

SECONDARY PROPHYLAXIS WITH rFVIIa IN HEMOPHILIA AND INHIBITORS: RECOMMENDATIONS FROM AN EXPERTS COMMITTEE FROM ARGENTINA

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Abstract Secondary prophylaxis with rFVIIa has been the subject of several publications in the past few years. However, there is no general consensus on how this treatment should be put into practice, as publications have been very heterogeneous in the dosing schedule they report. Furthermore, the mechanism of action of rFVIIa and its short half life have been used as arguments against its role in prophylaxis. There have been a series of recent publications that show that rFVIIa can traffic through the intact endothelium and be stored in the subendothelium of several organs for a prolonged period of time. In order to consensuate the role of rFVIIa in prophylaxis, a group of experts from Argentina, resumed available information regarding pharmacology and clinical experience with this treatment, and developed a series of recommendations to use this drug in the prophylaxis setting.

Key words: rFVIIa, prophylaxis, hemophilia, inhibitors

Resumen *Profilaxis secundaria con rFVIIa en pacientes con hemofilia e inhibidores: Recomendaciones de un comité de expertos de Argentina.* La profilaxis secundaria con factor VII activado recombinante (rFVIIa) ha sido objeto de varias publicaciones en los últimos años. Sin embargo, no existe un consenso general sobre cómo este tratamiento debe ser puesto en práctica, dado que las publicaciones han sido muy heterogéneas respecto del régimen de dosificación que publican. Además, el mecanismo de acción del rFVIIa y su vida media corta se han utilizado como argumentos en contra de su papel en la profilaxis. Ha habido una serie de publicaciones recientes que muestran que el rFVIIa puede atravesar el endotelio intacto y almacenarse en el subendotelio de diversos órganos durante un período prolongado de tiempo. Con el fin de consensuar el papel de rFVIIa en la profilaxis, un grupo de expertos de Argentina, ha recopilado la información disponible sobre la farmacología y la experiencia clínica con este tratamiento, y desarrolló una serie de recomendaciones para utilizar este fármaco en el ámbito de profilaxis.

Palabras clave: rFVIIa, profilaxis, hemofilia, inhibidores

Prophylaxis therapy with Factor VIII and Factor IX has been established as the best strategy to decrease the bleeding frequency and prevent joint damage in people with hemophilia A (HA) and B (HB) respectively^{1,2}. However, inhibitor patients, who can represent as much as 36% in severe HA and 8% in severe HB, can not benefit from this treatment³. This situation leaves inhibitor patients at a higher risk of developing recurrent joint bleeding and severe haemophilic arthropathy^{4,5}.

In February 2010, secondary prophylaxis for patients with hemophilia and inhibitors with recombinant activated factor VII (rFVIIa) was approved to be included in the label of NovoSeven® (Novo Nordisk, Bagsvaerd, Denmark)

by the "Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT)". This new accepted indication comes after new clinical and pharmacological evidence supporting the use of rFVIIa in prophylaxis emerged. All these publications proved prophylactic use of rFVIIa to be effective⁶⁻¹⁴, but as they use different dosing schedules they fail to provide physicians with a guide on how to implement this treatment.

To address this issue, a group of experts from the National Foundation of Hemophilia and the National Academy of Medicine held a consensus meeting to agree on recommendations for rFVIIa usage in secondary prophylaxis.

This article summarises the pharmacological and clinical evidence supporting this indication and the recommendations of the panel of experts on how to put into practice secondary prophylaxis in hemophilia patients with inhibitors.

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Pharmacological evidence

Since the 1990s, pharmacokinetics and pharmacodynamics of rFVIIa have been thoroughly investigated, proving this drug to have a short half life and a differential behaviour in children than in adults¹⁵⁻¹⁹. Pharmacokinetic studies have also shown that rFVIIa has a steady state volume of distribution which can be 5-7 times larger than the plasmatic volume (Table 1). This finding suggests accumulation of rFVIIa. Although this information has been available for more than a decade, it was not until recently, that redistribution through the intact endothelium and accumulation in the subendothelium of rFVIIa could be demonstrated¹⁷, providing evidence that this drug can be useful as prophylactic therapy.

