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Experiences with recombinant FVIIa in the emergency treatment of patients with autoimmune thrombocytopenia: a review of the literature

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Abstract Patients with severe and refractory autoimmune thrombocytopenia (ITP) have significant morbidity and mortality rates. Currently, high-dose methylprednisolone and/or high-dose IVIgG are recommended for the emergency treatment of such patients with uncontrolled bleeding. However, some patients do not immediately respond to these therapeutic regimes and may require additional treatment. Recombinant activated FVIIa (rFVIIa) is a prothrombotic agent that appears to be useful in the treatment of patients with life-threatening bleeding. It has also been used in the treatment of several patients with thrombocytopenia. We administered rFVIIa into a patient with refractory ITP and performed a systemic review of all published reports to assess the available evidence on the efficacy and safety of this drug in patients with ITP. The results indicate that rFVIIa may help in the emergency treatment of patients with ITP who do not respond to other therapies.

Keywords ITP · rFVIIa · Bleeding · Thrombocytopenia · Hemostasis · Hemorrhage

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Autoimmune thrombocytopenia

Autoimmune thrombocytopenia (ITP) is an immune-mediated disorder that may result from the production of glycoprotein specific autoantibodies, leading to platelet destruction by macrophages [25, 31, 32, 41]. The incidence of ITP ranges between 50 and 100 new cases per million each year, with roughly 50% of these cases occurring in children. It may occur with or without association to other diseases, i.e., infections particularly in children, autoimmune diseases, and malignancies. In general, the illness is acute and resolves spontaneously in children but remains chronic in most affected adults [12, 13, 16].

Clinical picture and therapy

ITP is characterized by low platelet counts, bleeding, and/or a risk of bleeding. Most patients with ITP primarily tolerate their thrombocytopenia relatively well and do not require specific treatment unless significant bleeding develops or the patient is subjected to a procedure associated with a risk of bleeding, i.e., surgery [7, 13, 18, 36, 37]. Patients with ITP have various therapeutical options which include corticosteroids, IVIgG, anti-D, and splenectomy. Approximately 30% of patients are refractory to these treatments. This group does not or only poorly responds to subsequent treatment and has a significantly higher risk of morbidity and mortality [30, 36, 37]. In addition, some of these patients suffer from severe and refractory disease and may develop life-threatening bleeding that requires immediate intervention. In such cases, emergency treatment includes high-dose IVIgG (1 g/kg/days for one–three consecutive days) and/or high-dose methylprednisolone (1–2 g/days for one–three consecutive days) [7, 13, 18, 30, 37]. However,

this treatment is not invariably effective, and a significant increase in the platelet count is usually not achieved until 48 to 72 h following initiation of therapy [9, 23]. Due to these uncertainties and the fact that serious bleeding cannot be immediately controlled in some cases, additional agents are sometimes required to stop bleeding. Platelet transfusion is infrequently administered in such cases, although there is no consensus regarding the optimal dose and strategy of treatment [1, 4, 6, 10, 11, 14, 47]. Thus, there is indeed a need for an abruptly effective agent for the treatment of patients with ITP and life-threatening bleeding.

Activated recombinant FVII

Recombinant FVII (rFVIIa) has been demonstrated to potentially stop bleeding in patients with hemophilia, severe thrombocytopenia, and in patients without coagulopathy [17, 29]. We have administered rFVIIa into a 17-year-old female who had a refractory ITP and a significant bleeding tendency. The drug was administered at a dose of 120 $\mu\text{g}/\text{kg}$ 10 min prior to and two times after a wisdom teeth extraction including osteotomy (Tables 1 and 2). Although a local treatment with tranexamic acid and fibrin was performed, we believe that rFVIIa was the main factor for achieving a satisfying hemostasis. Although there is evidence that rFVIIa may have been used in many patients with ITP (personal communication with various physicians), to date, only few reports have addressed this

question. A systematic review of all published clinical studies led to the identification of a total of 15 reports on rFVIIa and ITP (Table 1). In these studies, at least 17 patients (six children and 11 adults) with ITP were found to have been treated with rFVIIa. All these patients were defined as being refractory to different therapies. Unfortunately, prior to or during administration of rFVIIa, the platelet count was not monitored in most cases. In addition, all of the patients reported in these studies immediately received at least two additional types of drugs and/or were splenectomized (Table 2). Furthermore, the doses of rFVIIa which were utilized in those studies were highly variable and ranged between a single dose of 50 $\mu\text{g}/\text{kg}$ to more than 80 doses of 122 $\mu\text{g}/\text{kg}$. Nevertheless, we and all other reports with one exception came to the mutual conclusion that rFVIIa is useful in the management of uncontrolled bleeding in ITP (Table 2). In one patient (no. 17), rFVIIa showed only diminished or no effect, and bleed could not be stopped, ultimately resulting in death. Interestingly, serious side effects were not reported to be observed in any of the patients. In addition, two patients deceased despite the cessation of bleeding (Table 2).

