

## How I treat

# How we choose factor VIII to treat hemophilia

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**In high-income countries, the large availability of coagulation factors for replacement therapy of patients with hemophilia A has raised the life expectancy of these lifelong bleeders to that of males from the general population. The practicing clinician is offered a multitude of choices among several commercial brands of factor VIII extracted from human plasma or engineered from mammalian cell cultures by means of recombinant DNA technology.**

**This article has the goal to offer our opinions on how to choose among the different products, that we consider interchangeable relevant to their clinical efficacy in the control of bleeding and safety from pathogen transmission. Hence, the main determinants of our choices are price and the risk of occurrence of factor VIII inhibitory alloantibodies. With this as background, we present the rationale underlying the choices for different categories**

**of patients with severe hemophilia A: previously untreated patients, multiply treated patients, and patients undergoing immune tolerance induction with large doses of factor VIII to eradicate inhibitors. Mention is also made to the possible strategies that should be implemented to make available coagulation factors for replacement therapy in developing countries. (*Blood*. 2012;119(18):4108-4114)**

## Introduction

The management of hemophilia has dramatically improved in the last 25 years.<sup>1,2</sup> During the gloomy decade of the 1980s, many patients died of blood-borne infections by HIV and the hepatitis viruses. Subsequently, the implementation of virucidal methods and of nucleic acid amplification testing in the manufacturing process of coagulation factors extracted from human plasma,<sup>3,4</sup> as well as the production of factor VIII (FVIII) and factor IX (FIX) by recombinant DNA technology from mammalian cell cultures,<sup>4</sup> have made replacement therapy safe and widely available, at least in high-income countries. Throughout the 1990s, other important steps forward included the more extensive implementation of regular factor prophylaxis as a therapeutic regimen instead of episodic factor replacement at the time of bleeding,<sup>5</sup> and the improved clinical management of patients refractory to therapy because of the occurrence of alloantibodies inhibiting coagulant activity. Even though inhibitors still remain the most challenging problem, particularly in hemophilia A, plasma-derived and recombinant activated coagulation factors that bypass the defect induced by inhibitors manage to stop bleeding nearly as effectively as FVIII replacement in patients with no inhibitor.<sup>6,7</sup> Moreover, immune tolerance induction (ITI), based on the long-term intravenous infusion of large doses of FVIII, does eradicate inhibitors in as many as two-thirds of patients.<sup>8</sup>

All of these advances, together with the improved control of chronic HIV infection by antiretroviral agents and the possibility to eradicate hepatitis C virus infection by interferon-based therapies, have raised the life expectancy of patients with hemophilia to that of the general male population, at least in high-income countries. This target is far from being attained for other monogenic diseases, such as thalassemia, sickle cell anemia, cystic fibrosis, and muscular dystrophy. For instance, the median life expectancy at birth is 37 years in cystic fibrosis, whereas it is more than 70 years in persons with hemophilia from high-income countries.<sup>9,10</sup> Hence,

the precept for hemophilia care in the third millennium is building on strength.<sup>2</sup> The next goals are the production of highly engineered variants of coagulation factors with a longer plasma half-life, and ultimately the cure of this ancient scourge through somatic gene transfer. Both these potentially innovative approaches are currently attaining promising results, particularly in hemophilia B.<sup>11-13</sup>

In the frame of this optimistic position of hemophilia care delivery, the clinician is offered a multitude of choices for replacement therapy. There is evidence that all licensed coagulation factors, whether plasma-derived or recombinant, have a high degree of efficacy in the control of a typical bleeding episode, such as hemarthrosis, with a success rate of 90% or more after 1- or 2-factor doses.<sup>14,15</sup> Hence, with regards to efficacy, all products should be considered interchangeable, provided appropriate therapeutic dosages and regimens are adopted. They also have a very high degree of safety from pathogen risk because no case of transmission of blood-borne viruses has been documented in persons with hemophilia since the late 1980s to early 1990s.<sup>3</sup> The safety of current replacement therapies was recently confirmed by a prospective surveillance program ongoing since 2008 and based on regular monitoring of 22 242 European patients (European Haemophilia Safety Surveillance System; www.euhass.org). Canada and Australia will soon join this surveillance program.