In order to prevent hemarthrosis, rFVIIa must be able to reach the subendothelium after trafficking through the intact endothelial layer. Endothelial Cell Protein C Receptor (EPCR) has been postulated to aid rFVIIa in this task. Ghosh et al. examined the binding of radiolabeled FVIIa to endothelial cells and its subsequent internalization²⁰. They analyzed the behaviour of ¹²⁵I-FVIIa in non-stimulated and stimulated human umbilical vein endothelial cells (HUVEC) in the presence of unlabelled FVIIa and TF. They also examined the binding and internalization of ¹²⁵I-FVIIa to EPCR transfected CHO-K1 cells. With this model, they were able to demonstrate that ¹²⁵I-FVIIa bound to non-stimulated HUVEC cells. This binding was independent of TF and was effectively blocked by Protein C and monoclonal antibodies against EPCR. Furthermore, they also demonstrated a marked increase in ¹²⁵I-FVIIa binding to EPCR transfected CHO-K1 cells compared with the wild type. These results provide convincing evidence that EPCR serves as the binding site for FVII/FVIIa.

However, binding to endothelial cells does not imply accumulation in the subendothelium. To address this issue, Lopez-Vilchez et al., published a paper demonstrating the traffic of rFVIIa through the endothelial cells and its redistribution into the subendothelium²¹. Briefly, this group exposed cultured endothelial cells and umbilical veins to rFVIIa for 2 hours and combined immunocytochemical techniques with confocal microscopy to localize rFVIIa into the subendothelial compartments. The exposed vessels were then de-endothelized and exposed to flowing blood, determining platelet adhesion and fibrin deposition. The immunocytochemical studies revealed an enhanced presence of cytoplasmatic rFVIIa that relocate into the nuclear and peripheral areas in the 24 hours incubations. These studies also demonstrated that rFVIIa localized in the endothelium and extended deeper into the subendothelium of incubated umbilical veins. Perfusion studies showed that the redistributed rFVIIa improved fibrin generation and enhanced platelet throm-

TABLE 1.- rFVIIa Pharmacokinetics: Differences in children and adults*

	Children	Adults
Half Life (hours)	2.6	3.1
MRT (hours)	2.8	3.3
Clearance (mL kg ⁻¹ h ⁻¹)	58	39
Vss (mL kg ⁻¹ h ⁻¹)	164	128

*Adapted from reference 15

MRT: Mean Residence Time, Vss: Volume of Distribution at steady state

bus formation, rendering rFVIIa functional from this compartment once the endothelium has been denuded.

Finally, Gopalakrishnan et al. examined in a murine model, the extravascular distribution of rFVIIa administered in a pharmacological dose (120 µg/kg)²². They were able to demonstrate that rFVIIa associates with the vascular endothelium, enters into the extravascular spaces and binds to TF where it could be retained for prolonged periods of time. Most noticeable, they were able to find rFVIIa in the bone (in the zone of calcified cartilage) a week after administration.

Altogether, the evidence provided by these studies show that rFVIIa by binding with EPCR can traffic through the intact endothelium, accumulates in the subendothelium and remains functional for prolonged periods of time. The slow release of rFVIIa from the storage sites may be responsible for the prolonged effect of rFVIIa observed in clinical studies²⁰⁻²².

Clinical Evidence

Although until recently, rFVIIa was only approved for "on demand" treatment of bleeding episodes in inhibitor patients (both hemophilia A and B), there has been an increasing number of publications in the past few years where this drug was used for prophylaxis (Table 2)⁶⁻¹⁴.

Five reports, including data from 9 patients were published between the years 2000 and 2005⁶⁻¹⁰. These represent the first experience in the literature of prophylaxis in inhibitor patients. The overall efficacy was satisfactory with reduction of bleeding frequency in most patients.

