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REVIEW ARTICLE

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The evolution of factor VIIa in the treatment of bleeding in haemophilia with inhibitors

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Abstract

The use of activated factor VII (FVIIa) for the treatment of bleeding events in haemophilia patients with inhibitors was first reported over 30 years ago. Since then clinical trials, registries, case series, real-world experience and an understanding of its mechanism of action have transformed what was originally a scientific curiosity into one of the major treatments for inhibitor patients, with innovative therapeutic regimens, dose optimization and individualized care now widely practiced. Given current understanding and use, it might be easy to forget the years of clinical research that led up to this point; in this review, we lay out changes based on broad eras of rFVIIa use. These eras cover the original uncertainty associated with dosing, efficacy and safety; the transformation of care ushered in with its widespread use; and the optimization and individualization of patient care and the importance of specialized support provided by haemophilia treatment centres. Today with the introduction of novel prophylactic agents such as emicizumab, we once again find ourselves dealing with the uncertainties of how best to utilize rFVIIa and newer investigational variants such as marzeptacog alfa and eptacog beta; we hope that the experiences of the past three decades will serve as a guide for this new era of care.

KEYWORDS
comprehensive care, haemophilia, inhibitors, mechanism of action, personalized treatment, rFVIIa

1 | INTRODUCTION

Approximately 30% of patients with severe haemophilia A and up to 5% of patients with severe haemophilia B develop antibodies to factor VIII (FVIII) or factor IX (FIX) during their lifetime.[1] Patients with low titre inhibitors (<5 Bethesda Units) have traditionally been treated with higher doses of FVIII or FIX concentrates to achieve haemostasis during a bleed and to reduce the incidence of bleeding. Patients with higher titre inhibitors typically use bypassing agents, such as activated prothrombin complex concentrate (aPCC) or recombinant factor VIIa (rFVIIa).

The history of rFVIIa bypassing agent therapy for inhibitor-related haemorrhage covers three eras of care, each of which was driven by the need for improved patient outcomes. The first era was ushered in by observations that activated FVII could effect haemostasis in bleeding inhibitor patients; although there was uncertainty regarding dose, dosing interval and patient safety as clinicians attempted to understand how to use this new pharmacological tool. The second was an era in which our understanding of the coagulation pathway was transformed, and a combination of empirical dosing, clinical experience and mechanistic understanding were used to improve patient outcomes. Finally, the current era is one of

individualized patient care in which a holistic and personalized treatment model is widely accepted as optimal.

In this review, we lay out the progression of FVIIa scientific research and clinical observation that led to the current standard of care that exists in the treatment of inhibitor-related bleeding. The recent approval of emicizumab promises a new era in bleed prevention and is a welcome addition for the treatment of inhibitor patients; other novel haemostatic agents currently in clinical trials may follow. With new prophylactic agents come new challenges in effectively and safely utilizing each product alone and in combination with existing haemostatic agents. The risk of thrombosis associated with bypassing agents and novel prophylactic agents underscores the need for continued vigilance and for additional studies to guide clinicians as they navigate the uncertainties of this new era.[2] The knowledge, clinical experience and scientific insight gained over the past three decades of FVIIa administration, and highlighted in this review, may help guide clinicians during this time.

2 | THE ERA OF UNCERTAINTY

In 1972, Fekete noted that aPCC could effect haemostasis in inhibitor-related bleeding[3]; although transformative, over time it became clear that aPCC was not universally effective in treating all bleeds and reports of thrombosis raised safety concerns. The search for alternative therapeutic options subsequently led to the discovery of FVIIa, a minor component of aPCC.[4] Befitting a new agent, initial use of FVIIa was associated with a period of uncertainty as clinicians attempted to understand how to use it. Empirical dose-finding suggested that FVIIa was generally effective yet could have unpredictable efficacy.[5]

2.1 | Plasma-derived FVIIa (pd-FVIIa)

In 1983, Hedner and Kisiel demonstrated that trace quantities of laboratory-grade pd-FVIIa (50-100 U/kg) promoted haemostasis in two inhibitor patients.[4] Ten years later, a prospective clinical trial examining the treatment of 220 bleeding episodes with a commercial pd-FVIIa concentrate (Acset®, LFB, Les Ulis, France) was reported: 71% of mild/moderate bleeds resolved within 24 hours when pd-FVIIa (68-300 U/kg, 1 or 2 doses, q4-6 hours) was administered.[6] Increased efficacy was observed with higher doses, early treatment and administration of a second dose within 4 hours; observations that over time would become the standard of care.