If antihemophilic products are similarly safe and effective, what are the criteria that should direct our therapeutic choices in hemophilia A? Besides price, the most important determinant is the risk of development of FVIII inhibitors. The mechanism of this complication is complex and multifactorial, with the involvement of several patient- and environment-related mechanistic factors.<sup>16</sup> Among them is the possibility that FVIII products of different sources and brands may entail a different risk of inhibitor development. Whether or not there is a discordance among

products with regards to inhibitor risk is being actively debated.<sup>17,18</sup> With this as background, we are going to discuss the rationale underlying our therapeutic choices, distinguishing treatment of children with hemophilia A naive to any replacement therapy, that of patients who already received multiple factor infusions and the choice of the FVIII product to be used for ITI in patients who developed inhibitors. The strategies that may be implemented to make more widely available coagulation factors for replacement therapy in developing countries will also be mentioned.

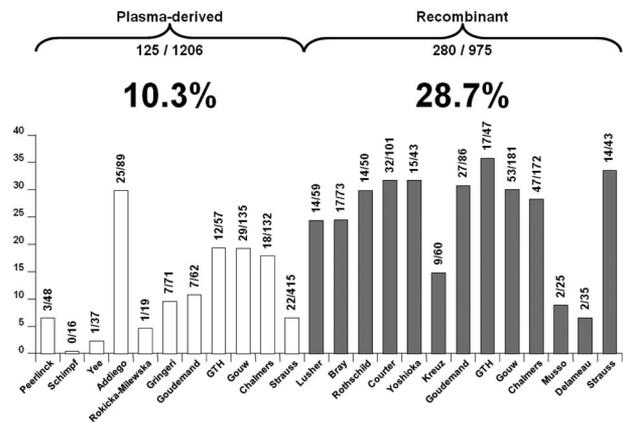
### The choice in previously untreated patients

The cumulative incidence of alloantibodies, which inactivate therapeutic FVIII by steric hindrance or proteolysis, ranges between 25% and 35% in severe hemophilia A.<sup>19</sup> Prevalence is lower (10%-20%) because some inhibitors disappear spontaneously or after eradication by ITI.<sup>20</sup> Inhibitors develop in newly diagnosed children at an average age of 2 to 3 years, more frequently after 10 to 20 days of exposure to FVIII, less frequently between 20 to 50 exposures, and seldom after 200 exposures.<sup>20</sup> Hence, efforts to reduce this complication are particularly cogent in previously untreated patients (PUPs).

#### Background

The early suggestion from Aledort<sup>21</sup> that the source of FVIII might influence the rate of inhibitor occurrence stems from the results of prospective studies carried out in PUPs to license early recombinant products in the 1990s, many of which recorded an unexpectedly high rate of inhibitors, ranging from 30% to 35%.<sup>21</sup> It is biologically plausible that bioengineered forms of FVIII produced from cultured mammalian cells may be more immunogenic than native FVIII from human plasma. For instance, there are posttranslational modifications of recombinant molecules in terms of glycosylation and sulphation that have a potential impact on immunogenicity.<sup>22-24</sup> The presence of VWF in most plasma-derived FVIII products (but not in FVIII purified from plasma by means of monoclonal antibodies nor in recombinant FVIII) may decrease immunogenicity via epitope masking and protection of the molecule from endocytosis by antigen-presenting cells.<sup>25,26</sup> Moreover, some plasma-derived FVIII products contain a number of potentially immunomodulatory human proteins not present in recombinant and monoclonally purified plasma-derived FVIII.<sup>26-28</sup>

