

BRIEF REPORT

Recombinant Factor VIIa Is Effective for Bleeding and Surgery in Patients With Glanzmann Thrombasthenia

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Recombinant activated factor VII (rFVIIa) was found to be effective and safe in treating 24 bleeding episodes and to prevent bleeding during one bilateral herniorrhaphy in four children with Glanzmann thrombasthenia. One of the patients had alloantibodies to platelet membrane glycoprotein (GP) IIb/IIIa and was refractory to platelet transfusion. rFVIIa was administered at 89 to 116 $\mu\text{g}/\text{kg}$ per injection every 2 hours, in association with antifibrinolytic drugs. Bleeding stopped in all cases, but platelet transfusion was required in

one. Two bleeding episodes recurred 36 and 63 hours after discontinuation of rFVIIa, but were successfully treated with additional doses. No adverse effects of rFVIIa were observed. Although the number of patients is small, our study suggests that rFVIIa may be an alternative to platelet transfusions in patients with a severe congenital thrombocytopathy.

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GLANZMANN THROMBASTHENIA is a congenital, hereditary hemorrhagic disorder caused by qualitative or quantitative abnormalities of platelet glycoprotein (GP) IIb/IIIa leading to excessive bleeding. Platelet transfusion is the standard treatment for severe bleeding and for surgical support. However, repeated platelet transfusions in such patients may result in alloimmunization to human leukocyte antigens (HLA) and/or platelet membrane GPIIb/IIIa, rendering future transfusions ineffective. Furthermore, platelet transfusions have risk for adverse reactions including virus transmission, and may not be readily available to patients living in remote areas.

In 1996, Tengborn and Petruson¹ first reported the successful use of recombinant factor VIIa (rFVIIa, NovoSeven [Novo Nordisk, Bagsvaerd, Denmark]) for a severe epistaxis in a boy with Glanzmann thrombasthenia. Additional case reports suggest the usefulness of this agent for bleeding and for surgical prophylaxis in other patients with congenital functional platelet disorders including Glanzmann thrombasthenia,²⁻⁴ Bernard-Soulier syndrome,⁵ and platelet type (pseudo) von Willebrand disease⁶ and acquired thrombocytopathies related to uremia⁷ or myelodysplastic syndrome.⁸ We report here the experience with the use of rFVIIa in 4 patients with Glanzmann thrombasthenia.

PATIENTS, MATERIALS, AND METHODS

Four children with type 1 Glanzmann thrombasthenia (Table 1) received treatment, after informed consent, with rFVIIa for bleeding episodes or for surgical prophylaxis in this open-label study. Patient 2 had alloantibodies to platelet GPIIb/IIIa, and was refractory to platelet transfusions. Patients 3 and 4 lived in remote areas with limited access to platelet transfusions. The study protocol was approved by the institutional ethics board and rFVIIa was supplied at no cost by Novo Nordisk Canada Inc (Mississauga, Ontario, Canada). Patients undergoing surgical procedures, or having bleeding episodes not controlled by conservative measures such as the use of local pressure, nasal packing, or topical thrombin, were administered rFVIIa at a standard dose of approximately 90 $\mu\text{g}/\text{kg}$ to the nearest vial (vial size: 1.2 mg or 2.4 mg; actual dose range: 89 to 116 $\mu\text{g}/\text{kg}$) every 2 hours until bleeding stopped. Gastrointestinal (GI) bleeding was considered to have stopped when the patient continued to be hemodynamically stable and the hemoglobin values remained stable. Bleeding episodes were considered severe when there was a decrease in the hemoglobin concentration by 20 g/L or more within 4 days preceding the start of rFVIIa or when there was compression of a vital organ. Follow-up maintenance doses of rFVIIa were at the discretion of the investigators. Antifibrinolytic agents such as ϵ -amino-caproic acid (Amicar; Wyeth-Ayerst, Caroline, Puerto Rico) (300 to 400 mg/kg/d) or tranexamic acid (Cyklokapron; Pharma-

cia & Upjohn, Stockholm, Sweden) (75 mg/kg/d) were used during and for 7 to 9 days after rFVIIa therapy for all but 2 bleeding episodes (1 mild oropharyngeal bleed and 1 facial hematoma) and for surgery. Platelet transfusions were allowed when in the judgment of the treating physician rFVIIa was not effective.

RESULTS

Twenty-four bleeding episodes were treated with rFVIIa after failure of local measures, including 13 nosebleeds, 7 oropharyngeal bleeds, 3 GI bleeds, and a posttraumatic facial hematoma (Table 1). Red blood cell transfusions were needed in 7 episodes (3 GI bleeds and 4 nosebleeds). Bleeding stopped within 6 hours of starting rFVIIa in 16 (67%) episodes, and between 6 and 24 hours in 7 (29%) episodes. The remaining GI bleed (patient 3) did not stop despite 24 rFVIIa injections over 2 days, but stopped promptly after one platelet transfusion. Two of the bleeds (GI, lip/frenulum cuts), which each initially stopped after 3 rFVIIa doses at 4 and 5 hours, respectively, recurred 36 and 63 hours later; in both cases, bleeding stopped after additional rFVIIa injections without rebleeding (Tables 1 and 2). The number of rFVIIa injections required to stop bleeding is shown in Table 2. Additional rFVIIa doses for maintenance were given after severe bleeds because of concern for recurrence (Table 2). The bilateral herniorrhaphy was performed without platelet transfusion, and no abnormal peri- or postoperative bleeding was observed. The child was discharged home 36 hours after the surgery with ϵ -amino caproic acid. No patient developed adverse effects with the use of rFVIIa.

