. *Blood*. 2004;103(4):1364-1369.
5. Aoki T, Harada Y, Matsubara E, et al. Thrombopoietin receptor agonists in refractory immune thrombocytopenia: differential responses to eltrombopag and romiplostim: a case report and possible explanations. *J Clin Pharm Ther*. 2012;37(6):729-732.

## To the editor:

### C1-esterase inhibitor concentrate rescues erythrocytes from complement-mediated destruction in autoimmune hemolytic anemia

In autoimmune hemolytic anemia (AIHA), autoantibody-mediated complement activation results in C3 deposition on RBCs and possibly the formation of the membrane attack complex cumulating in intravascular hemolysis.<sup>1-4</sup> In case of acute signs of tissue hypoxia, life-saving transfusion with RBC units is required. However, recovery of RBC transfusions is inadequate because autoantibodies react with recipient and donor cells.<sup>1</sup> We hypothesized that being it is a plasma-derived inhibitor of the classic complement pathway, C1-esterase-inhibitor (C1-INH) may improve the recovery of RBC transfusion in AIHA patients.<sup>5</sup> In the present study, we investigated whether C1-INH can enhance the efficacy of RBC transfusions.

A 64-year-old female patient suffering from a diffuse large B-cell non-Hodgkin lymphoma was admitted with AIHA with intravascular hemolysis because of warm IgM autoantibodies. Direct antiglobulin test (DAT) for complement C3d was strongly positive. Despite treatment (Figure 1A), the patient's anemia worsened and she became symptomatic at a hemoglobin level of 3.7 g/L. Three RBC units were transfused. However, recovery of RBC transfusion was modest, resulting in accelerated hemolysis reaching a hemoglobin level of 4.4 g/L 3.5 days after the transfusion. Hemoglobin levels increased and even transiently stabilized, but then quickly dropped to a nadir of 3.3 g/L after short-term high-dose methylprednisolone therapy. Because of progressive hypoxia-related confusion, transfusion of 3 RBC units was started. Knowing that plasma-purified C1-INH (Cetor) has an excellent safety profile,<sup>5,6</sup> we decided to coadminister C1-INH to enhance the efficacy of the RBC transfusion in this patient after a regime that turned out to be efficient in sepsis patients.<sup>6,7</sup> Before transfusion, 6000 U of C1-INH were administered intravenously. Three additional infusions of 4000, 2000, and 1000 U were administered 22, 38, and 50 hours, respectively, after the first

C1-INH dose. As evidenced by the DAT for C3d (Figure 1A inset) and lactate dehydrogenase levels, C1-INH administration indeed attenuated both complement deposition on RBCs and hemolysis. Moreover, recovery of RBC transfusion was much better compared with the first transfusion. In the further clinical course, there were no signs of hemolysis and the patient's hemoglobin levels stabilized.

To support the observed in vivo effects of C1-INH, we performed in vitro experiments with 5 selected patient sera samples with a positive DAT for complement C3d and patient serum-induced hemolysis of bromelain-treated RBCs. Hemolysis of human O-typed RBCs was induced by incubation with these patient sera (Figure 1B). As expected, monoclonal anti-C5 completely abrogated antibody-induced hemolysis. A fixed high concentration of C1-INH (20 U/mL) also inhibited a substantial part of the lysis (Figure 1C-D). To analyze the effect of C1-INH on C3 deposition on the RBC surface, flow cytometry was used after incubation of human RBCs with patient sera. To ensure that sufficient intact RBCs were left for analysis, incubations were performed in the presence of excess amounts of monoclonal anti-C5, completely abrogating lysis while leaving C3 deposition unaffected. Incubation of RBCs with patient sera resulted in significant C3 deposition, which could be significantly and dose dependently inhibited by C1-INH to background levels (Figure 1E-G). In conclusion, our results show that C1-INH has potential as an effective and safe therapy to control complement-induced RBC destruction in AIHA patients.

**Diana Wouters**  
 Department of Immunopathology,  
 Sanquin Research and Landsteiner Laboratory, Academic Medical Center,  
 University of Amsterdam,  
 Amsterdam, The Netherlands