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

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) respectively1,2. 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 arthropathy4,5.

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.
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 adults\textsuperscript{15-19}. 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 demonstrated\textsuperscript{17}, providing evidence that this drug can be useful as prophylactic therapy.

In order to prevent haemarthrosis, 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 internalization\textsuperscript{20}. They analyzed the behaviour of $^{125}$I-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 $^{125}$I-FVIIa to EPCR transfected CHO-K1 cells. With this model, they were able to demonstrate that $^{125}$I-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 $^{125}$I-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 subendothelium\textsuperscript{21}. 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-endothelialized and exposed to flowing blood, determining platelet thrombus formation, rendering FVIIa 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)\textsuperscript{22}. They were able to demonstrate that rFVIIa associates with the vascular endothelium, enters into the extravascular spaces and binds to TF were 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 FVIIa 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 FVIIa from the storage sites may be responsible for the prolonged effect of rFVIIa observed in clinical studies\textsuperscript{20-22}.

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)\textsuperscript{6-14}. Five reports, including data from 9 patients were published between the years 2000 and 2005\textsuperscript{5-10}. 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 patients\textsuperscript{11}. 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 1. rFVIIa Pharmacokinetics: Differences in children and adults

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half Life (hours)</td>
<td>2.6</td>
<td>3.1</td>
</tr>
<tr>
<td>MRT (hours)</td>
<td>2.8</td>
<td>3.3</td>
</tr>
<tr>
<td>Clearance (mL kg$^{-1}$ h$^{-1}$)</td>
<td>58</td>
<td>39</td>
</tr>
<tr>
<td>Vss (mL kg$^{-1}$ h$^{-1}$)</td>
<td>164</td>
<td>128</td>
</tr>
</tbody>
</table>

*Adapted from reference 15
MRT: Mean Residence Time, Vss: Volume of Distribution at steady state
Secondary 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.

Another interesting study was published by Jiménez-Yuste et al13. 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 schedule 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 prophyl-

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

*Patients were in ITI treatment.

** Resume of congresses presentations on prophylaxis with rFVIIa
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 patients. 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 bleeds 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 prophy-

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life threatening CNS bleeding</td>
<td>180-270 µg/kg</td>
<td>• At least six months after first episode·</td>
</tr>
<tr>
<td></td>
<td>every other day</td>
<td>• Indefinitely for further episodes</td>
</tr>
<tr>
<td>Recurrent Bleeding</td>
<td>90-270 µg/kg</td>
<td>• At least three months for the first course Consider more prolonged, higher doses or less interval for further courses</td>
</tr>
<tr>
<td></td>
<td>every other day*</td>
<td></td>
</tr>
<tr>
<td>Patients in preparation for ITI</td>
<td>Same as recurrent bleeding</td>
<td>• Until criteria to start ITI are fulfilled</td>
</tr>
<tr>
<td>Patients who failed or are not candidates for ITI</td>
<td>Same as recurrent bleeding</td>
<td>• Same as recurrent bleeding</td>
</tr>
<tr>
<td>Patients on active/intense physiotherapy</td>
<td>90-270 µg/kg three times per week*</td>
<td>• As long as intense physiotherapy is indicated</td>
</tr>
</tbody>
</table>

*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 fulfill 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 coincident 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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References


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 trambays, 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)