Treatment of Bleeding in Patients with Platelet Disorders: Is There a Place for Recombinant Factor VIIa?

Yves Laurian

Novo Nordisk Pharmaceutique SA, Boulogne-Billancourt, France

Key Words

Thrombocytopenia · Inherited thrombocytopathia · Glanzmann thrombasthenia · Bleeding · rFVIIa

Abstract

The mechanism of action of recombinant factor VIIa (rFVIIa), i.e. increased thrombin generation on the membrane of activated platelets, as well as the results from in vitro and ex vivo models of thrombocytopenia or inherited thrombocytopathia may support some potential of rFVIIa in thrombocytopenia/thrombocytopathia. rFVIIa was reported as effective to stop or to decrease bleeding in few patients with severe thrombocytopenia resistant to platelet transfusions; however data are still scarce and clinical studies are really needed to define efficacy/safety ratio as well as optimal treatment regimen in this potential indication. Some data in patients with Glanzmann thrombasthenia (GT) may support the use of rFVIIa outside its primary indication in the cases in which there is no real treatment alternative (GT patients with antibodies to GP IIb-IIIa or with platelet refractoriness).

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Introduction

Recombinant factor VIIa (rFVIIa; NovoSeven®) was approved for the treatment of bleeding episodes and the prevention of bleeding during surgery in patients with haemophilia and inhibitors and in patients with acquired haemophilia [1–5]. In this indication, rFVIIa demonstrated an excellent efficacy and safety profile [6, 7]. rFVIIa is produced without any human derivatives (no risk of transmission of viruses or other transmissible agents from human origin; no risk of anamnestic rise of the inhibitor titre) [1, 5]. Optimal results were observed when rFVIIa is used as first-line therapy [4, 8, 9] and with optimal treatment regimen [1–3].

Mode of Action

The proposed mechanism of action of rFVIIa in patients with haemophilia is an increased thrombin generation on the membrane of the activated platelets localized at the site of bleeding [10–12] allowing a better fibrin clot less prone to fibrinolysis and a better activation of factor XIII and of thrombin activable fibrinolysis inhibitor (TAFI). Decreased thrombin generation was previously reported in patients with thrombocytopenia, with Glanzmann thrombasthenia (GT) and with Bernard-Soulier

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Fax +41 61 306 12 34
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Yves Laurian, MD
Novo Nordisk Pharmaceutique SA
32, rue de Bellevue
F-92273 Boulogne-Billancourt (France)
Fax +33 1 46 84 59 53, E-Mail yvla@novonordisk.com

syndrome (BSS). This raises the question whether rFVIIa could be a potential candidate as a new haemostatic drug for bleeding in these patients. Some *in vitro/ex vivo* data [13–14] as well as some case reports [15, 16] may support rFVIIa as a drug with potentiality in platelet disorders.

Thrombocytopenia

High dose of recombinant factor VIIa was reported

- to shorten significantly the microvascular bleeding time in thrombocytopenic rabbits
- to increase the initial thrombin generation, resulting in faster platelet activation in an *in vitro* model of severe thrombocytopenia [13]
- to enhance fibrin deposition in a chamber under flow conditions using thrombocytopenic blood [14].

However, high dose of rFVIIa did not increase, in the *in vitro* model of thrombocytopenia, the rate of thrombin generation which remains very low when compared to normal [13] and there was no improvement of platelet deposition on subendothelium under flow conditions [14].

A study was undertaken in 74 patients with moderate to severe thrombocytopenia related to either impaired platelet production or immune destruction to evaluate the safety of rFVIIa in patients with thrombocytopenia but normal coagulation factors [15]. Each patient received a single dose of 50 and/or 100 µg/kg. A total of 111 injections were given. The clinical tolerance was excellent, except one anaphylactoid reaction in a patient with previous history of such reactions with other drugs. A reduction of the bleeding time was found in 55/105 cases after a single dose of rFVIIa (50 or 100 µg/kg). This reduction was significantly more pronounced when the platelet count exceeded $20 \times 10^9/l$. However, these results must be discussed with caution since no venostasis pressure was applied in patients with impaired platelet production (47 patients; 66 cases). Ten minor/moderate bleeds (neck incision, epistaxis, uterine bleed) were treated with a single dose of rFVIIa (50 or 100 µg/kg) in 8 patients with moderate to severe thrombocytopenia (3 patients with platelets $\leq 10 \times 10^9/l$; 3 patients with 11–20 and 2 patients >20–33) [15]. Bleeding stopped in 7 cases and slowed down or almost ceased in the last 3 cases. There was no clear correlation between shortening of bleeding time and stop of bleeding. Since then no result of clinical trials have been published. Only case stories have appeared in the literature [17, 18].

