CASE REPORT

Use of Recombinant Factor VIIa in a Pediatric Patient With Initial Presentation of Refractory Acute Immune Thrombocytopenic Purpura and Severe Bleeding

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Severe bleeding in acute immune thrombocytopenic purpura (ITP) is rare but can cause significant complications to the patient. Here we report the case of a pediatric patient with acute ITP and hematuria refractory to anti-D immune globulin, high dose intravenous immunoglobulin G, and high dose steroids. Her hematuria was successfully treated with recombinant factor VIIa (rFVIIa). While further investigation on the use of rFVIIa in ITP is warranted, this case report contributes to the pediatric literature for its use during the course of an initial presentation of ITP with hemorrhagic complications.

INDEX TERMS immune thrombocytopenic purpura, pediatrics, recombinant factor VIIa

J Pediatr Pharmacol Ther 2012;17(3):274–280

INTRODUCTION

Acute immune thrombocytopenic purpura (ITP) occurs in approximately 2.5 to 5 per 100,000 children.^{1,2} It often follows a recent history of viral illness and typically resolves within 6 months.³ Severe bleeding is a rare complication of ITP, with the incidence of intracranial hemorrhage ranging from 0.1% to 1%.^{4–6} Other severe bleeding manifestations can present as epistaxis, gastrointestinal bleeding, menorrhagia, and hematuria.⁷ Since ITP resolves spontaneously in most children, treatment is controversial; however, in children in children requiring therapy due to severe thrombocytopenia or bleeding, the 3 standard treatments include intravenous anti-D immune globulin, intravenous immunoglobulin G (IVIG), and steroids.^{8,9} Limited data for the use of recombinant factor VIIa (rFVIIa) in ITP are available. Herein, we describe the use of rFVIIa in a 12-year-old female with an initial presentation of acute ITP and hematuria unresponsive to other pharmacological treatment.

CASE REPORT

A 12-year-old (36 kg) Caucasian female with no significant past medical history presents with hematuria, petechiae, and ecchymosis. Two weeks prior to admission, she was treated with loratadine and mometasone for an upper respiratory infection and was placed on amoxicillin for left otitis media; dosages were not reported.

Initial vital signs were within normal limits. The head, ears, eyes, nose, and throat examination showed petechiae in the pharynx, oral mucosa, and tongue; in addition, a small left subconjunctival hemorrhage was detected. There was no suprapubic or costovertebral angle tenderness. The dermatologic examination was significant for scattered ecchymoses and diffuse petechiae to all 4 extremities and the abdomen. The remainder of the physical examination was within normal limits.

Laboratory investigation showed severe thrombocytopenia with platelets of $1 \times 10^9/L$ (Table 1). Other pertinent laboratory results were:

Table 1. Hospital Timeline and Selected Laboratory Findings

Time (hr)*	Action	Laboratory Results
–4.5	Blood draw	Platelets $1 \times 10^9/L$
0	Treated with anti-D immune globulin 75 mcg/kg	
8	Blood draw	Platelets $1 \times 10^9/L$
16	Received IVIG 2 g/kg	
20.5	Blood draw	Platelets $0 \times 10^9/L$
59.5	Transferred to pediatric intensive care unit	
66	Blood draw	Platelets $2 \times 10^9/L$
72.5	Received methylprednisolone 30 mg/kg/day divided every 6 hr	—
87.5	Received recombinant factor VIIa 30 mcg/kg	—
88.5	Nurse reported resolution of gross hematuria	—
89.5	IVIG 2 g/kg	—
103.5	Blood draw and urinalysis	Platelets $13 \times 10^9/L$ RBC in urinalysis 3–5 HPFs

HPF, high-power field; hr, hour; IVIG, intravenous immunoglobulin G; RBC, red blood cell

* Time in relation to administration of anti-D immune globulin

hemoglobin of 12.9 g/dL, hematocrit of 36.6%, international normalized ratio of 1.26 (normal range), urinalysis with too numerous to count red blood cells, white blood cells (15–20/high-power field [HPF]), positive nitrite, positive ketones (40 mg/dL), and proteins (≥ 300 mg/dL). Urine culture was negative. All other initial laboratory tests were normal. Additional laboratory studies investigating systemic lupus erythematosus revealed a positive antinuclear antibody level; however, complement component 3 and 4 levels were normal, and double stranded DNA was negative.