A systematic review by Wight and Paisley<sup>29</sup> also supports the views that the source of FVIII may influence inhibitor development. A disparate cumulative incidence of inhibitors between plasma-derived (0%-12%)<sup>30,31</sup> and recombinant FVIII products (36%-38.7%)<sup>32,33</sup> was found in PUPs.<sup>29</sup> These results were received with some skepticism by the hemophilia community because the studies included in the analysis were very heterogeneous with regards to size, design, population, inhibitor definition, and also inhibitor incidence (Figure 1). Most importantly, potentially immune-modifying factors pertaining to the patient, such as severity of the plasma FVIII defect, type of gene mutation, family history of inhibitor, ethnicity, and treatment regimen (prophylaxis vs episodic treatment, early vs late prophylaxis), were heterogeneous. There was a high degree of heterogeneity also in study design (prospective or retrospective), frequency of inhibitor testing, and length of follow-up. In the attempt to control for these and other variables, Iorio et al performed another systematic review and found that the incidence of inhibitors was nearly 2-fold higher in patients treated



**Figure 1. Cumulative incidence of FVIII inhibitors in previously untreated or minimally treated patients with hemophilia A exposed only to single plasma-derived FVIII products (left panel open bars) or recombinant products (right panel closed bars).** The data from these studies were the broad basis of the systematic reviews.<sup>28,33,34</sup> The names in the horizontal axis are those of the first authors of the corresponding articles, which are cited in the aforementioned systematic reviews.

with recombinant FVIII (27.4%) than in those treated exclusively with plasma-derived FVIII (14.3%).<sup>34</sup> However, the effect of the source of FVIII on inhibitor incidence was no longer statistically significant after ANOVA because study design and period, inhibitor testing frequency, and patient follow-up length were identified as critical determinants of the differences in inhibitor incidence rather than the source of FVIII. In a more recent systematic review, Franchini et al chose to analyze only prospective studies that included PUPs (minimally treated patients were excluded).<sup>35</sup> Using these criteria, their patient population was much smaller than that of Iorio et al<sup>33</sup> (800 vs 2094 patients) but more homogeneous. There was still a higher incidence rate of inhibitors in recipients of recombinant FVIII (27% vs 21%), but the difference between the 2 sources of FVIII was smaller and not statistically significant.<sup>35</sup>

On the whole, neither systematic review can be taken as definite evidence that recombinant FVIII is more immunogenic than plasma-derived FVIII. This state of uncertainty on 2 competing sources of factor replacement therapy provides ethical and scientific justification for the independent randomized controlled Study on Inhibitors in Plasma-Product Exposed Toddlers (SIPPET; <http://www.clinicaltrials.gov>, #NCT01064284; EUDRACT, #2009-011186-88), which is currently ongoing in 24 countries from 4 continents and is aimed at demonstrating a 50% lower incidence of inhibitors for plasma-derived FVIII.<sup>36</sup> Final results will be analyzed cumulatively to compare inhibitor incidence in the 2 broad classes (plasma-derived and recombinant) of FVIII source. The reason for grouping by class is that clinicians need ascertainment of relative categorical inhibitor risk because distinct coagulation factor concentrates cannot be accurately assigned an absolute inhibitor risk.

#### How we choose

At the time of planning treatment of newly diagnosed boys with severe hemophilia, we inform their families on the possibility to participate to the randomized SIPPET trial. To this end, we provide information on the available current knowledge on risk factors for inhibitors, including data suggesting but not proving that plasma-derived FVIII may elicit less inhibitors; on the fact that recombinant FVIII is still perceived to be safer than plasma-derived FVIII in terms of risk of pathogen transmission and that the 2 sources of FVIII have equal

**Table 1. Incidence of FVIII inhibitor (both high and low titer) by age category in patients with severe hemophilia A in the United Kingdom between 1990 and 2009**

Age category, y	Incidence, % (per 1000 patient-years)
0-4	64.3
5-9	9.4
10-49	5.3
50-59	5.2
> 60	10.5