After these preliminary reports, Konkle et al. published in 2007 the first prospective, multicenter, randomized, double blind study in inhibitor patients¹¹. This study included 22 hemophilia A and B patients with inhibitors and a history of heavy bleeding. After a three months observation period, patients were randomized to receive rFVIIa 90 or 270 µg/kg once daily for three months. The prophylaxis period was followed by an observation period of three

TABLE 2.– Summary of the clinical experience with rFVIIa as prophylaxis

Publication	N° of subjects	rFVIIa regimen	Duration	Outcomes
Brackmann et al. ^{6*}	4	90 µg/kg, twice daily	2 to 27 months	All patients decreased the inhibitor titre
Cooper et al. ⁷	1	240 µg/kg, every 6-8 hours	80 days	Reduction in Bleeding episodes
Saxon et al. ⁸	1	90 µg/kg, once daily	21 weeks	Reduction in bleeding episodes and days of immobility
Bryant et al. ⁹	1	300 µg/kg, 3 times weekly, plus prednisone	5 months	Reduction in Bleeding episodes
Young et al. ¹⁰	2	200 µg/kg, every 6-12 hours	12 to 25 months	Reduction in Bleeding episodes in both patients
Konkle et al. ¹¹	22	90 or 270 µg/kg, once daily	3 months	45 and 59% bleeding frequency reduction in each arm
Morfini et al. [12]	13	Variable. 200-250 to 1540 µg /kg/week	4 months to 4 years	92% of patients experience bleeding reductions
Jimenez-Yuste et al. ¹³	5	90 or 100 µg/kg, daily	6 to 22 months	All patients experienced bleeding reductions
Auerswald et al. ^{24**}	34	Variable. From 90-180 µg /kg, daily to 90 µg /kg, 3 times weekly	1.9 to >32 months	Overall reduction of bleeding episodes in all patients

*Patients were in ITI treatment.

** Resume of congresses presentations on prophylaxis with rFVIIa

months in which patients received “on demand” therapy. Both arms showed a significant reduction in bleeding episodes in the prophylaxis period compared with the previous observation period (59% reduction for the 270 µg/kg arm and 45% for the 90 µg/kg arm – $p < 0.0001$ for both schedules). Most strikingly, these reductions persisted in the 3 months follow up period with a 50% reduction for the 270 µg/kg patients ($p < 0.0001$) and 27% for the 90 µg/kg ones ($p < 0.01$). Although orthopaedic joint scores did not change throughout the study, the reduction in bleeding frequency was more pronounced in joint bleeds, and a subsequent quality of life analysis published by Hoots et al. showed a significant improvement in school/work absenteeism, pain and EQ-5D and VAS scores²³. This trial is the first and only prospective evidence of the efficacy of a bypassing agent as prophylaxis therapy for hemophilia patients with inhibitors and was the basis for the approval of prophylaxis in the Argentinean label.

Following Konkle et al. publication, a retrospective survey of 10 hemophilia centres was published by Morfini et al.¹². This paper included data from 13 different inhibitor patients who received completely different schedules of prophylaxis with rFVIIa. The dosages varied not only in the doses but also in the interval between doses (doses: 200-1540 µg/kg per week – interval: twice daily to twice a

week). Despite these differences, 12/13 patients experienced a significant reduction in bleeding frequency.

Another interesting study was published by Jiménez-Yuste et al.¹³. The authors reported the outcome of 5 patients with severe hemophilia A and inhibitors. Patients received 90-100 µg/kg for 6-22 months. When bleeding frequency was compared between the prophylaxis period to the period of identical length prior to therapy, a reduction from a median of 4 (3-10) bleeding episodes to 1(0-5) was reported. Only 1/5 patients developed a target joint during prophylaxis, however, the total number of bleeds were reduced in all 5 patients.

In a recent review of the literature, Auerswald et al. identified 34 additional patients reported in several conference abstracts who received different prophylaxis regimens²⁴. The overall results of these reports prove rFVIIa to be an effective treatment in the prophylaxis setting regardless the dosing scheduled chosen by the treating physicians.

It is noteworthy to point out that none of the studies described above reported thromboembolic events, making rFVIIa safe as well as effective.

