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CRITICAL REVIEW

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Safety and efficacy of recombinant activated coagulation factor VII in congenital hemophilia with inhibitors in the home treatment setting: A review of clinical studies and registries

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Abstract

Self-administration of factor and bypassing agents by persons with hemophilia in the home setting is recommended to facilitate earlier intervention after bleeding episodes. The objective of this review was to summarize recombinant activated coagulation factor VII (rFVIIa) safety and efficacy data from clinical trials and patient registries documenting use in the home treatment setting in people with congenital hemophilia with inhibitors (CHwI). A total of 16 studies and registries were identified for inclusion; 14 evaluated on-demand treatment of acute bleeding episodes (865 patients, 9024 bleeding episodes) and 2 evaluated use for secondary prophylaxis (108 patients, 42,861 prophylaxis days). In the on-demand studies, efficacy was consistently high (81%-96%), and thrombotic events were uncommon (n = 3). In the secondary prophylaxis studies, rFVIIa was associated with a 45% to 59% reduction in bleeding episodes and no thrombotic events. These data support the clinical practice of administering rFVIIa in patients in the home treatment setting after initiation under a physician's care.

1 | INTRODUCTION

The management of congenital hemophilia in the home treatment setting is common and is advocated by current treatment guidelines, which, in light of the many potential advantages of home treatment relative to administration in treatment centers, recommend its use "where appropriate and possible."[1] This practice may facilitate earlier initiation of therapy after bleed onset, resulting in more rapid recovery from bleeding as well as reduced pain, dysfunction, emergency department visits, hospitalizations, long-term disability, and costs.[2–7] Self-administration of replacement clotting factor products in the home setting may also facilitate earlier initiation of routine prophylaxis, which may reduce the risk of developing arthropathy and thereby improve long-term musculoskeletal outcomes.[8,9] Moreover, patients may experience improvements in health-related quality of life because of greater freedoms accompanied by home treatment.[10] However, clotting factor replacement may be complicated by the development of inhibitors, where even high doses of clotting factor replacement products may be insufficient to prevent or control bleeding, requiring use of alternative "bypassing" agents for management.

Recombinant activated coagulation factor VII (rFVIIa, NovoSeven® RT, Novo Nordisk A/S, Bagsværd, Denmark) is a highly purified recombinant protein[11] that is approved for the treatment of bleeding episodes and the prevention of bleeding during surgery or invasive procedures in adults and children with congenital hemophilia with inhibitors (CHwI) as well as other congenital and acquired bleeding disorders.[12] The clinical use of rFVIIa in patients with CHwI is supported by a wealth of data spanning nearly 30 years.[13,14] Current prescribing information stipulates that treatment should be initiated under the direction of a qualified health care professional and provides patient instructions for reconstitution and administration.[12]

The rFVIIa formulation is well-suited for home use. It is room-temperature stable, and thus does not require refrigeration when temperatures do not exceed 25°C (77°F).[12,15] It retains its activity and stability for extended periods after reconstitution (for 6 hours at 25°C [77°F] and for 24 hours at 5°C [41°F]).[16] Current US prescribing information recommends administration within 3 hours after reconstitution.[12] The rFVIIa injection is of low volume (1–8 mL, depending on the dose) and can be administered rapidly (over a period of

2–5 minutes).[12,17,18] These attributes enhance the ease of rFVIIa use and would be expected to facilitate self-administration at home. Many patients who received rFVIIa in clinical trials and patient registries were treated in the home setting. This review aims to summarize efficacy and safety (thromboembolic events) data from Novo Nordisk clinical trials and patient registries that evaluated rFVIIa home treatment in people with CHwI.