rFVIIa has some potential in thrombocytopenia, but many questions remain unsolved:

- Efficacy/safety ratio and cost-effectiveness?
- Minimal number of platelets required to get efficacy of rFVIIa?
- Treatment regimen (dose of rFVIIa per injection; number of doses to stop the bleed; interval between doses)?
- Need for additional doses to avoid recurrence of bleeding when stopped?
- Use of rFVIIa alone or in addition to platelets transfusion when very low platelet count?
- Benefit of addition of platelets transfusion in case of complete platelet refractoriness with no circulating platelets?

Only a full clinical development with randomised studies may answer these questions and allow to evaluate the possible place of rFVIIa in patients with bleeding related to severe thrombocytopenia.

Inherited Thrombocytopathia

Inherited platelet function disorders with bleeding tendency are very rare, including Glanzmann thrombasthenia (GT), Bernard-Soulier syndrome (BSS), pseudo-Willebrand and few other diseases [5]. The treatment of bleeding or prevention of bleeding for surgery/invasive procedure is based on platelet transfusion when local measures and antifibrinolytic drug failed. However platelet transfusions may be responsible for development of antibodies to GP IIb-IIIa, GP Ib or HLA with high-risk of future platelet refractoriness [19, 20]. Moreover platelet concentrates have a low but real residual risk of viral contamination.

Decreased thrombin generation was previously reported in patients with GT and in patients with BSS. rFVIIa was reported to increase local fibrin deposition as well as partially restore platelet aggregates in GLZ as well as in BSS [14]. These data may support rFVIIa as a potential haemostatic candidate in these patients.

rFVIIa was reported to stop or prevent bleeding in patients with GLZ with or without antibody to GP IIb-IIIa [16, 19–27]. The result of a pilot study was published [19] on the use of rFVIIa to treat 24 bleeding episodes and to prevent bleeding during one bilateral herniorrhaphy in 4 patients with GT. rFVIIa was administered at 89 to 116 µg/kg per injection every 2 h, in association with antifibrinolytic drugs. Bleeding stopped with rFVIIa in all, but one case and there was no abnormal bleeding during and after the surgical procedure. In two cases, the

bleeding recurred 36 and 63 h after discontinuation of rFVIIa, but the two episodes were successfully treated with additional doses of rFVIIa. Data on the use of rFVIIa in patients with GLZ were collected in an international data collection [26, 27]. In the last presentation of these data [27], intention to treat analysis with rFVIIa showed efficacy in all 11 evaluable invasive/surgical procedures and in 73% of the 55 bleeding episodes (fig. 1).

Taking into account these data [16, 19–27], rFVIIa may be particularly helpful in GT patients with antibodies to GP IIb-IIIa or to HLA or in patients with platelet inefficacy, since treatment alternatives are scarce and may not be efficacious [19, 20, 26, 27].

In other inherited thrombocytopathia, a single patient with BSS [28] and one with pseudo von Willebrand disease [29] were reported to be treated efficiently with rFVIIa.

Acquired Thrombocytopathia

Recombinant FVIIa was reported as efficient for few bleeds related to uremic syndrome [30, 31] and to acquired thrombocytopathia related to myelodysplastic syndrome [32], but no other data have been yet published in peer-reviewed paper on acquired thrombocytopathia.

Discussion

rFVIIa is a drug with real potentiality in platelet disorders. Clinical data may support the use of rFVIIa, outside its primary indication, in GT patients with antibodies to

GP IIb-IIIa or to HLA or with platelet inefficacy due to the absence of real alternative treatment [19, 20, 22, 26, 27]. For patients with thrombocytopenia, clinical data are still too scarce and there is a major need for full clinical development, including randomised double-blind study whenever possible, to demonstrate efficacy and safety of rFVIIa as well as cost-efficacy. Clinical development was recently started. While awaiting the results of such studies, some question the use of rFVIIa outside its indication in cases of persistent life-threatening bleeds despite adequate platelet transfusions [17, 18]; however there is no data yet to support any treatment regimen as well as the use or not of concomitant platelet transfusions.

Fig. 1. Intention to treat with recombinant factor VIIa in patients with Glanzmann thrombasthenia.

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