Data are from Hay et al.<sup>40</sup>

efficacy pertaining to the control of bleeding. If randomization is not accepted, patients who choose either source of FVIII are encouraged to be enrolled and followed up in prospective observational studies or registries such as RODIN (Research Of Determinants of Inhibitor development among previously untreated patients with hemophilia; www.rodinstudy.nl), the GTH (German Thrombosis and Haemostasis Society) PUP Study,<sup>37</sup> PEDNET (European Paediatric Network for Haemophilia Management),<sup>38</sup> and EUHASS, (European Haemophilia Safety Surveillance), with the goal to contribute to data for clinical research and pharmaco-vigilance. Another option is to encourage patients to participate in studies involving PUPs and designed to license new FVIII products because enrolled participants are usually tested at frequent and regular intervals during the first few days of FVIII exposure that entail the highest risk for inhibitor development. Hence, inhibitors are usually diagnosed early before reaching high titers, thereby allowing the early implementation of ITI.

At these times of global economic crisis, we and the patient family also take into important consideration the price of FVIII, even when costs are defrayed by a third party payer. In our as well as in other countries, recombinant FVIII costs from 50% up to 100% more than plasma-derived FVIII, and its price has not substantially decreased after more than 20 years since licensing, at a time when the original research and development costs are undoubtedly retrieved and the FVIII yield from cultured cells is likely to have increased. Neither there was a decrease in the price of plasma-derived FVIII because of safety-targeted changes introduced in donor plasma (nucleic acid testing) and manufacturing process (adoption of 2 or 3 virus-removing or inactivation methods). On the whole, our attitude, based on sharing the decision on FVIII choice between the clinician, the patient, and his family, reflects that of an international consumer organization, such as the World Federation of Hemophilia<sup>39</sup>: “the WFH does not express a preference for recombinant over plasma-derived concentrates and the choice between these classes of products must be made according to local criteria.”<sup>39</sup>

## The choice in previously treated patients

Previously treated patients (PTPs) with severe hemophilia and multiple FVIII exposures (usually defined 150-200 lifetime or more) have a much smaller risk of developing an inhibitor than PUPs. The most recent information on the epidemiology of inhibitors in PTPs stems from a study carried out by the United Kingdom Hemophilia Center Director Organization.<sup>40</sup> Inhibitors occur a low rate in PTPs throughout life, although the rate rises in old age (Table 1). There are several possible mechanisms for these late inhibitors, such as delayed detection or relapse of previously low-titer inhibitors, peak moments of intensive exposure to replacement therapy (ie, for surgical procedures), and the decline with aging of natural immune tolerance.<sup>40</sup>

**Table 2. De novo inhibitors occurring in previously treated patients with hemophilia A who switched from plasma-derived to recombinant FVIII during prospective licensure studies**

Recombinant product	No. of patients	No. of de novo inhibitors
Recombinate (full-length) <sup>43</sup>	69	0
Kogenate (full-length) <sup>44</sup>	86	1
Kogenate-FS (full-length) <sup>45</sup>	73	0
Refacto (B-domainless) <sup>46</sup>	113	1
Advate (full-length) <sup>47</sup>	108	1
Refacto (B-domainless) <sup>48</sup>	204	3

## Background

In the past, inhibitors did unexpectedly develop in a few PTPs who changed their routinely used plasma-derived FVIII to move to new products.<sup>41,42</sup> Even though this occurrence has been documented seldom and only at the time of switching to products with peculiar physicochemical features related to the method used for viral inactivation,<sup>41,42</sup> these observations generated concern with regards to the safety of changing from one product to another. The first piece of evidence that the risk of de novo inhibitor development associated with switching is actually small came from prospective premarketing studies carried out in the early 1990s for licensure of several recombinant FVIII brands, in which PTPs were changed from plasma-derived FVIII to the new recombinant products. Table 2 shows that in these PTPs studies, during which inhibitor incidence was monitored at regular intervals, de novo inhibitors occurred at a low rate.<sup>43-48</sup> In a Canadian hemophilia center prospective study, the occurrence of de novo inhibitors among PTPs switched first from plasma-derived FVIII to a recombinant FVIII product,<sup>49</sup> and then to another recombinant product was very low<sup>50</sup> (Table 3). