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Recombinant activated factor VII in the treatment of bleeds and for the prevention of surgery-related bleeding in congenital haemophilia with inhibitors

Elena Santagostino[a,*], Miguel Escobar[b], Margareth Ozelo[c], Luigi Solimeno[d], Per Arkhammar[e], Hye Youn Lee[f], Gabriela Rosu[f], Paul Giangrande[g]

[a] Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Cà Granda Foundation Maggiore Policlinico Hospital, Milan, Italy
[b] Gulf States Hemophilia and Thrombophilia Center, University of Texas Health Science Center, Houston, TX, USA
[c] IHTC, Cláudio L.P. Correa, Hemocentro Unicamp, INCT do Sangue, University of Campinas, Campinas, São Paulo, Brazil
[d] Ortho-trauma Unit, Emergency Department, IRCCS Cà Granda Foundation Maggiore Policlinico Hospital, Milan, Italy
[e] Novo Nordisk A/S, Søborg, Denmark
[f] Novo Nordisk Health Care AG, Zürich, Switzerland
[g] Oxford Haemophilia and Thrombosis Centre, Oxford University Hospitals NHS Trust, Oxford, UK

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ABSTRACT

The availability of recombinant activated factor VII (rFVIIa, eptacog alfa activated) has greatly advanced the care of patients with haemophilia A or B who have developed inhibitors against the infused replacement factor. Recombinant FVIIa is licensed for the on-demand treatment of bleeding episodes and the prevention of bleeding in surgery or invasive procedures in patients with congenital haemophilia with inhibitors. This article attempts to review in detail the extensive evidence of rFVIIa in congenital haemophilia patients with inhibitors. Patients with acute bleeding episodes are best treated on demand at home, to achieve the short- and long-term benefits of rapid bleed control. Key prospective studies have shown that rFVIIa achieves consistently high efficacy rates in the management of acute (including joint) bleeds in inhibitor patients in the home treatment setting. Substantial post-approval data from key registries also support the on-demand efficacy profile of rFVIIa established by the prospective clinical trials. The availability of rFVIIa has allowed major surgery to become a reality for inhibitor patients. Studies in key surgery, including orthopaedic procedures, have found that rFVIIa provides consistently high efficacy rates. Importantly, the wealth of data does not raise any unexpected safety concerns surrounding rFVIIa use; this is likely because rFVIIa is a recombinant product with a localised mechanism of action at the site of vascular injury. In summary, rFVIIa is established as an effective and well-tolerated first-line treatment for on-demand bleeding control and bleed prevention during minor and major (including elective orthopaedic) surgery in inhibitor patients. Use of rFVIIa has been a major step towards narrowing the gap in outcomes between inhibitor patients and non-inhibitor patients.

1. Introduction

The most serious and challenging complication of haemophilia treatment is the development of alloantibodies, or inhibitors, against infused factor (F) VIII (FVIII; haemophilia A) or FIX (haemophilia B) [1–3]. Inhibitor development occurs more frequently among patients with severe or moderately severe haemophilia, and is more common in haemophilia A than in haemophilia B; approximately 30% of patients with severe haemophilia A develop inhibitors, while the corresponding figure for severe haemophilia B is 1–6% [1,2].

In haemophilia patients with high-responding inhibitors, standard replacement therapy with FVIII or FIX concentrates is usually ineffective, resulting in poor control of haemorrhagic episodes [1,4]. This, in turn, increases the risk of morbidity, mortality, orthopaedic complications and disability, as well as reduced quality of life, compared with patients without inhibitors [1,2,5–7]. The ultimate goal of treatment for these patients is eradication of the inhibitor through immune tolerance induction (ITI) [1,2,8], which involves frequent and long-term administration of factor concentrates in an attempt to tolerise the immune system to FVIII or FIX, and thus restore responsiveness to factor replacement therapy [1,2]. However, ITI fails in approximately 30% of inhibitor patients with haemophilia A [2,8], and is not commonly attempted in those with haemophilia B, as re-exposure to FIX may trigger severe anaphylactoid reactions and nephrotic syndrome [2,8].

When ITI fails or is not feasible, the treatment of bleeding episodes, and the prevention or reduction of bleed-related morbidity, remain significant challenges. In patients with transient,

* Corresponding author.
E-mail address: Hemophilia_ctr@policlinico.mi.it (E. Santagostino).
Tel.: +39 02 55035273; fax: +39 02 55032072.

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low-responding and/or low-titre (<5 Bethesda units [BU]/mL) inhibitors, increased doses of FVIII or FIX may be sufficient to overcome the inhibitor and provide haemostasis [1,2,8]. In most patients with high-responding and high-titre (>5 BU/mL) inhibitors, however, treatment with bypassing agents is required [1,8].

The two bypassing agents currently licensed for use in inhibitor patients are recombinant activated factor VII (rFVIIa, eptacog alfa activated, NovoSeven®, Novo Nordisk A/S, Bagsvaerd, Denmark) and plasma-derived activated prothrombin complex concentrate (pd-aPCC, Factor Eight Inhibitor Bypassing Activity, FEIBA®, Baxter, Deerfield, IL, USA). These agents are able to manage bleeding in the presence of inhibitors; they do not attempt to restore the normal pathways of haemostasis, but instead, boost thrombin generation despite a lack of platelet-surface FVIIIa–FIXa ('tenase') activity [9,10].