All these publications denote a growing interest in the field, plus evidence an unmet need for standardization of this treatment. Overall, there are more than 80 patients reported in the literature that received rFVIIa as prophylaxis.

laxis with good results, regardless of the scheduled used. Congenital hemophilia is a rare disorder and inhibitor patients represent a minority amongst them, so although these numbers seem small, they represent a large amount of inhibitor patients worldwide.

It is highly improbable that another prospective, randomized trial can define which of the different dosing schedules reported in the literature is the best for inhibitor patients, so we decided to review all data and agreed on a schedule that is effective, safe and feasible in an outpatient setting, as we believe this are the three characteristics that a prophylaxis regime should have.

Recommendations

The National Academy of Medicine and the Hemophilia Foundation have been working together in the interdisciplinary care of hemophilia patients for more than 60 years. Together they assist in the care of more than 2000 patients from all around the country and represent the institutions with more experience in the area. Given its position in hemophilia, the authors (who belong to these institutions) agreed to translate their experience and the available information into the recommendations that follow (Table 3).

After reviewing all the clinical data, 5 categories of patients were identified that would benefit from prophylaxis. Patients who suffered a life threatening bleeding, specifically a bleeding in the central nervous system (CNS), those with recurrent bleeding episodes, those in preparation for immune tolerance induction (ITI), those who fail or are not suitable for ITI and those patient in need for active and/or prolonged physiotherapy.

We based our recommendation for CNS bleeding in the last consensus for this indication in non-inhibitor pa-

tients²⁵. According to this, all inhibitor patients with an intracranial haemorrhage should receive treatment with a bypassing agent for as long as 30 days. After completing treatment, if the patient is stable, it should be put in a prophylaxis schedule. For this indication we recommend 180-270 µg/kg every other day for at least six months. This timeline was adopted in concordance with recommendations for non-inhibitor patients, however the authors believe the duration can be prolonged further. In the case of a second episode, it was agreed that prophylaxis should be maintained indefinitely, as the risk for a new episode and sequels increases dramatically with additional bleedings.

Most papers reporting prophylaxis with rFVIIa are based on inhibitor patients who suffer recurrent bleeding episodes. This indication although not life threatening, carries a big concern for hemophilia caregivers, as frequent joint bleedings are associated with increase morbidity, decrease in the quality of life and increase in the cost of care of these patients. However, there is no clear definition on what should be considered recurrent bleeding. Konkle et al., in their prospective evaluation, required patients to suffered 4 bleedings per month as an inclusion criteria and a total of ≥ 12 bleeds requiring haemostatic treatment in the pre-prophylaxis observation period to be randomized and receive prophylaxis therapy. Using this work as background, we agreed that any patient suffering ≥ 3 bleedings per month is a suitable candidate for prophylaxis. It was also acknowledge by the authors that some episodes can not be evaluated in this manner if sequels want to be avoided. So, in the case of bleeding into iliopsoas muscle, into other big volume muscles or gastrointestinal bleedings which their natural history is to recur, we agreed that ≥ 2 episodes in the same area should be considered in the same way as a recurrent bleeding and will make the patient suitable for prophylaxis.

TABLE 3.– Recommendations for the use of rFVIIa as prophylaxis

Indication	Dose	Duration
Life threatening CNS bleeding	180-270 µg/kg every other day	<ul style="list-style-type: none"> • At least six months after first episode. • Indefinitely for further episodes
Recurrent Bleeding	90-270 µg/kg every other day*	<ul style="list-style-type: none"> • At least three months for the first course • Consider more prolonged, higher doses or less interval for further courses
Patients in preparation for ITI	Same as recurrent bleeding	<ul style="list-style-type: none"> • Until criteria to start ITI are fulfilled
Patients who failed or are not candidates for ITI	Same as recurrent bleeding	<ul style="list-style-type: none"> • Same as recurrent bleeding
Patients on active/intense physiotherapy	90-270 µg/kg three times per week*	<ul style="list-style-type: none"> • As long as intense physiotherapy is indicated