How rFVIIa may improve hemostasis in ITP

The question as to how and to what extent rFVIIa has stopped bleeding in the reported patients with ITP remains speculative. On the one hand, this prothrombic agent was

Table 1 Studies reporting the administration of activated recombinant FVII to ITP patients

Report	Patient (no.)	Age (years)	Sex	pl $\times 10^3/\mu\text{l}^a$	Prior treatment
Minniti et al. [33]	1	11	M	8	IVIgG, Anti-D, Steroids
	2	8	M	7	?
Klamroth et al. [26]	3	45	?	10–15	?
Gerotziapas et al. [19]	4	75	M	9	Chemotherapy, Pred
Waddington et al. [45]	5	68	F	17	Pred
Culic [15]	6	8	F	13	?
Hadacova and Hoch [21]	7	36	M	?	Steroids
Serban et al. [40]	8 (?)	?	?	?	?
Virchis et al. [43]	9	51	F	1	Splx, Steroids, Aza
Vyhovs'ka et al. [44]	10 (?)	?	?	?	?
Busani et al. [8]	11	52	F	30	Anti-CD 20
Barnes et al. [3]	12	16	F	4?	IVIgG, Steroids, Cyclosp, BMT, Anti-CD, Anti-TNF α
Morath et al. [35]	13	46	M	54	Pred, Tacrolimus, IVIgG
Wrobel et al. [46]	14	14	M	<10	Pred, Dexa, IVIgG, Anti-CD 20, Cyclosp Pred, MP, IVIgG
	15	7	M	10	
Aguilar and Lucia [2]	16	78	M	?	Pred, IVIgG
Baxter et al. [5]	17	70	F	<10	Splx, Steroids
This study	18	17	F	2	Pred, IVIgG, Vinc, MM, Dexa, Steroids

pl Platelet, *Pred* prednisolon, *Splx* splenectomy, *Aza* azathioprine, *Cyclosp* cyclosporine, *BMT* bone marrow transplantation, *Dexa* dexamethasone, *MP* methylprednisolone, *MM* Mycophenolatmofetil

^a The platelet count has not been invariably determined prior to FVIIa administration.

Table 2 Administered rFVIIa into the reported patients with bleeding and/or bleeding risks

Patient	Treatment prior to/during rFVIIa administration	Reason for treatment	rFVIIa ($\mu\text{g}/\text{kg}$)/time	Outcome
1	Pl, RBCs, FFP, Cry/Splx	ICH	3 \times 50, 2 \times 75, 1 \times 90/36 h	No further bleeding
2	IVIgG, RBCs, Vinc, MP/Pl IVIgG, Splx	Hematuria	1 \times 50	No further bleeding
3	Pred, IVIgG	Parathyroid op	1 \times 90 (bolus), 45/(2 h) ^b day 1, 45/ (3 h) ^b day 2, 45/(4 h) ^b day 3	Satisfying hemostasis during surgery
4	Dexa, IVIgG, Pl, Pl, RBCs	Bleeding	1 \times 90	Bleeding was stopped, Splx without complication
5 (Jw)	Pred, IVIgG, MP, Splx, aa, Tranex, Cry	Bleeding	3 \times 90	Hemostasis was achieved, but the patient died
6	Steroids, Pl, Tranex	Epistaxis	1 \times 85	Bleeding was stopped
7 ^a	Pl	Splx	?	Splx without complications
8 (?)	?	?	40–140 (2–4 h) ^b ?	?
9 (Jw)	Pred, Cycloph	Bleeding	90	Bleeding was stopped
10 ^a (?)	?	?	?	?
11	IVIgG, Dexa, Pl	ICH	2 \times 90	2 \times bleeding was stopped
12	Pl, FFP, Tranex	ICH	122/(2 h) ^b , 122 (4–8 h) ^b 3 weeks, 122/(daily) 5 days	No further hemorrhage
13	Plasmaph, IVIgG, Steroids, Cycloph, FFP, RBCs	Bleeding	?	Bleeding was stopped, but the patient died
14	Splx, Tranex, Desmo, Pl	Splx	3 \times 40–70	No major bleeding during Splx
15	Anti-CD20/Splx	Splx	3 \times 40–70	No complication occurred post Splx
16	Pl, Aminocaproic acid	Postoperative bleeding	2 \times 90/(2 h) ^b , 90/(4 h) ^b day 1, 90/ (6 h) ^b day 2	Bleeding was stopped
17	Pl, Desmo, Cry, RBCs	Postoperative bleeding	9 \times 101/daily, 1 \times 50.5	died
18		Tranex, fibrin, wisdom teeth extraction with osteotomy	1 \times 120 (bolus), 2 \times 120 (2 and 6 h after OP)	No major bleeding