The patient was admitted to the general pediatric ward for presumed ITP. After premedication with acetaminophen 325 mg orally, diphenhydramine 36 mg intravenously, and methylprednisolone 250 mg intravenously every 6 hours, she was given 75 mcg/kg of anti-D immune globulin (WinRho SDF, CangeneBioPharma, Inc, Baltimore, Maryland). Approximately 4 hours after anti-D immune globulin administration, the patient developed chills, tremors, fever (102°F), and had 1 episode of hematemesis. This continued for 15 minutes and resolved after administration of acetaminophen, ondansetron, and a normal saline bolus. Eight hours after administration of the anti-D immune globulin, platelets remained at $1 \times 10^9/L$, anemia developed (hemoglobin of 10.4 g/dL and hematocrit of 30.1%), and no resolution of hematuria was seen; as such, 16 hours after administration, the patient was premedicated with acetaminophen and diphenhydramine and

treated with 2 g/kg (larger than recommended) of IVIG (Gamunex-C, TelecrisBiotherapeutics, Research Triangle Park, North Carolina). Despite this additional therapy, platelet recovery did not occur, and 4 hours later her platelet count was $0 \times 10^9/L$. A renal ultrasound was obtained showing a mild degree of pelvicaliectasis in the right kidney and no calculi.

On the fourth day of hospitalization, the patient suddenly developed a temporal headache and was transferred to the pediatric intensive care unit due to the concern of intracranial hemorrhage. Nevertheless, her neurological examination throughout the hospital stayed unremarkable and nonfocal. Shortly after arriving to the pediatric intensive care unit, vital signs were: a heart rate of 123 beats/minute, respiratory rate of 32 breaths/minute, and blood pressure of 101/54 mm Hg. Her anemia worsened with hemoglobin of 7.3 g/dL and hematocrit of 20.8%. Based on her clinical status, 2 units of packed red blood cells were transfused.

The patient continued to remain profoundly thrombocytopenic, with a platelet count of $2 \times 10^9/L$. She received methylprednisolone pulse dosing (approximately 30 mg/kg/day divided into 4 doses). Despite these measures, she continued to have gross hematuria with resultant anemia as well as persistent, refractory thrombocytopenia. A decision was then made to administer 30 mcg/kg of rFVIIa (NovoSeven RT, Novo Nordisk, Princeton, New Jersey). Within an hour, the nurse reported resolution of gross he-

maturia. Repeat urinalysis 15 hours after rFVIIa administration showed 3 to 5 red blood cells/HPF. After premedication with acetaminophen and diphenhydramine, a second course of IVIG 2 g/kg was given 2 hours after rFVIIa administration. Sixteen hours after administration of rFVIIa, the platelet count increased to 13×10^9 /L. Based on her improved clinical and hematologic status, on hospital day 6, the patient was stable for discharge from the unit and was sent home. As an outpatient, she remained on prednisone 0.8 mg/kg by mouth every 12 hours, with a tapering schedule. She returned to the clinic 2 days after hospital discharge where her platelets were 234×10^9 /L, and she had no new clinical signs of bleeding. Her 6-week follow-up visit revealed a platelet count of 506×10^9 /L, and no additional medications were required. Follow-up at week 12 showed a stable platelet count of 475×10^9 /L.

DISCUSSION

Platelet counts $< 10 \times 10^9$ /L can cause severe bleeding in approximately 3% of children with ITP.¹ It is postulated that platelet destruction in ITP is caused by autoantibodies that target glycoprotein complexes (IIb/IIIa and/or Ib/IX)¹⁰ or by T-cell mediated cytotoxicity.¹¹ Although rare, intracranial hemorrhage is the most severe complication of ITP.^{4,5} Epistaxis, gastrointestinal bleeding, menorrhagia, and as seen in this case, hematuria, are other ways in which significant bleeding diatheses in ITP can present.⁷ At this time, intravenous anti-D immune globulin, IVIG, and steroids are the 3 most accepted medications used for acute treatment of ITP.⁸ Factor VIIa offers another pharmacological option and helps stabilize patients with bleeding complications resulting from refractory ITP.

rFVIIa is used to impede bleeding. It is indicated in patients who have hemophilia with inhibitors and in those with congenital factor VII deficiency for both bleeding episodes and surgery.¹² Use of rFVIIa was also reported in patients with aplastic anemia,¹³ Glanzmann thrombasthemia,¹⁴ intracranial hemorrhage, advanced liver disease, trauma, cardiac, and spinal surgery; however, these indications are not currently approved by the Food and Drug Administration.¹² rFVIIa facilitates thrombin generation and fibrin clot formation through an intricate pathway. First, factor VIIa binds to

tissue factor at the injury site and activates factor IX and factor X (FX). Activated FX promotes thrombin formation, which then activates both platelets and factors V, VIII, and XI.¹⁵ At larger doses, factor VIIa binds to activated platelets and activates FX directly, stimulating thrombin formation.¹⁵ Despite the reduced platelet numbers seen in ITP, rFVIIa enhances platelet effectiveness by generating thrombin, therefore allowing for improved localized hemostasis.¹⁶