2 | METHODS

2.1 | Clinical data sources

Studies evaluating the efficacy and safety of rFVIIa for the management of CHwI (bleed treatment and perioperative management [approved indications in the US][12] and secondary prophylaxis [investigational use in the US]) in the home setting were identified through a search of the clinical trials database. Both clinical trials (phases 1 through 4) and patient registries (prospective and retrospective) were considered for inclusion. Combinations of clinical trial reports and publications were used as data sources. These sources included both published and unpublished (data on file, Novo Nordisk) data that have been included in periodic safety updates to regulatory authorities.

2.2 | Efficacy outcomes

Reported efficacy rates from the individual studies were extracted and efficacy definitions were recorded (Table 1).

2.3 | Safety outcomes

All reports of thromboembolic events (TEs) were recorded. Adverse events other than TEs were not included in the current review. Safety reporting requirements particularly in post-approval safety studies (PASS) are different for studies conducted in Japan, and specifically differences in reporting of all adverse events irrespective of relationship to product compared with PASS focus on adverse drug reactions possibly/probably related to products.

2.4 | Statistical methodology

All data were summarized; no statistical analyses were performed.

3 | RESULTS

A total of 16 studies evaluating rFVIIa home use were identified (Figure 1). Fourteen of these studies assessed on-demand use (for the treatment of bleeding episodes) and 2 evaluated use for the prevention of bleeding in patients with established joint disease (secondary prophylaxis).

3.1 | On-demand treatment studies

A total of 793 patients were treated for 8758 bleeding episodes in the on-demand treatment studies (three phase 2 trials, two phase 3 trials, and nine phase 4 registries; Table 1). Both standard doses (90 mcg/kg) and high single doses (270 mcg/kg) were represented. Dosing in observational studies was variable (at the discretion of the prescribing physician). No attempt to differentiate efficacy based on dosing regimen was made for the purpose of this review. Efficacy was consistently high across the 12 on-demand treatment studies for which efficacy outcomes were reported (691 patients; 7543 bleeding episodes). Using typical response criteria (which included the evaluation of bleeding, and in some studies, consideration of the need for additional hemostatic agents; see Table 1 for description of efficacy), rFVIIa provided effective hemostasis in 81% to 96% of the bleeding episodes.

Safety data were reported as part of the protocols as primary or secondary endpoints. For the current review, only the rates of TEs for all bleeding episodes in the 14 studies were extracted (perioperative management entered on bleeding episode forms was included in one registry).[19] Overall, TEs were rare. A total of 3 events were identified in 8758 episodes (0.034%), 2 in a single 10-year Japanese postmarketing study[20]: 1 visual field defect with suspected cerebral infarction and 1 central venous occlusion. No further information is available about these two events. The third (thrombus of the arteriovenous fistula leading to study withdrawal) was in the adept™2 trial, which compared vatreptacog alfa with rFVIIa.[21] In trials and registries where full safety information about the events including causality was available the overall thrombotic rate was 1/7040 bleeds (0.014%).

3.2 | Secondary prophylaxis studies

A total of 108 patients were treated with rFVIIa for a total of 42,861 treatment days in the 2 secondary prophylaxis studies (one phase 2 and one phase 4; Table 2). Dosing in the phase 2 prospective study (22 patients, 1885 prophylaxis days) was 90 mcg/kg or 270 mcg/kg daily.[22] Dosing in the phase 4 retrospective study (86 patients, 40 976 treatment days) varied and often changed over time.[23] Efficacy was evaluated as the frequency of bleeds during the prophylaxis period compared with the frequency of bleeds during a pre-prophylaxis period, and in both studies prophylaxis vs. pre-prophylaxis was associated with reductions in bleeding frequency. In the phase 2 study, efficacy was evaluated as the number of bleeds per month during the 3-month prophylaxis period compared with the 3-month pre-prophylaxis period. Bleeding frequency in this study was reduced by 45% with the 90 mcg/kg dose (n = 11) and 59% with the 270 mcg/kg dose (n = 11; both $P < .0001$ vs. the pre-prophylaxis period).[22] In the phase 4 study where the period of prophylaxis depended on retrospective review of available medical records (range, 22 to 3651 days), bleeding frequency was reduced by 46% (95% CI, −54.0 to −38.2) for the total bleeding population (n = 74; defined as patients with at least 1 bleed during the pre-prophylaxis period [12/86 patients were excluded from the analysis of change in bleed rate because they had no bleeds during the pre-prophylaxis period]) and 52% (95% CI, −60.7 to −43.3) for the frequent bleeding population subset (n = 36; defined as patients having at least 1 bleed per month during the pre-prophylaxis period).[23] There were no TEs reported in either of these studies. [22,23]