The availability of bypassing agents has greatly advanced the care of haemophilia patients with inhibitors [4]. In the UK, for example, the mortality rate for these patients was twice that observed in patients without inhibitors between 1977 and 1992; however, the mortality rate was similar for patients with and without inhibitors between 1993 and 1999 – a period that corresponded with increased use of pd-aPCC, increased popularity of ITI and the introduction of rFVIIa [6]. During this time, rFVIIa was seen as particularly innovative, as it was the first and only recombinant FVII product available for inhibitor patients, that also targets the site of injury. Therefore, it was predicted to provide inhibitor patients with a safe and effective haemostatic treatment. From 1988 to 1999, rFVIIa was available on an emergency and compassionate use basis at sites in Europe and North America, and early experience revealed it to be a major breakthrough in the treatment of haemophilia patients with inhibitors, as it provided life-saving therapy in life-threatening situations. In an open-label, uncontrolled, emergency-use study, for example, rFVIIa was well tolerated and effectively controlled life-threatening intracranial haemorrhage in 10/11 patients with haemophilia who were previously unresponsive to alternative therapies [11]. The benefits of improved care are not yet fully realised worldwide, however: economic constraints in developing countries mean that many patients in these regions receive no, or minimally adequate, treatment, resulting in a greater burden of disability, pain and early death [12,13].

Recombinant FVIIa is currently licensed for the on-demand treatment of bleeding episodes and for the prevention of bleeding in surgery or invasive procedures in patients with congenital haemophilia and inhibitors [14]. It was first approved in Europe in 1996 at a labelled dose of 90 μg/kg every 2–3 hours, and in the United States in 1999 at 90 μg/kg every 2 hours [14,15]. More recently, a single dose regimen of 270 μg/kg was approved by the European Medicines Agency (EMA) in March 2007; this was followed by other approvals worldwide [14]. Data on the pharmacokinetics (PK) and safety of rFVIIa at a single dose of 270 μg/kg show that it has a PK profile in line with what can be expected in comparison to that observed for the standard 90 μg/kg dose [16], and that it also has the same tolerability, safety and dose-dependent activity profiles established by the 90 μg/kg dose [16]. In this article, we review the wealth of data on the clinical efficacy of rFVIIa in inhibitor patients, paying particular attention to on-demand therapy for acute bleeds and prevention of surgical bleeds.

2. On-demand therapy for acute bleeds

2.1. The importance of rapid bleeding control

A growing body of evidence suggests that the benefits of rapid bleed control include fast pain relief [17–19], early restoration of joint mobility [19] and reduced hospitalisation [20,21]. Together, these immediate benefits of rapid bleed control can decrease joint damage in the short term and may translate into long-term reductions in arthropathy, disability and the need for orthopaedic intervention, with subsequent improvements in quality of life [5]. Timely administration of treatment is crucial to achieving rapid bleed control; clinical guidelines, including those from the World Federation of Hemophilia [22], recommend treating acute bleeds within 2 hours of onset to ensure favourable outcomes in all patients with haemophilia. Home treatment is widely considered to be the best way of avoiding treatment delays [5].

2.2. Prospective studies of rFVIIa in home treatment

Five key prospective studies (including two phase III) demonstrated that rFVIIa achieves consistently high efficacy rates when used to manage acute (including joint) bleeds in haemophilia patients with inhibitors in the home treatment setting (Table 1). These data provided an important step towards the goal of providing inhibitor patients with treatment outcomes matching those of non-inhibitor patients.

The first phase III trial was a multicentre, open-label, 1-year, single-arm study in which 56 patients were administered up to three doses of rFVIIa (90 μg/kg) at 3-hourly intervals within 8 hours of the onset of a mild or moderate bleed [23]. Once the subject considered that rFVIIa had been 'effective' with regard to haemostasis (after 1–3 doses), one further (maintenance) dose was administered. Haemostasis was rated 'effective' in 566/614 (92%) evaluable bleeds; mean time to treatment initiation for successfully treated cases was 1.1 hours, and a mean of 2.2 injections was required for haemostasis. These findings led to the conclusion that early administration of rFVIIa achieves haemostasis after 1–3 doses [23]. Furthermore, efficacy (in terms of both achieving and maintaining haemostasis) was similar for all joint, target joint and muscle bleeds, and outcomes were comparable for mild and moderate bleeds [23].

The second phase III trial, representing the largest of its kind ever conducted in patients with congenital haemophilia A or B with inhibitors, had an international, randomised, double-blind, cross-over design and compared vatreptacog alfa (a modified rFVIIa molecule) with a standard rFVIIa regimen (1–3 × 90 μg/kg) in the treatment of all bleeds, including joint bleeds (Table 1) [24]. In total, 567 bleeds in 69 patients were treated. Of these, 227 bleeds in 57 patients were treated with rFVIIa, which achieved an efficacy rate of 93% at 12 hours. Median time to treatment initiation was 0.4 hours (mean, 1.3 hours). Importantly, rFVIIa provided rapid bleed control: late-treated bleeds (>2 hours) responded as well to treatment as early-treated bleeds (≤2 hours) when evaluating the need for additional haemostatic medication after 12 hours; early-treated bleeds had a better response when evaluated at 24 or 48 hours. These results confirmed the well-established efficacy of rFVIIa since its market authorisation 20 years ago [24].

Three randomised crossover trials demonstrated comparable efficacy between a single high dose of rFVIIa and standard-dose rFVIIa in the treatment of joint bleeds in the home treatment setting. In the first, 18 inhibitor patients were randomised to a standard rFVIIa dosing regimen of 90 μg/kg every 3 hours or a single dose of 270 μg/kg, and were instructed to treat four consecutive joint bleeds (ankles, knees or elbows) within 6 hours of onset [25]. Treatment success ('effective' treatment and a visual analogue scale [VAS] score ≥70) over 48 hours was similar between the two dosing regimens (31–66% for the standard dose; 25–64% for the high dose), although the number of infusions needed was significantly higher for the standard versus high dose regimen (Table 1). A partial response ('partially effective'