Superior Mesenteric Vein Thrombosis Following Treatment of Refractory Immune Thrombocytopenic Purpura with Romiplostim

Dhaval Shah, John Nelson, Gurpreet Lamba, Sivamurthy Kyathari and Karen Seiter*

Division of Hematology/Oncology, New York Medical College, Valhalla, New York 10595, USA

Abstract: Romiplostim is a thrombopoietin receptor agonist approved for the treatment of thrombocytopenia in patients with chronic idiopathic thrombocytopenic purpura (ITP) who had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Although thrombotic and embolic complications have been reported in patients receiving romiplostim, these have generally involved coronary artery or cerebral vascular events. Currently we report a patient with severe ITP treated with romiplostim who developed mesenteric venous thrombosis after a hemicolecctomy to resect colon cancer.

Keywords: ITP, Superior mesenteric vein thrombosis, romiplostim.

INTRODUCTION

Front line therapy of chronic immune thrombocytopenic purpura (ITP) includes corticosteroids and intravenous immunoglobulin [1, 2]. Although 60-70% of patients respond to such treatments, the disease recurs in 10-30%. Treatment options for relapsed patients include splenectomy and/or rituximab [3, 4]. Romiplostim is a thrombopoietin receptor agonist that was recently approved by the United States Federal Drug Administration (FDA) for the treatment of thrombocytopenia in patients with chronic ITP who had an insufficient response to corticosteroids, immunoglobulins, or splenectomy [5]. The most common toxicities include arthralgia, dizziness, insomnia and myalgia. Although thrombotic and embolic complications have been reported in patients receiving romiplostim, these have generally involved coronary artery or cerebral vascular events [5-7]. These reports are summarized in Table 1. Currently we report a patient with severe secondary immune thrombocytopenia treated with romiplostim who developed mesenteric venous thrombosis after a hemicolecctomy to resect a colon cancer.

A 77 year old woman presented to another hospital with melanoitic stools. She had a history of hypertension, stroke, chronic hepatitis B and C infection, hypothyroidism, and hypercholesterolemia. Medications upon admission included aspirin and clopidogrel 75 mg daily. The physical examination was significant for mild splenomegaly. The complete blood count (CBC) showed a white blood count of 5,000/mm³ with an unremarkable differential, a hemoglobin count of 153,000/mm³, a laparoscopic assisted right hemicolectomy and partial omentectomy was performed. Pathology revealed a T2N0M0 moderately differentiated adenocarcinoma of the cecum. Postoperatively the platelet count increased to 189,000/mm³. The fifth dose of

*Address correspondence to this author at the Room 250 Munger Pavilion, New York Medical College, Valhalla, New York, 10595, USA; Tel: 914 493 7514; Fax: 914 594 4420; E-mail: karen_seiter@nymc.edu

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romiplostim was decreased to 2 mcg/kg and prednisone was decreased to 10 mg daily. One week postoperatively the platelet count abruptly dropped to 21,000/mm³. Steroids were increased and the weekly romiplostim dose was returned to 3 mcg/kg for her sixth dose. Two days later the platelet count increased to 56,000/mm³ and the steroids were decreased. Prior to the seventh dose of romiplostim, the platelet count had increased to 160,000/mm³. The patient complained of severe abdominal pain. CT scan of abdomen demonstrated an occlusive venous thrombosis in the superior mesenteric vein terminating at the confluence with the splenic vein. She was then treated with full dose heparin. Her abdominal pain improved and heparin was changed to warfarin. The platelet count remained above 150,000/mm³, reaching a maximum of 253,000/mm³ and she did not receive any further doses of romiplostim. Evaluations of protein C, protein S, prothrombin gene 20210, and factor VIII were normal. A repeat lupus anticoagulant titer was strongly positive at 2.68:1 (normal titer < 1.2:1).

Within days of initial discharge, the patient was readmitted with abdominal pain and fever. A second laparotomy revealed abdominal fluid collections with polymicrobial infection. The patient died of septic shock with no further thrombotic issues.

**DISCUSSION**

Traditionally ITP was thought to result from production of antiplatelet antibodies which cause peripheral destruction of platelets. Recently, additional pathogenetic mechanisms have been discovered including decreased platelet production and an inappropriately low serum thrombopoietin level [8]. These data prompted the development of pharmacologic TPO-mimetic agents for these patients. Early studies of a polyethylene glycol-conjugated recombinant human megakaryocyte growth and development factor, a recombinant thrombopoietin, were associated with the development of antibodies which cross-reacted with endogenous thrombopoietin, causing persistent prolonged thrombocytopenia [9, 10].