TABLE 1 On-demand treatment of bleeding with rFVIIa

Trial ID	Year	Trial phase/ type	Number of patients	Number of bleeding episodes	Dose	Efficacy rate and definition	Safety
F7HAEM-1510[33,34,a]	2002–2004	2 Double-blind	22	42	270 mcg/kg × 1 or 90 mcg/kg × 3	88% controlled without the need for additional hemostatic agents	No TEs
F7HAEM-2068[35,36,a]	2001–2006	2 Double-blind	24	45	270 mcg/kg × 1 or 90 mcg/kg × 3	91%-92% achieved hemostasis within 9 hours of first dose of rFVIIa without the use of rescue medication	No TEs
NN7128–1907 (Pioneer 1)[37]	2009–2011	2 Double-blind	23	359	Varied per local standard practice	84%[b]	No TEs
F7HT/USA/1/ USA (US Home TRx)[2]	NA	3 Open-label	56	877	90 mcg/kg (1–3 doses); individualized based on weight	92% achieved hemostasis or experienced significantly decreased bleeding	No TEs
NN1731–3562 (adept™2)[21]	2011–2012	3 Double-blind	57	227	90 mcg/kg (1–3 doses)	93% received no additional hemostatic medication within 12 hours after the first rFVIIa dose	1 TE
HRS/HTRS Registry[38]	2000–2002	4 Registry	42	793	Varied (<100 mcg/kg/dose, 27%; 100–150 mcg/kg/dose, 28%; 150–200 mcg/kg, 25%; or >200 mcg/kg, 21%)	87% achieved complete hemostatic control within 72 hours	No TEs
HTRS Registry[19]	2004–2008	4 Registry	129	2041	Varied (range, 38–400 mcg/kg/infusion)	89%-93% achieved hemostasis	No TEs
F7HAEM-1965 (DOSE)[39]	2008–2009	4 Observational	35	158	Varied (range, 30 mcg/kg/dose to 400 mcg/kg/dose)	Not assessed (diaries)	No TEs
F7HAEM-3507 (ONE)[40]	2008–2010	4 Registry	102	496	Varied (stratified by initial dose: low [≤120 mcg/kg], 31%; intermediate [>120 to <250 mcg/kg], 26%; or high [≥250 mcg/kg], 43%)	85%-96% achieved complete or partial hemostasis (self-reported) within 9 hours after first injection	No TEs
NN7025–3061 (SMART-7)[41,42]	2010–2015	4 Observational	51	592	Varied (median 277.8, mean 569.5)	91.3%	No TEs
F7HAEM-3537 (UKHCDO Registry)[43,44]	2008–2011	4 Registry	67[f]	1057[f]	Varied (CHwI initial dose: ≤90 mcg/kg, 16%; >90 to <180 mcg/kg, 35%; ≥180 to <270 mcg/kg, 18%; ≥270 mcg/kg, 10%)	Not reported (diaries)	No TEs
F7HAEM-1947[20,31,45,a]	1999–2010	4 Observational	144[c]	1718[c]	N/A[e]	88%	2 TEs[d]
F7HAEM-1921 (WIRK Registry)[46]	2008–2010	4 Registry	14	269	Varied (mean initial dose, 150.5 mcg/kg)	90% experienced complete hemostasis or significantly reduced bleeding within 9 hours after initiating treatment	No TEs
F7HAEM-3850[47,a]	2010–2012	4 Observational	27	84	Varied (initial dose: ≤120 mcg/kg, 55%; >120 to <250 mcg/kg, 12%; ≥250 mcg/kg, 33%)	88% home treated	No TEs
Total			**793**	**8758**			**3 TEs**

Abbreviations: HRS, Hemophilia Research Society; HTRS, Hemophilia and Thrombosis Research Society; NA, not available; rFVIIa, recombinant activated coagulation factor VII; TE, thromboembolic event; UKHCDO, United Kingdom Centre Doctors' Organisation.