Pl Platelet transfusion, RBCs red blood cell transfusion, FFP fresh frozen plasma, Cry cryoprecipitate, Splx Splenectomy, Vinc vincristine, MP methylprednisolone, Dexa dexamethasone, aa aminocaproic acid, Tranex tranexamic acid, Cycloph cyclophosphamide, BMT bone marrow transplantation, plasmaph plasmapheresis, Desmo desmopressin, ICH intracranial hemorrhage, op operation, Jw Jehovahs witness

^aText not in English

^bEvery \times hours

administered to the patients immediately following or even during the administration of other agents that may also lead to a rapid increase in platelet counts and/or a rapid reduction of bleeding, i.e., IVIgG, steroids, platelet transfusion, tranexamic acid, desmopressin, or aminocaproic acid, respectively. Thus, the effect observed in all responsive patients and cases can not be solely attributed to rFVIIa.

On the other hand, there are a number of reports describing the successful use of rFVIIa to stop bleeding in patients with nonimmune thrombocytopenia [20, 27, 28, 42]. These studies indicate that rFVIIa is effective in the treatment of bleeding in patients with thrombocytopenia and/or thrombocytopeny, without a combination with other hemostatic agents. Therefore, it is probable that rFVIIa may improve hemostasis and stop bleeding in patients with ITP.

The mechanism by which rFVIIa stops bleeding in these patients remains unclear. In vitro experiments have

demonstrated that high concentrations of FVIIa induce platelet activation, generate platelet surface factor IXa and Xa which lead to thrombin generation on the platelet surface, and also to the formation of hemostatic plaque despite low platelet numbers [22, 34]. Moreover, very high concentrations of rFVIIa may also result in a saturation of all available tissue factor exposed at the site of injury, as well as in extravascular spaces, leading to local thrombin generation and thrombus formation [38]. These processes appear to occur without systemic activation of blood coagulation in treated patients [24, 39]. Based on these findings, it is not surprising that rFVIIa may also help patients with ITP and uncontrolled bleeding. Whatever the mechanism may be, further advanced studies are required in order to determine the optimal dosage required and to clarify its true effect in this group of patients.

Concluding remarks

Although infrequent, the phenomenon that platelet counts may gradually, rapidly, or even abruptly increase in ITP patients who seem to be absolutely refractory to available therapies is well known. This is particularly the case when the affected patients receive a mixture of different drugs that may either solely or in combination increase the platelet count and/or improve hemostasis in bleeding patients. Although it is extremely difficult to retain restraint for bleeding patients, the physicians involved in the treatment of such patients should avoid in administering a combinations of drugs. In addition, future studies need to address the question as to whether rFVIIa alone is effective in the treatment of patients with ITP and uncontrolled bleeding. There are several possibilities which may help in answering this major question: (1) patients who would be treated with rFVIIa must be selected, i.e., patients who present with active bleeding that would be compensated without any serious complications if rFVIIa administration is not successful, (2) circumventing the administration of drug mixtures that do not allow for an accurate interpretation of hemostatic results, (3) the interval of administered drugs should be extended as much as possible to obtain somewhat authentic results, and (4) it is paramount that all treated patients with ITP be described, not only successfully treated patients. Only by doing so then can we be able to provide a proper and legitimate recommendation for the use of rFVIIa in ITP.

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