Romiplostim is a second generation TPO-mimetic agent; it is a recombinant antibody with four c-mpl binding peptides linked to an immunoglobulin Fc carrier domain [11]. Romiplostim was approved for treatment of refractory ITP based on the results of two parallel phase III double blind, placebo controlled clinical trials in which patients (with or without prior splenectomy) received romiplostim weekly for 24 weeks. The primary end-point in both studies was a sustained increase in platelet count. Overall bleeding and thrombotic events were similar in both the romiplostim and placebo groups [5]. Thrombosis occurred in one patient assigned to placebo (pulmonary embolism) and in two assigned to romiplostim (popliteal artery thrombosis and a cerebrovascular event, respectively). During the extension study, 7 additional thrombotic events occurred in four patients including coronary artery occlusion, calf vein thrombosis and two patients with multiple events. One patient had portal vein thrombosis but no other details are available. Seven of the ten thromboembolic events occurred at platelet counts below the median peak platelet count of 167,000/mm³ for all patients treated with romiplostim in both the phase III and extension studies [6, 7].

Our patient’s platelet count was exceptionally labile reaching a peak of 154,000/mm³ prior to surgery and falling to 21,000/mm³ post operatively. The highest platelet count was 253,000/mm³ five days after she was diagnosed with superior mesenteric vein thrombosis. The platelet count was monitored daily and the FDA approved dosing was followed. It is recommended that romiplostim be discontinued if the platelet count is greater than 400,000/mm³, a platelet count which our patient never achieved. Our patient also had many coexisting risk factors for venous thrombosis. The patient was bed ridden and had recently undergone major abdominal surgery to resect an adenocarcinoma of the colon. She had received multiple courses of high dose steroids and a short course of aminocaproic acid in an attempt to treat her life-threatening hemorrhage. There was underlying liver cirrhosis which is associated with increased abdominal venous thrombosis [12]. The patient also met criteria for antiphospholipid syndrome with a lupus anticoagulant. We suspect that the combination of these events led to her superior mesenteric vein thrombosis. It may be that special care should be used when romiplostim is given in the setting of multiple risk factors for venous thrombosis. It is possible that a lower platelet count should be targeted in these individuals, however it should also be noted that as soon as our patient’s romiplostim dose was decreased her platelet count dropped precipitously. Of note, patients with active malignancies were excluded from the Phase III trial. As more complex patients are treated outside the setting of a

**Table 1. Thrombosis in Patients Treated with Romiplostim**

<table>
<thead>
<tr>
<th>Event</th>
<th>Refs.</th>
<th>Age/Sex</th>
<th>Risk Factors</th>
<th>Severity*</th>
<th>Rx Duration (Days)</th>
<th>Platelet Count (/mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Popliteal artery thrombosis</td>
<td>[5]</td>
<td>82/NA</td>
<td>Yes †</td>
<td>NA</td>
<td>NA</td>
<td>111,000</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>[5]</td>
<td>NA</td>
<td>Yes ‡</td>
<td>4</td>
<td>147</td>
<td>107,000</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>[7]</td>
<td>85/F</td>
<td>NA</td>
<td>4</td>
<td>60</td>
<td>NA</td>
</tr>
<tr>
<td>Portal Vein thrombosis</td>
<td>[7]</td>
<td>44/F</td>
<td>NA</td>
<td>3</td>
<td>823</td>
<td>NA</td>
</tr>
<tr>
<td>Deep Vein thrombosis</td>
<td>[7]</td>
<td>44/F</td>
<td>NA</td>
<td>2</td>
<td>908</td>
<td>NA</td>
</tr>
<tr>
<td>Transverse Sinus thrombosis</td>
<td>[7]</td>
<td>63/M</td>
<td>NA</td>
<td>3</td>
<td>363</td>
<td>NA</td>
</tr>
<tr>
<td>Thrombosis §</td>
<td>[7]</td>
<td>57/F</td>
<td>NA</td>
<td>4</td>
<td>95</td>
<td>NA</td>
</tr>
</tbody>
</table>

Refs., reference; Rx, treatment; * Severity: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal.
† Extensive peripheral vascular disease, atrial fibrillation, history of radial artery thrombectomy. ‡ Cerebrovascular disease, Congestive heart failure, diabetes and hypertension. § Thrombosed inflammatory fibrosis (preferred term thrombosis) was diagnosed at the site of a central line place 13 years previously for blood draws because of poor vascular access.
临床，它被预期到，将会揭露额外的毒性。

**ACKNOWLEDGEMENT**

None declared.

**CONFLICT OF INTEREST**

None declared.

**REFERENCES**