[a]Unpublished data.

[b]Efficacy included 3 response grades: excellent, good, and moderate.

[c]Patients with evaluable efficacy.

[d]One visual field defect with suspected cerebral infarction, one central venous occlusion.

[e]Information limited to one abstract in English and citations to that abstract.

[f]Out of a total of 139 patients and 1356 episodes across all indicated diagnoses.

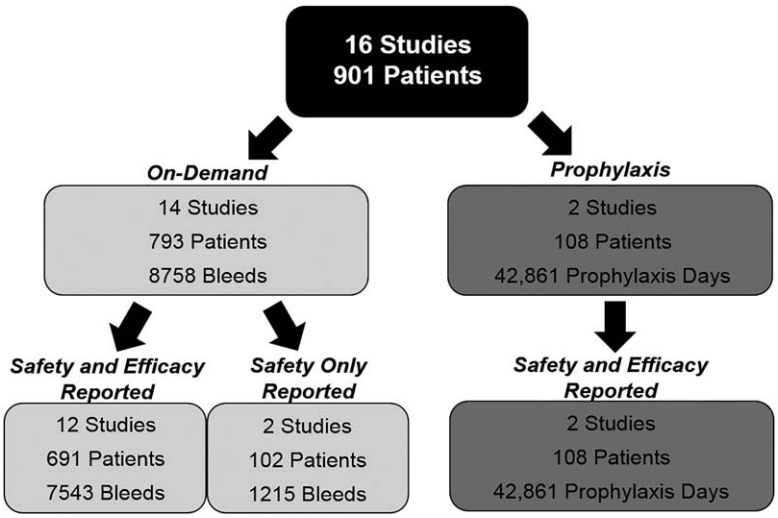

FIGURE 1 Patients identified in studies of rFVIIa treatment of congenital hemophilia with inhibitors in a home setting

4 | DISCUSSION

The current review provides a summary of evidence regarding the efficacy and safety of rFVIIa in the home treatment setting. The rate of efficacy for the on-demand treatment of acute bleeding episodes across 12 studies and registries comprising 7543 bleeding episodes was high (84%-96%) and TEs were uncommon (n = 3). Administration for secondary prophylaxis in 2 studies/registries (~43 000 prophylaxis days), was associated with a 45%-59% reduction in bleeding episodes and no TEs.

The high rate of efficacy described herein is consistent with the range of efficacy reported in registration trials (71%-93%),[12,24–27] which comprised both patients treated at home and patients who received rFVIIa at hemophilia treatment centers. These findings suggest that patients who opt to self-administer rFVIIa at home or at their location may experience efficacy similar to what they would expect if rFVIIa were administered at a hemophilia treatment center in early clinical studies. Furthermore, treatment at home may facilitate more timely administration,[2,3] and thus more rapid recovery.

