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Use of Recombinant Factor VIIa in Inherited and Acquired von Willebrand Disease

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Recombinant factor VIIa (rFVIIa) is increasingly used outside the labeled indications for the treatment of life-threatening bleeding episodes after failure of respective standard therapy. In this article, the authors focus on the use of the agent in patients with inherited or acquired von Willebrand disease (vWD). Although the current experience is sparse, published cases indicate the high efficacy of rFVIIa for the treatment of patients refractory to conventional treatment. The agent may be used in

patients with congenital vWD complicated by alloantibodies directed against substituted von Willebrand factor or in the presence of concomitant hemostatic defects as well as acquired vWD with hitherto limited therapeutic options. Controlled clinical studies are necessary to define the use of rFVIIa in this clinical setting.

Keywords: recombinant factor VIIa; von Willebrand disease; bleeding

Introduction

Recombinant factor VIIa (rFVIIa; NovoSeven, NovoNordisc, Denmark) was originally introduced in clinical practice for the prophylaxis and treatment of hemorrhage in patients suffering from congenital and acquired hemophilia. To date, the agent has further been approved for Glanzmann's thrombasthenia refractory to platelet transfusion and, most recently, for congenital factor VII deficiency.¹

Factor VIIa is essential for adequate hemostasis. In case of injury, the coagulation factor complexes with subendothelial tissue factor (TF), which is exposed to the flowing blood by vascular injury. According to the current cell-based model of hemostasis, the factor VIIa-TF complex induces an activation of plasmatic factors and also platelets, which finally results in the generation of thrombin and, thus, the formation of a stable fibrin clot. Applied in

highly supraphysiological dosage, rFVIIa is able to bind to the surface of activated platelets. This binding is only possible after the shape change of platelets and happens at the site of injury. At the surface of activated platelets, rFVIIa induces a thrombin burst that allows rapid fibrin formation and control of bleeding.² Because the effect of rFVIIa is restricted to sites of TF exposure, systemic activation of hemostasis and, thus, the risk of thromboembolic complications is minimized.³ The mode of action also provides a rationale for the use of the agent in currently nonapproved indications. rFVIIa proved to be effective in different inherited, acquired, and drug-induced hemostatic disorders and is increasingly used in the setting of traumatic and perioperative bleeding, irrespective of the presence of hemostatic defects.¹

Among other hemostatic defects, rFVIIa has also been used in patients suffering from inherited and acquired von Willebrand disease (vWD). Although clinical studies regarding this issue are currently missing, published cases suggest a high efficacy in this entity. Here, we focus on current experience regarding the use of rFVIIa in the prophylaxis and treatment of hemorrhage in patients with vWD. Potential indications and dosage in von Willebrand patients are summarized and discussed.

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von Willebrand Disease

vWD is a prevalent inherited bleeding disorder caused by deficiency (type 1), dysfunction (type 2), or absence (type 3) of von Willebrand factor (vWF). Type 2 vWD is further divided into 4 subtypes, based on more distinct differences.⁴ Apart from inherited vWD, acquired forms of this disorder may also occur, which are most frequently associated with underlying disorders, such as hematological malignancies, or induced by a variety of pharmaceutical agents.^{5,6} vWF mediates platelet adhesion at the sites of vascular injury and, additionally, provides a carrier that stabilizes coagulation factor VIII:C in plasma. In vWD, impaired platelet adhesion and, in severe cases, additional factor VIII:C deficiency predisposes to bleeding.⁷ The clinical pattern of bleeding manifestations in affected patients is highly variable, ranging from bleeding only in the case of trauma and surgery to spontaneous bleeding episodes in severe cases, which preferentially affect mucocutaneous regions.

Different agents are established in the prophylaxis and treatment of bleeding in patients suffering from vWD. Therapy aims to the correction of impaired platelet adhesion and of plasmatic hemostasis because of secondary factor VIII:C deficiency.⁸ Patients suffering from vWD, particularly type 1, can be treated with the vasopressin analog desmopressin, which liberates endogenously produced vWF and factor VIII:C from the endothelium, consequently leading to normalization of the bleeding time.⁹ In patients responsive to treatment, desmopressin has a high clinical efficacy.^{10,11} However, some patients with severe type 1 (eg, those with vWF plasma levels below 10%) and patients with type 2 vWD may not respond sufficiently to desmopressin.¹² In these patients, as well as those with absence of the vWF (type 3), substitution with vWF-containing factor VIII:C clotting concentrates is required. This treatment shows a high clinical efficacy and allows prophylaxis and control of bleeding manifestations in the majority (>90%) of patients.^{13,14} In addition to desmopressin and vWF concentrates, antifibrinolytic agents can also be used as monotherapy or in combination, particularly for the prophylaxis and treatment of mucocutaneous hemorrhage. Platelet transfusions that substitute vWF stored in platelet granules and, additionally, provide hemostatic effects may be used in selected cases.⁹ In patients with acquired vWD, the efficacy of standard treatment

may be considerably limited because of rapid clearance of endogenously produced or substituted vWF with significantly reduced half-life in plasma.⁹

Causes for Failure of Standard Treatment in vWD

Inherited vWD

In the majority of cases, patients with inherited vWD can effectively be treated with desmopressin, vWF-containing factor VIII:C concentrates, and antifibrinolytics.⁸ In very rare cases, the efficacy of treatment may be reduced, mainly because of vWF alloantibodies or concomitant hemostatic defects.

Alloantibodies directed against vWF may complicate the treatment of patients suffering from vWD. Induced by prior vWF substitution, these alloantibodies are restricted to patients with type 3 inherited vWD, particularly those with large deletions within the vWF gene.^{15,16} These alloantibodies can induce substitution refractoriness either by directly interfering with vWF function if the antibody is directed against functional domains or by reducing the half-life of the substituted vWF. In addition, alloantibodies may lead to acute allergic or immune reactions following vWF application, which can be potentially life threatening.^{17,18}

Additional hemostatic defects may also impair the efficacy of standard treatment in patients suffering from inherited vWD. Although incidental concomitance of other inherited defects of plasmatic and platelet-related hemostasis is rare,¹⁹⁻²¹ concomitant acquired defects may be present in a considerable number of patients. Hemostatic defects secondary to hepatic, renal, or hematologic diseases²²⁻²⁴ and, particularly, pharmaceutical inhibition of platelet function may be the most frequent findings.

Acquired vWD

In contrast to inherited vWD, the treatment of patients suffering from acquired vWD is a therapeutic challenge.^{5,6,25} Specific treatment of the underlying disorder can induce a remission of the hemostatic defect but is effective in every patient (eg, in the case of advanced hematologic or solid neoplasms). In some cases treatment is not tolerated because of age, immunologic status, or underlying disease. Thus, apart from the treatment of the underlying disease, prophylaxis and treatment of acute bleeding

Table 1. Published Cases of Use of rFVIIa for the Prophylaxis and Therapy of Bleeding in Patients With vWD

Year	Author	Indications	Patients/ Episodes (n/n)	Efficacy (%)	rFVIIa dosage		
					Dosage (µg/kg)	Doses (n)	Interval (hours)
1993	Majumdar et al ³²	vWD type 3, factor VIII:C inhibitor, postoperative bleeding	1/1	1 (100%)	90	54	2-6
1996	Ciavarella et al ²⁹	vWD type 3, vWF inhibitor, perioperative prophylaxis	2/2	2 (100%)	90-200	~24	2-3
2000	Grossmann et al ³⁰	vWD type 3, vWF inhibitor, acute bleeding complications	1/5	4 (80%)	90-130; CI, 20/hour	1 (CI)	5-24 CI
2001	Friederich et al ³¹	Acquired vWD in monoclonal gammopathy, acute bleeding complications	1/3	3 (100%)	90; CI, 17.5/hour	1 (+CI)	CI
2001	Meijer et al ²⁶	vWD type 1, acute bleeding from angiodysplasia	1/8	8 (100%)	80	1-5	24
2001	Tarantino et al ²⁷	vWD type 1, acute bleeding complications	1/3	3 (100%)	82-200	2-3	2-4
Total			7/22	21 (95%)	80-200	1-54	2-24

NOTE: vWD = von Willebrand disease; rFVIIa = recombinant factor VIIa; CI = continuous infusion; vWF = von Willebrand factor.

manifestations are an important aspect of therapy. Because in acquired vWD endogenously produced or administered vWF is rapidly cleared from the plasma by different mechanisms, including (a) presence of vWF autoantibodies, (b) adsorption of the vWF to malignant cells because of aberrant receptor expression, and (c) proteolysis, the efficacy of standard treatment is limited. Immunosuppressive agents to induce an elimination of inhibitors, application of intravenous immunoglobulins, or, in rare cases, immunoadsorption have been recommended. However, severe bleeding manifestations refractory to all these treatment approaches may occur, bearing a considerable risk of fatality.⁶

Current Experience With rFVIIa in Patients With vWD

Rare cases of failure to standard treatment in patients with congenital and acquired forms of vWD require alternative therapeutic approaches for an effective prophylaxis and treatment of hemorrhage. rFVIIa has been used in patients with inherited type 1,^{26,27} type 2a,²⁸ and type 3^{29,30} vWD as well as in patients suffering from acquired vWD of different etiology.³¹⁻³³ The cases are summarized in Table 1.

In the cases reported, single bolus dosage and application intervals of rFVIIa were considerably variable. Repetitive bolus applications of 80 to 200 µg/kg

body weight in intervals of 2 to 3 hours were used most frequently and proved to be effective.^{26-29,32,33} For the treatment of hemorrhage, 1 to 54 bolus applications were necessary depending on site and severity of hemorrhage. The clinical response was excellent with more than 95% overall efficacy. Less frequently, therapeutic schedules with 1 initial bolus application followed by continuous infusion of rFVIIa were employed.^{30,31} Although experience in young children and newborns is currently not available, higher single bolus applications of 150 to 200 µg/kg body weight may be required because of the age-dependent higher clearance in children,³⁴ analogous to the use of rFVIIa for other indications in this age group.

Severe side effects of rFVIIa were rare. Only 1 patient with type 2A vWD and presence of cardiovascular risk factors developed acute myocardial infarction following parallel application of 3000 IE vWF concentrate (Haemate HS) and rFVIIa (2 × 90 µg/kg body weight).³⁵ This case illustrates that combination of rFVIIa with other hemostatic agents may increase the risk for thrombotic complications, particularly in predisposed individuals.

The current experience regarding the use of rFVIIa in patients with vWD is restricted to a few cases refractory to standard therapy. Data from registries or even from clinical studies addressing the use of the agent in patients with vWD are currently not available. We recently treated 2 patients with

rFVIIa, one with type 3 vWD and the other with severe type 2A vWD. Both patients had developed spontaneous bleeding from the gastrointestinal tract despite daily prophylaxis with 30 to 50 IE vWF/factor VIII concentrate (Haemate HS) without adequate explanation. In both patients, however, daily application of rFVIIa (100 µg/kg body weight twice daily) led to an abrupt cessation of bleeding. Thus, our cases illustrate the efficacy of rFVIIa in patients with vWD and otherwise refractory bleeding.

Controlled clinical studies and establishment of a registry of von Willebrand patients treated with rFVIIa should help standardize the use of the agent in this particular setting.

Conclusion

In summary, the cases reported suggest a high efficacy of rFVIIa in the prophylaxis and treatment of hemorrhage in patients suffering from vWD refractory to standard therapy. Although currently available therapeutic strategies in this clinical setting, mainly including desmopressin, vWF-containing clotting factor concentrates, and antifibrinolytics, are highly effective, prophylaxis and treatment may be challenging in the presence of vWF alloantibodies, concomitant hemostatic abnormalities, and, in general, patients with acquired vWD. In these rare situations, patients may not respond adequately to desmopressin application and substitution with vWF-containing clotting factor concentrates or even be completely refractory. Off-label use of rFVIIa appears to be a promising therapeutic option in these cases. Applied in supraphysiological dosage, the agent generates a thrombin burst that leads to formation of fibrin and platelet activation. These effects appear to be capable to compensate the vWF defect and allow an adequate control of bleeding. Although the risk of thromboembolic complications after rFVIIa application appears to be low, these side effects should be carefully kept in mind, in the presence of cardiovascular disease. Potential indications for the off-label use of rFVIIa in patients with vWD according to the authors' suggestions are summarized in Table 2.

According to current experience, a single bolus dosage of rFVIIa of 100 µg/kg body weight can be recommended. Depending on clinical symptoms and response to treatment, repetitive application of bolus with initial intervals of 2 to 3 hours until bleeding stops may be required. Because high peak levels of rFVIIa are crucial for the pharmacological effect, we plead for repetitive bolus applications but not

Table 2. Potential Indications for Off-Label Use of rFVIIa in Patients With vWD as Suggested by the Authors

Inherited vWD (almost only type 3)
Alloantibodies directed against vWF
Refractoriness to conventional treatment
Allergic reactions
Inefficacy of treatment
Concomitant inherited or acquired hemostatic disorders
Acquired vWD
Autoantibodies directed against vWF
Adsorption of vWF to malignant cells
Proteolysis of vWF

NOTE: rFVIIa = recombinant factor VIIa; vWD = von Willebrand disease; vWF = von Willebrand factor.

continuous infusion. To provide the maximum effect, hypothermia and acidosis should be corrected before application and sufficient levels of fibrinogen and platelets are required.

Because the knowledge regarding the use of the agent in this setting is currently sparse, rFVIIa should only be suggested as a "salvage therapy" in vWD patients with otherwise refractory bleeding under strict outweighing of risks and benefits, including rare but potentially life-threatening acquired variants of this bleeding disorder. To gain more information about the use of rFVIIa in vWD, establishment of a registry of patients treated should be considered.

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