*Consider doses used as "on demand" therapy for the selection of initial dose

laxis. The dosing schedule we recommend for these patients is 90-270 µg/kg every other day. Physicians should take in consideration the dose used for each patient while on "on-demand" treatment, as if they respond to that dose, it will probably be wise to start with it and in the case of lack of efficacy upscale the dosage or reduce the interval between doses. The duration of treatment in these patients is the more heterogeneous variable reported in the literature, with reports of prophylaxis duration varying from 80 days to 50 months. Taking into consideration the results reported by Konkle et al., we recommend treating patients for at least 3 months. If after this first course of prophylaxis, the patient presents again with criteria of recurrent bleeding, physicians could opt for a new course of prophylaxis but in this case, our recommendation is to increase the duration of treatment.

With regards to patients who are candidates for ITI and those who fail or are not suitable for this treatment, we recommend evaluating them in accordance with their bleeding frequency. Should they fulfil any of the criteria described above, they should be put on prophylaxis; otherwise it is our recommendation to continue "on demand" treatment with rFVIIa. Dosing and duration of treatment should also be the same as for recurrent bleeders. In the particular case of patients in preparation for ITI, prophylactic treatment should continue until the initiation of immune tolerance. At this moment, each patient should be evaluated individually and determine the best course of action according to prior history and ITI regimen chosen.

The last recommendation includes patients in need for active or intense physiotherapy^{24, 25}. This indication can come after a surgery or in an attempt to recover mobility of a moderate to severe arthropathy. We recommend using 90-270 µg/kg three times a week coincidental with the physiotherapy sessions. As for the previous recommendations, our advice is to start with the usual dose required for "on demand" therapy and upscale it if necessary.

In conclusion; the introduction of prophylaxis with factor VIII has proven to be a major advance in the treatment of hemophilia patients without inhibitors. This strategy allowed patients to live a nearly normal life with significant fewer complications. However, the treatment of hemophilia patients with inhibitors still remains as one of the biggest challenges that physicians involved in this field have to face. Prophylaxis with rFVIIa has emerged as a viable option for these patients, specifically for patients with life threatening bleeds and for recurrent bleeders. There is still no consensus on the dosing schedule to be used. However, based on the pharmacological evidence, that supports the use of rFVIIa in daily or every other day doses; and the clinical evidence that prove this drug to be efficacious in almost all patients who received prophylaxis, we develop these recommendations guide-

line in an attempt to help physicians in the difficult task of treating inhibitor patients. They are based on the experience of the biggest institutions of Argentina dedicated to the care of people with hemophilia. However, each patient is different from the next one, so it is our advice to use these recommendations as a guide and tailor the prophylaxis therapy for each patient.

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[...]

La avenida que se denomina "Sarmiento", y que flanquean Palmas y Plátanos Occidentales, desde la calle Santa Fe al Oeste hasta la margen del Río al Este, establecía una grande línea de subdivisión entre las secciones, y una arena para los carruajes, con aceras laterales, sombreadas por doble hilera de árboles para ejercicio a pie. Esta avenida, además, era aconsejada por el propósito de poner en contacto inmediato el Parque con la calle Santa Fe, que por su amplitud y pavimento continuo, por estar iluminada a gas en toda su extensión y servida con tramways, daría fácil acceso a las personas de modestas condiciones de existencia, que acudirían al Parque a buscar el recreo y solaz, que requiere la higiene y reclama el espíritu tras las tareas del día.

[...]

Domingo Faustino Sarmiento (1811-1888)

Documentación que Sarmiento presentó al Presidente de la República [Avellaneda] el día 11 de noviembre de 1875, con motivo de la inauguración de la primera sección del nuevo paseo habilitado para el público. Sarmiento era el Presidente de la Comisión Auxiliar del "Parque 3 de febrero". *Revista del Jardín Zoológico de Buenos Aires*. 1916; Año XII, Mayo de 1916, N° 45, p 5.

En: www.proyectosarmiento.com.ar; consultado el 22-3-10