The low rate of TEs is also consistent with previous observations. The current US prescribing information indicates that 0.2% of bleeding episodes in patients with CHwI in clinical trials were complicated by TEs.[12] Rates of TEs reported in previously published cumulative reviews of safety in both clinical trials and clinical use (postmarketing surveillance, registries, regulatory sources, and investigator-initiated trials) are similarly low (<0.004%).[28–31] There were a total of 25 TEs among 700 000 standard dose infusions in patients with CHwI or acquired hemophilia who received rFVIIa between licensure in 1996 and April 2003;[29] 30 TEs among 800 000 standard dose infusions in patients with CHwI or acquired hemophilia who received rFVIIa between May 2003 and December 2006;[30] and no recorded TEs among 2000 bleeding episodes in patients with CHwI who received rFVIIa between 2004 and 2008.[28] In a recent safety update of data from post-marketing sources, observational studies, registries, spontaneous reporting, and literature cases comprising an estimated 4 million standard doses of rFVIIa used across all approved indications between 1996 and 2013, 138 TEs were reported in patients with CHwI or acquired hemophilia.[31]

The results of this review must be interpreted in light of certain limitations. First, the data were derived from multiple studies and registries that used varied regimens and response criteria and had differing patient populations; there was no single established and validated means for assessment of efficacy. Thus, efficacy as defined in this review encompasses a range of responses, including the extent and duration of bleeding as well as the need for additional hemostatic agents. Additionally, whereas the inclusion of patient registries allowed for a larger set of patient data, the less rigorous (uncontrolled) nature of registries versus clinical studies should be noted. Furthermore,

TABLE 2 Secondary prophylaxis with rFVIIa

Trial ID	Year	Trial phase/type	Number of patients	Number of prophylaxis days	Dose	Efficacy	Safety
F7HAEM-1505[22,32]	2004–2005	2/Double-blind	22	1885	90 mcg/kg or 270 mcg/kg	45%-59% reduction	No TEs
F7HAEM-3695 (PRO-PACT)[23]	2009–2010	4/Observational	86	40 976	Varied	46%-52% reduction	No TEs
Total			**108**	**42 861**			**0 TEs**

rFVIIa, recombinant activated coagulation factor VII; TE, thromboembolic event.

combination of data from different dosing regimens prevents drawing conclusions about the relative efficacy of these dosing strategies. Second, not all the studies included were specifically designed to assess treatment in the home setting, one in which the assessment of efficacy remains challenging and relies on patient and/or caregiver reporting and the extent to which they communicate with the study center in determining treatment (greater for phase 2–3 studies than phase 4 observational registries). However, the primary assessment in this review is around safety, and the inclusion in registries of what is most often a required affirmation about presence/absence of adverse reactions associated with treatment minimizes the risk of underreporting of safety events.

Many potential areas for future research remain. Mitigating the development of arthropathy and disability remains a key goal for hemophilia treatment; thus, the impact of home treatment on these long-term outcomes should be assessed. Effects on quality of life should also be further explored. Hoots and colleagues (2008)[32] concluded that secondary prophylaxis with rFVIIa (which was self-administered in the home setting[22]) may improve health-related quality of life in frequently bleeding patients who have CHwI. Observed improvements included significantly reduced bleeding-related hospitalizations and school or work absences as well as a trend towards reduced pain and enhanced mobility.[32] These improvements would be expected to reduce costs relative to administration at treatment centers; however, such cost comparisons remain to be performed. Finally, the identification of any demographic or clinical characteristics associated with beneficial outcomes could aid the identification of patients most likely to benefit from home treatment.

In conclusion, this review of data from Novo Nordisk clinical trials and patient registries supports the safety and efficacy of rFVIIa when self-administered or administered by a trained caregiver in the home treatment setting. Extensive registry data confirm the findings of clinical trials and support that rFVIIa can be used under the direction of qualified health care professionals by patients and caregivers trained to infuse at home or the patient's location rapidly after the onset of a bleed to maximize the chances for a rapid and successful resolution of the episode, or to routinely infuse to prevent bleeding when so directed by a health care professional.

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CONFLICT OF INTEREST

Nothing to report.

DISCLOSURES

Dr. Young has served as a consultant to Novo Nordisk. Dr. Pipe has served as a consultant to Novo Nordisk. Dr. Escobar has served as a consultant to Novo Nordisk, and he participates in clinical studies that are sponsored by Novo Nordisk. David L. Cooper is an employee of Novo Nordisk.

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