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Table 1. Use of rFVIIa in Four Patients With Glanzmann Thrombasthenia

Patient No.	Age (yr)/Sex	Bleeding Episodes (n)				Surgery (n)	Clinical Efficacy*			
		Nose	Oropharynx	GI	Hematoma		Excellent	Good	Recurrence	Ineffective
1†	6/M	—	1	1	—	1	3/3	—	—	—
2†‡	0.8/F	10	6	1	1	—	12/18	4/18	2§/18	—
3	3/F	1	—	1	—	—	—	1/2	—	1 /2
4	2/F	2	—	—	—	—	—	2/2	—	—

*Response according to number of hours to stop bleeding after start of rFVIIa—Excellent: ≤ 6 hours without recurrence; Good: $>6 \leq 24$ hours without recurrence; Recurrence: ≤ 24 hours but with recurrence of bleeding; Ineffective: >24 hours and/or requiring platelet transfusion to stop bleeding.

†Patients 1 and 2 are siblings.

‡Patient 2 had alloantibodies against GPIIb/IIIa.

§Bleeds stopped with no further recurrences after additional doses of rFVIIa.

||Bleed stopped after platelet transfusion.

DISCUSSION

rFVIIa has been used extensively for patients with inhibitors to factor VIII or IX (congenital or acquired hemophilia)⁹ and in a limited number of patients with a variety of congenital and acquired platelet functional disorders.¹⁻⁸ Our study, though limited in the number of patients, represents the largest experience in the use of rFVIIa in patients with Glanzmann thrombasthenia. rFVIIa was effective in treating 23 of the 24 bleeding episodes and in 1 surgical procedure in these patients with or without anti-IIb/IIIa antibodies. Bleeding stopped promptly in many cases.

Maintenance doses of rFVIIa after the cessation of bleeding were used early in our study according to previous reports.^{1,5,9} As we gained experience, we observed that many of the bleeding episodes did not rebleed in the absence of maintenance doses. It is possible that in patients with normal plasma coagulation systems, once a primary platelet plug has formed to stop bleeding, a permanent clot is readily formed by the fibrin deposition and stabilization. In this respect, antifibrinolytic agents to prevent clot lysis seem to be an important adjunct to rFVIIa therapy. However maintenance doses may be needed for some severe bleeds, posttraumatic bleeds, GI bleeds, and after surgery.

The experience so far suggests the use of rFVIIa in patients with Glanzmann thrombasthenia and other platelet defects is

safe. Only one serious side effect has been reported so far: a bilateral deep vein thrombosis and pulmonary embolism observed 6 days after discontinuation of high-dose rFVIIa administered by continuous infusion for 15 days to cover a bowel resection in a 72-year-old woman with Glanzmann thrombasthenia.³ Thromboembolic complication did not occur in the treatment of other patients, including surgery in our patient covered by intermittent rFVIIa injections and in 3 other patients covered by continuous rFVIIa infusion for 3 to 7 days.^{2,4} This raised the question of whether the sustained thrombin generation by continuous rFVIIa infusion over a prolonged period of time in the presence of normal plasma coagulation systems might have contributed to thromboembolism in this high-risk situation.

In summary, rFVIIa is an attractive alternative to platelet transfusions for the treatment of dysfunctional platelet-related bleeding. However, this needs to be confirmed on a larger population. We need additional studies to define the minimal effective dose, the ideal way to administer rFVIIa, the relative role of rFVIIa and antifibrinolytic agents in these patients, as well as the cost and benefit of using rFVIIa over platelet transfusion, especially in patients without platelet or HLA antibodies. To gather more data on clinical experience with the use of rFVIIa in patients with Glanzmann disease and other congenital platelet disorders, an “International Registry on

Table 2. rFVIIa Doses Required for the 24 Bleeding Episodes and One Surgical Procedure

Bleeding Site	Severity*	Bleeding Episodes (n)	No. Doses rFVIIa to Stop Bleeding			Maintenance rFVIIa Doses After Cessation of Bleeding		
			Mean	Median	Range	Mean	Median	Range
Nose	Severe	8	3.9	2.5	1-11	3.3	2.5	1-7
	Mild	5	3.8	2	1-11	0.8	0	0-3
Oropharynx	Severe	2	3.5	3.5	3 + 4, † 4‡	—	—	1‡
	Mild	5	1	1	—	0.8	0	0-3
Hematoma	Mild	1	—	—	1	—	—	2
GI (patient 1)	Severe	1	—	—	2	—	—	4
GI (patient 2)	Severe	1	—	—	3 + 6§	—	—	—
GI (patient 3)	Severe	1	—	—	25	—	—	7
Surgery	—	1	—	—	1§	—	—	12¶

*Severe: decrease in hemoglobin by 20 g/L or more within the 4 days preceding the start of rFVIIa, or compression of a vital organ.

†Lip/frenulum bleed stopped after 3 doses; rebled when wound reopened 63 hours later, requiring 4 additional doses.

‡As a result, in this category of severe oropharyngeal bleeds, only the episode that required 4 doses to stop had a maintenance dose of 1.

§Bleeding stopped after 3 doses; rebled 36 hours later, requiring 6 additional doses.

||Platelet transfusion used between the 24th and 25th dose with prompt cessation of bleeding.

¶One rFVIIa dose just before surgery (bilateral herniorrhaphy) and 12 doses over the next 24 hours.

Recombinant Factor VIIa and Congenital Platelet Disorders'' has recently been established (forms available from the first author). We hope that the data collected will allow assessment of the role of rFVIIa in these platelet disorders, and assist in the design of formal studies to address specific issues associated with the treatment of these patients. Finally, studies to define the mechanism by which rFVIIa affects hemostasis in these patients are also needed.

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