Although these reports noted that pd-FVIIa was safe and efficacious with no evidence of thrombosis, historical concerns over viral contamination of other plasma-derived concentrates ultimately led to the introduction of the recombinant variant, eptacog alfa.

2.2 | Recombinant FVIIa (eptacog alfa)

In 1993, Macik et al[7] reported the treatment of bleeding episodes in 15 patients with rFVIIa. The majority of bleeding episodes (20/22) required 2 doses; lower doses (17.5 μg/kg) had a lower response rate than higher doses (35 μg/kg and 70 μg/kg). A PK analysis suggested that to obtain adequate haemostasis, rFVIIa plasma levels must remain above 6 U/mL for several hours. As pharmacokinetic response was variable, doses of up to 120 μg/kg were recommended to ensure sustained haemostasis.[8]

A double-blinded study with stricter control over the timing of subsequent doses confirmed the efficacy of 35 and 70 μg/kg doses when administered every 2-3 hours.[9] Overall, 71% of bleeds were considered to have an effective/excellent response by 12 hours; however, no dose-response was observed.[9] As both this study and that by Macik et al required patients to be treated in a hospital setting, the impact of time to treatment remained unknown.

Prior to regulatory approval, rFVIIa was available to patients through an international compassionate use programme.[10] Doses in this programme ranged from 60 to 120 μg/kg, with the most common being 90 μg/kg. It was this 90 μg/kg dose, which was determined predominantly by clinical observation rather than prospective clinical trial, that was initially approved by regulatory authorities (European Union, 1996 and US, 1999).

Together these studies confirmed the haemostatic activity of rFVIIa and the requirement for repeat dosing every 2-3 hours. Early mechanistic studies suggested that FVIIa exerted proteolytic activity in the presence of tissue factor (TF), suggesting greatest activity at the site of injury[4]; although this theory was supported by the lack of thrombotic events reported in early clinical trials, concern about thrombotic risk remained, particularly in less well-controlled, real-world situations.[5]

3 | THE ERA OF TRANSFORMATIVE CARE

Following early studies confirming efficacy, clinicians quickly began to focus on establishing treatment paradigms to achieve rapid and predictable haemostasis and to prevent long-term sequelae. An increasing body of clinical data led to improved treatment regimens and patient outcomes, with home-based treatment becoming the standard of care; however, clinical assays continued to be unavailable, and the relationship between clinical dose, FVIIa level, and efficacy remained largely unknown. Furthermore, clinical observation questioned the need to maintain FVIIa:C above a minimal level; instead the importance of an increased initial thrombin burst gained momentum with the introduction of high-dose regimens.[11]

3.1 | Early treatment

The first large-scale study to examine home-based treatment was reported by Key et al in 1998.[12] Effective and sustained haemostasis was achieved in 88% of evaluable rFVIIa-treated bleeding events (90 μg/kg; 1-3 doses at 3-hour intervals followed by a single maintenance dose). The increased efficacy was unlikely due entirely to the higher dose compared with earlier studies (70 μg/kg); instead, by eliminating the need to travel for treatment, the mean time to first

administration was reduced to 1.6 hours, compared with > 8 hours in the double-blinded study[9] and 20 hours in the original dose-finding study.[7] Early treatment resulted in improved clinical outcomes, the administration of fewer doses and a reduction in overall costs. An analysis of the US Hemophilia Research Society (HRS) registry from 2000 to 2002 indicated that at least 80% of rFVIIa treatments took place in the home[13] suggesting a very rapid uptake of home-based administration and an apparent realization that the benefits of self-infusion outweighed other concerns.

3.2 | Dosing

In 2003, Kenet et al[11] proposed the use of rFVIIa megadoses (300 μg/kg). In this study (114 bleeding events), hemarthrosis efficacy was 83%, 3-4 hours following a single megadose; with 100% efficacy being achieved with a second 300 μg/kg dose if required. Reflecting the unknown potential for thrombotic events with repeat high-dose rFVIIa, caution was advised and this strategy was recommended for use only in young patients due to their higher clearance.[14] Despite the potential convenience of a single dose, a review of the US Hemostasis and Thrombosis Research Society (HTRS) registry (covering a 4 year period following this report) revealed that only 8% of recorded bleeding episodes received a dose greater than 250 μg/kg[15] (the mean dose being approximately 100-120 μg/kg).[16] Even in children, who were expected to benefit from higher doses, the median initial dose was just 120μg/kg. A subsequent analysis by Shapiro et al revealed that only 2.7% of individual doses were greater than 240 μg/kg and over 60% of doses were less than 120 μg/kg.[17] Although there remained a preference towards lower-dose regimens, this analysis clearly showed that a range of doses were being utilized by clinicians to optimize treatment regimens.

Interestingly, the HTRS registry suggested regimens involving initial doses >200 μg/kg were more efficacious than regimens with doses <200 μg/kg (97% vs 84%, $P < .001$)[13]; however, these observations could not be confirmed in multiple prospective studies which compared a single 270 μg/kg dose to 3 × 90 μg/kg (q3 hours) doses.[18-20] All prospective studies reported comparable efficacy, time to efficacy and safety of both high- and low-dose regimens. High-dose rFVIIa (270 μg/kg) was approved for use in the EU in 2007. In the US, only low-dose rFVIIa (90 μg/kg) is approved for the treatment of inhibitor-related bleeding, although in practice higher doses are utilized where necessary.

3.3 | Safety

Over time, clinical experience and data suggested the risk of thrombotic events in haemophilia patients treated with rFVIIa was low and in many cases was associated with pre-existing risk factors. Abshire and Kenet reported on 700 000 90 μg/kg doses administered to inhibitor patients and patients with acquired haemophilia: 25 thrombotic events were associated with rFVIIa administration and 20 of these patients had complications predisposing them to thrombosis.[14] A second safety update covering 800 000 doses uncovered 30 thrombotic events.[21] The lack of reported thrombotic events in patients using 270 μg/kg doses suggested higher doses were also safe for use.[17-20,22]

4 | THE ERA OF CARE OPTIMIZATION

Following 2 decades of clinical experience, early and intensive rFVIIa treatment is now accepted by clinicians and supported by national guidelines[23]; however, these treatment regimens are not always routinely followed by patients. To address this, haemophilia treatment centres have evolved into centres where specialized teams provide not just medical care, but also education, training and psychosocial support. As a result, this era is defined by the introduction of innovative protocols driven by scientific research, individualized care and psychosocial support to permit the patient to be as independent as possible. Observational studies suggest that a wide range of rFVIIa doses are routinely administered, reflecting clinicians' and patients' prior experiences and the specific type of bleeding event being treated; with the use of higher initial doses becoming more common.

4.1 | Dosing

By now, multiple clinical trials had demonstrated comparable safety and efficacy of low-and high-dose rFVIIa regimens.[18-20] Furthermore, reviews of registry data made it clear that a wide range of initial doses were being utilized to optimize and individualize care in real-world situations.[17,24,25] Interestingly, these registries also noted a movement towards the more frequent use of higher initial doses: the ONE Registry noted that high initial doses (≥250 μg/kg) were used in 43% (211/494) of bleeding episodes,[24] and the DOSE study reported that 35% of initial doses were ≥240 μg/kg.[25] This may reflect increasing clinician comfort with high-dose rFVIIa as reported by Young et al[25] and also by Sorensen et al[23], who noted that half of haemophilia clinicians would recommend a 270 μg/kg initial dose. It may also reflect the long-held assumption that high-dose rFVIIa might optimize early thrombin generation and aid long-term clot stability.[24] Young et al noted that high-dose regimens administered at short intervals may be beneficial for problematic bleeds.[26]

Although overall efficacy outcomes may not differ based on dosing regimen,[18-20] improvements in patient convenience were reported with higher-dose regimens: when initial doses ≥270 μg/kg were administered, only 23% of bleeds required additional rFVIIa administration; whereas when lower initial doses (<180 μg/kg) were employed, 56% of bleeds required additional infusions to achieve haemostasis.[27]

4.2 | Combination therapy

As an alternative to high-dose rFVIIa, the use of a combined rFVIIa/FVIII[28-30] therapy has been proposed. Klintman et al[29] reported that

inhibitor plasma samples spiked with rFVIIa and FVIII had increased thrombin generation compared with that of a single haemostatic agent. In a small clinical trial, this combination therapy improved haemostasis in inhibitor patients.[28] Specifically, subjects were screened for haemostatic response and these ex vivo data were used to individualize clinical dosing regimens; haemostasis was achieved with a single rFVIIa/FVIII administration in 90% of bleeding events. Doshi et al proposed a rationale for the use and individualization of rFVIIa/FVIII treatment based on the kinetics of different anti-FVIII antibodies[30]: antibodies that exhibited fast and complete inhibition kinetics showed no added benefit, whereas antibodies with slow kinetics or incomplete inhibition of FVIII showed enhanced thrombin generation.

Sequential rFVIIa/aPCC dosing has been used in cases of unresponsive bleeding; both additive and synergistic effects have been documented.[31] Multiple case series have reported the safety and efficacy of such regimens when administered under controlled conditions[31-33]; however, no standard protocol exists. The known risk of thrombotic side effects[33] generally limits the use of this regimen to a hospital setting and experienced healthcare providers.

4.3 | Prophylaxis

Driven by isolated case reports in the literature, Konkle et al[34] reported a randomized, double-blinded rFVIIa prophylaxis study in 2007. A once-daily rFVIIa regimen (90 μg/kg or 270 μg/kg) over a 3-month period resulted in a statistically significant decrease in bleeding frequency (45% and 59% reduction, respectively) with no thrombotic events reported. The authors noted an improvement in health-reated quality of life, including hospitalization, absenteeism, pain and mobility.[22,34] Additionally, once prophylaxis was discontinued, there continued to be a significant protective effect lasting for at least an additional 3 months. The success of this once-daily regimen could not be explained based on the 2.5 hours half-life of rFVIIa; hypotheses included very low circulating levels providing protection; a reduction in inflammatory synovitis reducing the incidence of bleeding; the distribution of rFVIIa into extravascular tissue; and alternate mechanisms of action.

Although rFVIIa is not indicated for prophylactic use in inhibitor patients, results from the observational PRO-PACT study (46% decrease in bleed frequency) support its use.[35] Published guidelines support the administration of bypassing agent prophylaxis for inhibitor patients who experience frequent bleeds, including those on immune tolerance induction therapy.[36] More rigorous criteria are used by some clinicians, including the initiation of prophylaxis immediately following a single joint bleed—an approach predicated on the need to preserve long-term joint function.[37]

Regardless of the rationale behind any specific dosing regimen, there now exists a clear emphasis on individualizing patient care, with the goals of bleed prevention, rapid haemostasis, patient convenience and predictable efficacy impacting product(s), dose and timing. Algorithms for the treatment and prevention of bleeding episodes have been proposed, and over time suggestions made for their improvement.[23,26]

4.4 | Patient support

The advantages of early and in-home treatment are well established and guidelines recommend treatment initiation within 1 hour; however, in a worldwide survey, Sorensen noted that a third of bleeding events were not treated within 2 hours of identification.[23] The reasons behind this were not explored, but this study also noted that half the clinicians questioned failed to provide educational materials—an observation that conflicts with the prevailing view that a substantial effort should be devoted to education, particularly around early bleed identification and treatment.[1]

Influences such as failing to notice a bleed or its severity, daily schedule, infusion inconvenience, venous access and psychosocial barriers impact patient adherence.[38] These factors are routinely addressed by trained personnel at specialized haemophilia treatment centres (HTCs), who can reinforce the concept that adherence failure leads to rebleeding, possible hospitalization, long-term arthropathy and reduced quality of life. With the introduction of dose-intense regimens such as prophylaxis and ITI, emphasis on assessing and supporting adherence became a major focus for HTC care teams with social workers and psychologists working closely as part of the HTC team to reinforce the importance of adherence. The value of this multidisciplinary approach was reviewed and restated by an expert panel in 2011.[39]

4.5 | Improved understanding of the mechanism of action

The understanding of FVIIa mechanism of action has evolved over time. Originally, biological activity was assumed to be primarily TF-dependent; this accounted for the lack of systemic activation, but could not explain the need for high doses. Later studies demonstrated that high-dose rFVIIa could promote thrombin generation on a platelet surface in the absence of TF.[40] As rFVIIa binds to activated platelets with low affinity and activated platelets are only present at a site of injury, this theory could more effectively explain clinical observations. A model employing a biphasic response has been proposed, whereby the dominant mechanism of action changes depending on rFVIIa concentration.[41] This model was able to explain the comparable haemostatic efficacies of the 270 μg/kg and 3 × 90μg/kg protocols, and the clinical effect of other investigative variants.[42]

More recently, a growing body of data has suggested that rFVIIa action, and its longevity of action, may also be driven by affinity for endothelial protein C receptor (EPCR). This receptor may play multiple roles in the haemostatic action of rFVIIa: for example, it may enhance thrombin generation by reducing FVa inactivation[43]; enhance barrier protection via a PAR1-mediated pathway[44]; and facilitate endocytosis, resulting in the storage of rFVIIa in extravascular tissue for extended periods of time (≥7 days in one study).[45] Other studies have suggested EPCR may allow uptake into megakaryocytes, producing platelet-like particles that incorporate rFVIIa.[46] These studies provide a possible explanation for the success of once-daily rFVIIa

prophylaxis and the continued protection following prophylaxis discontinuation.[34]

Further supporting the role of EPCR in haemostasis, a rFVIIa variant with no EPCR affinity, N7-GP, was shown to have half the FVIIa plasma activity of eptacog alfa (despite a twofold higher clinical dose) and lacked the same long-term protective effect that was previously seen with eptacog alfa following discontinuation of prophylaxis.[34,47,48] Conversely, another variant with greater EPCR affinity, eptacog beta, appears to have increased efficacy and reduced dosing requirements compared to comparable eptacog alfa dosing regimens.[49,50]

4.6 | New rFVIIa variants

In addition to advances in treatment and patient support, the development of rFVIIa variants with improved half-life and biological activity has been an ongoing goal. Two early investigational variants, vatreptacog alfa and BAY 86-6150, had increased biological activity from specific amino acid mutations; however, both failed in clinical trials due to the observation of antidrug antibodies.[51,52] The clinical development of a glycopegylated variant with an extended half-life (N7-GP) was similarly halted due to the lack of a dose-response and inferior activity compared with eptacog alfa.[48]

Two investigational variants continue to show promising clinical data: eptacog beta (on-demand) and marzeptacog alfa (prophylaxis); neither product is currently indicated for use. Eptacog beta is a variant with a unique post-translational modification profile; based on 468 treated bleeds in 27 subjects, it has a high single dose haemostatic success rate (85%) and a low rebleeding rate at 24 hours (0.2%), possibly due to its increased EPCR activity.[49,50] Eptacog beta also showed increased efficacy and a reduction in time to haemostasis with a higher initial dose compared with multiple smaller doses.[49]

Marzeptacog alfa has sevenfold increased in vitro activity and a 9.5 hours half-life (subcutaneous administration).[53] A phase 2/3 study was designed to determine an individualized daily dose (30-120 μg/kg) that prevents spontaneous bleeding; interim results from 5 subjects suggest a clinically significant reduction in annualized bleed rate with 3 subjects achieving zero bleeds over the 50-day administration period. One fatality unrelated to study drug was reported.

The development of new rFVIIa variants offers the potential for additional therapeutic options for bleed treatment and supports the current clinical focus on outcome optimization.

5 | THE NEW ERA OF UNCERTAINTY (FOR NOVEL PROPHYLACTIC AGENTS)

Having spent two decades optimizing rFVIIa treatment, today, clinicians and patients see a vastly altered therapeutic landscape with new products exhibiting unique mechanisms of action in clinical use and/or development. One of these products, emicizumab, has been approved for use in haemophilia A patients with or without inhibitors as a once-weekly, every other-week and every four-week prophylactic agent.[54,55] Others, such as fitusiran (an antithrombin knockdown agent) offer the possibility of treatment for patients with haemophilia A or B. Although potentially transformative, both products have shown unexpected thrombotic safety concerns when used with other haemostatic agents to treat breakthrough bleeds.[2,54,56]

5.1 | Use of bypassing agents with emicizumab

The increased risk of atypical thrombotic events (eg thrombotic microangiopathy, TMA) when treating bleeds with aPCC (>100 U/kg/day for >24 hours) while on emicizumab has resulted in the recommendation that reduced doses of bypassing agent be used.[2] Interestingly, this recommendation harkens back to the early use of rFVIIa, where low doses were routinely used out of an abundance of caution, which in turn was based on prior clinical experience with aPCC. Current guidelines state that bleeding events should be preferably managed with rFVIIa (90-120 μg/kg with 1-3 doses administered no more frequently than every 2 hours).[57,58] aPCC use with emicizumab should be avoided if possible; if aPCC use is necessary, the initial dose should be ≤ 50 U/kg and the total dose should not exceed 100U/kg/day. Duration of aPCC use should also be limited as TMA is associated with aPCC use for >24 hours. Guidelines note that patients who receive >1 dose of aPCC (or for >24 hours) should be evaluated for clinical symptoms of thromboembolic events; monitoring should continue daily until 48 hours following the last dose of aPCC. For patients who discontinue emicizumab, rFVIIa may need to be used preferentially for up to 6 months following the last dose of emicizumab due to its 28 day half-life.

These atypical thrombotic events have been attributed to a synergistic hypercoagulant effect that occurs with combined emicizumab/aPCC dosing; a result that increases thrombin generation above the normal physiological range.[59] A similar hypercoagulant effect with emicizumab/rFVIIa has not been observed; instead, thrombin generation is additive and remains below normal levels. This result is consistent with the lack of thrombotic events thus far observed with emicizumab/rFVIIa use and may be related to its short half-life, lack of binding to emicizumab and rFVIIa clearance mechanisms that include antithrombin and tissue factor pathway inhibitor.[60]

Severe bleeds should continue to be treated quickly and aggressively. It is not yet clear whether non-severe bleeds should be treated as quickly and as aggressively as they are with rFVIIa alone; or whether they should be left untreated to see if they resolve on their own. It is recommended that a medical evaluation of muscle and joint bleeds should be completed to confirm an active bleed prior to treatment with rFVIIa.[58] It is not known how this 'watchful waiting' may impact long-term sequelae, including arthropathy.

It remains to be seen how other investigational rFVIIa variants might be used with emicizumab. Given the low incidence of bleeding events on emicizumab prophylaxis, these questions may take years to be resolved. Regardless, bypassing agents will remain

essential for control of breakthrough bleeds, and options beyond aPCC and eptacog alfa may offer clinicians new choices for treatment optimization.

6 | CONCLUSIONS

FVIIa use has evolved from a scientific and clinical curiosity, where haemostasis could be achieved with low doses (50 U/kg) in a hospital setting, to a major clinical treatment option for inhibitor patients, administered at levels several hundred-fold higher than that found in normal plasma. Thrombotic adverse events have been relatively uncommon even with high-dose regimens, at least in patients lacking a predisposition to thrombosis. Based on seminal clinical trials and more than three decades of clinical experience, recommendations and algorithms have been developed to provide general guidance; but to an ever greater extent individualized care has become the norm with regimens designed to meet each patient's unique treatment responses in addition to their activites and lifestyle. Comprehensive models of care have evolved to help patients achieve their goals through shared decision-making, education and adherence to treatment regimens.

We are now entering an era of new prophylactic agents with novel mechanisms of action. While exciting for clinicians and patients, there are new uncertainties. Similar to the questions faced in the early years of rFVIIa use, we have new questions regarding rFVIIa treatment: when to treat; how much to administer; how to assess response; and how to monitor for adverse events. With the substantial decrease in annualized bleeding rate with these new agents, patients may potentially need to 'relearn' how to detect bleeding, how to infuse bypassing agents, and how to safely achieve haemostasis. The experiences and rationale behind the advances with rFVIIa use should not be forgotten, as the lessons clinicians learned during those years may inform the development of new clinical trials and protocols for the treatment of breakthrough bleeds in patients using novel prophylactic agents.

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AUTHORS' CONTRIBUTIONS

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