Data regarding the use of rFVIIa in children with ITP are limited. Previous reports describe the use of rFVIIa in children with acute, chronic, and refractory ITP (Table 2).¹⁷⁻²² Excluding this case report, 8 other children were reported to have been treated with rFVIIa, ranging in age from 3 years to 17 years. Six of them were classified as having chronic ITP¹⁷⁻²⁰ (ranging between 3 and 11 years in duration, and one in which the duration was not reported).¹⁷ In one of these children, ITP was not classified as acute or chronic but was described as refractory.²¹ One abstract described the use of rFVIIa in 2 children with acute ITP. Both children were treated with rFVIIa as bleeding prophylaxis prior to and after splenectomy. The first child was treated 2 months after initial presentation, and the second child was treated during the initial presentation of acute ITP.²² Reasons for treatments were diverse and included: intracranial hemorrhage, severe headache, presplenectomy, splenectomy, epistaxis, injury, pneumonia with severe hemorrhagic diathesis, and wisdom teeth extraction with osteotomy. The dosing for rFVIIa in licensed indications ranges between 15 and 30 mcg/kg every 4 to 6 hours in congenital factor VII deficiency and 90 mcg/kg every 2 hours for hemostatic dosing in hemophilia.¹² It is, therefore, not surprising that in these 8 cases of off-label use, the doses varied from 40 to 122 mcg/kg.

rFVIIa can stop active bleeding quickly, but the effect is brief with an approximate half-life of 1.3 hours in children thus sometimes requiring frequent redosing.²³ In our patient, only 1 dose of rFVIIa was necessary to control bleeding; however, it is likely that the platelet recovery later that night was due to the pulse steroids or the second dose of IVIG. Regarding the safety of rFVIIa, between 1996 and 2003, only 24 thrombotic adverse events were reported with the use of rFVIIa out of approximately 500,000 doses that were administered.²⁴ A recent study reporting on the safety

Table 2. Summary of Reported Use of rFVIIa in Children With Acute, Chronic, and Refractory ITP

Source	Age (Sex)	Duration of ITP	Previous Treatments	Platelet Count	Reason for Treatment	rFVIIa Regimen	Other Treatments Given in Combination With rFVIIa	Outcome
Minniti and Weinthal ²²	11 yr (male)	2 mo	IVIg Anti-D immune globulin Steroid therapy	8 × 10 ⁹ /L (time not specified)	Intracranial hemorrhage	50 mcg/kg every 2 hr × 3 75 mcg/kg every 3 hr × 2 90 mcg/kg × 1	Platelets PRBC FFP Cryoprecipitate Emergent splenectomy	No further bleeding
Čulic ¹⁸	8 yr (male)	1 wk	Not reported	7 × 10 ⁹ /L (on admission)	Epistaxis Microhematuria	50 mcg/kg	Anti-D immune globulin IVIg	No further bleeding
				1–5 × 10 ⁹ /L (time not specified)	Mucosal bleeding Presplenectomy		PRBC Vincristine High-dose methylprednisolone (30 mg/kg) Platelets Emergent splenectomy	
	8 yr (female)	3 yr	Deep nose tampon Corticosteroids Erythrocyte transfusions	3 × 10 ⁹ /L (on admission) 13 × 10 ⁹ /L (on day 9)	Epistaxis Severe headache	85 mcg/kg	Deep nose tampon Corticosteroids Platelet transfusions (6 units) Tranexamic acid	Bleeding decreased after several minutes and stopped after 1 hr. Headache resolved; however, on day 30, patient with recurrent epistaxis (see next row)
Vyhov's'ka et al ²⁰	Same child; 8 yr and 1 mo (female)	3 yr and 1 mo	Deep nose tampon Corticosteroids Erythrocyte transfusions Platelet transfusions Tranexamic acid rFVIIa	13 × 10 ⁹ /L (on day 30) 13–42 × 10 ⁹ /L (on day 34)	Epistaxis	85 mcg/kg	Deep nose tampon Platelet transfusions (4 units)	Bleeding stopped 1 hr after administration of rFVIIa.
	16 yr (male)	11 yr	Dehydration therapy Steroids E-aminocaproic acid Ethamsylate Atropine Symptomatic treatments	Not reported	Injury not specified	50 mcg/kg given 14 hr after injury 50 mcg/kg given 18 hr after injury	Not reported	Reaction to the injection was not observed. Patient's condition remained serious, but progression of neurological symptoms was not observed.

ITP, immune thrombocytopenic purpura; IVIg, intravenous immunoglobulin G; rFVIIa, recombinant factor VIIa; TNFa, tumor necrosis factor α ; min, minutes; hr, hours; mo, months; yr, years; wk, weeks
Adapted with permission from Salama et al¹⁷

Table 2. Summary of Reported Use of rFVIIa in Children With Acute, Chronic, and Refractory ITP (*cont.*)

Source	Age (Sex)	Duration of ITP	Previous Treatments	Platelet Count	Reason for Treatment	rFVIIa Regimen	Other Treatments Given in Combination With rFVIIa	Outcome
Barnes et al ¹⁷	16 yr (female)	"Chronic immune thrombocytopenia purpura"—no duration given	IVIg Corticosteroids Cyclophosphamide Autologous bone marrow transplantation at 11 yr of age Anti-CD20 monoclonal antibody Anti-TNF α monoclonal antibody	4 $\times$ 10 ⁹ /L (on admission: 36 hr after onset of severe headache) 5 $\times$ 10 ⁹ /L (on discharge: day 22)	Large intracranial hemorrhage	Initially 122 mcg/kg every 2 hr Then: 122 mcg/kg every 4–8 hr $\times$ 3 wk Then: 122 mcg/kg daily $\times$ 5 days.	Platelet transfusions Fresh frozen plasma Tranexamic acid High-dose IV dexamethasone	Resolving intracranial hemorrhage No residual neurological damage
Wróbel et al ¹⁹	3 yr and 9 mo (male)	3 yr and 5 mo	Prednisone Dexamethasone Methylprednisolone IVIg Anti-CD20 monoclonal antibody (Rituximab) Cyclosporine	Not reported	Pneumonia with severe hemorrhagic diathesis Splenectomy	40–70 mcg/kg $\times$ 3 at 0, 2, and 4 hr after surgery.	Tranexamic acid Desmopressin Platelet transfusion	No major bleeding during or after splenectomy
	7 yr (male)	3 yr	Methylprednisolone IVIg Anti-CD20 monoclonal antibody (Rituximab)	Not reported	Splenectomy	40–70 mcg/kg $\times$ 3 at 0, 2, and 4 hr after surgery	Tranexamic acid Desmopressin Platelet transfusion	No complications
Salama et al ²¹	17 yr (female)	"Refractory ITP"—no duration given	Prednisolone IVIg Vincristine Mycophenolate mofetil Dexamethasone	2 $\times$ 10 ⁹ /L (time not specified)	Wisdom teeth extraction with osteotomy	120 mcg/kg 10 min prior to surgery 120 mcg/kg $\times$ 2 (at 2 and 6 hr post operatively)	Tranexamic acid Fibrin	No major bleeding
Current case	12 yr (female)	Initial presentation	None	1 $\times$ 10 ⁹ /L (on admission)	Hematuria	30 mcg/kg $\times$ 1 on day 5 of initial presentation	Anti-D immune globulin IVIg Methylprednisolone	Resolution of gross hematuria within 1 hr

ITP, immune thrombocytopenic purpura; IVIg, intravenous immunoglobulin G; rFVIIa, recombinant factor VIIa; TNF α , tumor necrosis factor α ; min, minutes; hr, hours; mo, months; yr, years; wk, weeks
Adapted with permission from Salama et al²¹

of the off-label use of rFVIIa collected from 35 randomized clinical trials showed a higher risk of arterial, but not venous, thromboembolic events most notably among the elderly.²⁵ A clinical trial evaluating the off-label use of factor VIIa in the pediatric population revealed that thrombotic events occurred in 4.3% of children, of which the highest incidence developed in the neonatal population.²⁶ When assessing the risks and benefits of using rFVIIa, cost of therapy should be computed into the analysis.

In summary, for children presenting with acute ITP and severe bleeding refractory to standard therapy, rFVIIa offers a rapid and safe alternative for stabilization. Limited data exists to support the routine use of rFVIIa in this setting and in this population; therefore, further investigation is needed.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

ACKNOWLEDGMENT Presented in part at the Annual Meeting of the Society of Critical Care Medicine, February 2012, Houston, Texas.

ABBREVIATIONS FX, factor X; HPF, high-power field; ITP, immune thrombocytopenic purpura; IVIG, intravenous immunoglobulin G; rFVIIa, recombinant factor VIIa

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