



## References

- 1 Moore CP, Sarti DA, Louie JS. Ultrasonographic demonstration of popliteal cysts in rheumatoid arthritis. *Arthritis Rheum* 1975; 18: 577–80.
- 2 Fritschy D, Fasel J, Imbert JC, Bianchi S, Verdonk R, Wirth CJ. The popliteal cyst. *Knee Surg Sports Traumatol Arthrosc* 2006; 14: 623–8.
- 3 Rodrigue V, Shaughnessy WJ, Schmidt KA, Slaby JA, Gilchrist GS, Pruthi RK. Haemorrhage into a popliteal cyst: an unusual complication of haemophilia A. *Haemophilia* 2002; 8: 725–8.

## Experience with a single dose of recombinant activated factor VII for the management of mild-to-moderate bleeds in haemophilia

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The development of inhibitors to factor VIII or factor IX remains one of the most challenging complications in the management of haemophilia, and greatly compromises the efficacy of replacement therapy. Despite the option of inhibitor eradication via immune tolerance therapy, it is estimated that around 30% of patients do not respond to immune tolerance therapy and will have inhibitors for life [1].

Today, recombinant activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk, Bagsværd, Denmark) is considered the first-line treatment option for controlling bleeding in haemophilia patients with inhibitors [2]. Standard dosing of rFVIIa facilitates haemostasis by activating factor X directly on the platelet surface, thereby bypassing the tenase complex. At higher rFVIIa doses the action is increased further, resulting in a more stable haemostatic plug with greater resistance to fibrinolysis [3]. There has, therefore, been debate over the most effective dosing regimen for rFVIIa in the management of bleeding episodes in haemophilia patients with inhibitors, and in particular, interest in the use of a single, higher dose treatment that may offer the same haemostatic benefit as the traditional standard dosing regimen of rFVIIa 90 µg kg<sup>-1</sup> given every 2–3 h, but in a more convenient dosing regimen.

Here, we report our experience on the use of an initial single bolus dose of rFVIIa (180 µg kg<sup>-1</sup> in children and 150 µg kg<sup>-1</sup> in adults) for the management of mild-to-moderate bleeding episodes in haemophilia A patients with inhibitors.

To be eligible for inclusion in the study, patients had to have a confirmed diagnosis and history of haemophilia with inhibitors and mild-to-moderate bleeds. Patients gave informed consent (for children the parent or legal guardian provided this) to receive treatment with rFVIIa. All enrolled patients were treated within 12 h of the onset of a bleeding episode. Patients were excluded from the study if they had severe bleeds, presented for treatment more than 12 h after the onset of a bleeding episode, or could not be shown to have haemophilia with inhibitors.

Between March 2006 and January 2008, a total of 35 bleeding episodes in haemophilia A patients with inhibitors were treated with

rFVIIa, 27 episodes in five children up to 14 years of age (180 µg kg<sup>-1</sup>) and eight episodes in three adult patients (150 µg kg<sup>-1</sup>). The use of a higher dose of rFVIIa in children reflects the known faster clearance of rFVIIa in paediatric patients.

Bleeding episodes were moderate in 21 (60%) cases and mild in 14 (40%) cases. All doses of rFVIIa were given as a single bolus injection. If bleeding persisted after initial dosing at either 180 µg kg<sup>-1</sup> or 150 µg kg<sup>-1</sup>, a further bolus dose of rFVIIa (90 µg kg<sup>-1</sup>) could be given at 3-hourly intervals until haemostasis was achieved.

Treatment response to rFVIIa dose was classified as good, partial or lack of response. A good response was bleeding that stopped following the initial single dose of 180 or 150 µg kg<sup>-1</sup> rFVIIa; a partial response was bleeding that stopped following a second dose of 90 µg kg<sup>-1</sup> rFVIIa; and a lack of response was characterized when bleeding symptoms persisted after administration of two doses of rFVIIa. Treatment was considered effective if bleeding resolved with up to two doses of rFVIIa (good and partial responses). Treatment was considered ineffective if more than two doses of rFVIIa were needed to stop the bleeding (lack of response to rFVIIa doses). Additional assessments made during the study included clinical evaluation of pain, pain relief and tenderness as reported by the patients, plus measurable changes in haematoma size, joint mobility and bleeding arrest. These parameters were evaluated at presentation and 3 h after each rFVIIa infusion.

A single dose of rFVIIa 180 µg kg<sup>-1</sup> stopped mild-to-moderate bleeding in 59% of bleeding episodes in children. Haemostasis was achieved after a second dose of 90 µg kg<sup>-1</sup> rFVIIa in a further 37% of bleeding episodes. One bleeding episode in a child did not stop after two doses of rFVIIa (4%). In adult patients, a good response was achieved in 37.5% of cases. Haemostasis was achieved after a second dose of 90 µg kg<sup>-1</sup> rFVIIa in the remaining 62.5% of bleeding episodes (Table 1). The response rate was lower in adults, probably because a higher dose of rFVIIa is necessary for a further increase of thrombin

**Table 1.** Treatment response to rFVIIa doses in inhibitor patients with mild-to-moderate bleeds.

	rFVIIa dose (µg kg <sup>-1</sup> )	Response to rFVIIa, n (%)		
		Good	Partial	Lack of response
Children (n = 27)	180	16 (59)	10 (37)	1 (4)
Adults (n = 8)	150	3 (37.5)	5 (62.5)	
Total (n = 35)		19 (54)	15 (43)	1 (3)

n, number of bleeding episodes.

Good, haemostasis achieved with initial single dose of rFVIIa; Partial, haemostasis required an additional 90 µg kg<sup>-1</sup> dose of rFVIIa; Lack of response, bleeding continued after two doses of rFVIIa.

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generation. In addition, it is likely that the adults had worse arthropathy than the children, which may be another reason for their lower response. The bleeding response was rated as good in 71% of patients with mild bleeds and in 42% of those with moderate bleeds. Overall, in 97% of bleeding episodes the event stopped with only two doses of rFVIIa (average 1.5 doses). In the 29 joint bleeds, pain and tenderness disappeared and joint mobility improved after the first dose of rFVIIa in 18 cases (62%). The remaining haemarthroses responded to a second dose. In all three reported haematomas, the pain disappeared and haematoma size diminished after two doses of rFVIIa.

It was noted that the response to rFVIIa varied in the three patients with oral bleeding. In one case, arrest of bleeding was achieved with the first dose of rFVIIa, whereas a second dose of rFVIIa was required for the second case, and the remaining patient started to re-bleed within 24 h, despite attaining full haemostasis initially.

No adverse events were reported during the administration of rFVIIa in this patient cohort.

The recent literature contains a number of reports of the use of a higher and single dose of rFVIIa to achieve bleeding control in haemophilia patients with inhibitors. Overall, these studies demonstrate that a single dose of rFVIIa 270  $\mu\text{g kg}^{-1}$  optimizes on-demand treatment by offering the same level of efficacy and safety as dosing schedules of rFVIIa 90  $\mu\text{g kg}^{-1}$  given every 2–3 h [4,5].

## References

- 1 Young G, Blain R, Nakagawa P, Nugent DJ. Individualization of bypassing agent treatment for haemophilia patients with inhibitors utilizing thromboelastography. *Haemophilia* 2006; **12**: 598–604.
- 2 Kempton CL, White GC II. How we treat a hemophilia A patient with factor VIII inhibitor. *Blood* 2009; **113**: 11–7.
- 3 Hedner U. Mechanism of action, development and clinical experience of recombinant FVIIa. *J Biotechnol* 2006; **124**: 747–57.
- 4 Young G, Shafer FE, Rojas P, Seremetis S. Single 270  $\mu\text{g kg}^{-1}$ -dose rFVIIa vs. standard 90  $\mu\text{g kg}^{-1}$ -dose rFVIIa and APCC for home treatment of joint bleeds in haemophilia patients with inhibitors: a randomized comparison. *Haemophilia* 2008; **14**: 287–94.
- 5 Kavakli K, Makris M, Zulfikar B, Erhardtsen E, Abrams ZS, Kenet G; NovoSeven trial (F7HAEM-1510) investigators. Home treatment of haemarthroses using a single dose regimen of recombinant activated factor VII in patients with haemophilia and inhibitors. A multi-centre, randomised, double-blind, cross-over trial. *Thromb Haemost* 2006; **95**: 600–5.

# Re: Discordant pair analysis of rFVIIa and pd-aPCC response

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Individuals with haemophilia are routinely encouraged to initiate treatment for haemarthroses within the first few hours after onset of symptoms to maximize the chances of rapid bleed resolution and minimize potential damage to joints. However, the two treatment options for patients with haemophilia with inhibitors are very different. Recombinant activated coagulation factor VII (rFVIIa; NovoSeven<sup>®</sup>, Novo Nordisk A/S, Bagsvaerd, Denmark) has a short half-life (2.5 h) and is approved for dosing every 2 h to maximize control of bleeding through a targeted mechanism of action. Plasma derived-activated prothrombin concentrates [pd-aPCC, Factor Eight Inhibitor Bypassing Activity (FEIBA<sup>™</sup>); Baxter AG, Vienna, Austria] have a slightly longer half-life (4–7 h) administered typically every

12 h [1]. Currently there are only two studies that have compared these two bypassing agents [2,3].

In the publication of their study comparing rFVIIa and pd-aPCC, Astermark *et al.* report that there were significant discordant pairs early after bleed treatment was initiated reflecting that patients had earlier responses to one product as opposed to the other [2]. In the absence of data showing specific responses of these patients to both products, the interpretation by many has been that certain patients respond better to one or the other product. This idea of differential response has been highlighted in recent scientific or CME activities supported by that trial's Sponsor [4].

Astermark *et al.* comment that the rate of discordant pairs with regard to efficacy of treatment declines over time, with 43.8% at 2 h showing different responses to the two bypassing agents, declining to 31.9% at 6 h and 31.1% at 12 h. The authors also note, in agreement with the findings of Lusher *et al.* [5], that earlier initiation of treatment so as to facilitate effective rapid resolution of bleeding, thereby potentially minimizing the damage particularly to joints, and reducing the amount of product required to achieve haemostasis, is particularly important in the population of patients who may bleed frequently [2]. Recent studies have reinforced this observation with respect to earlier treatment with rFVIIa and higher efficacy [6].

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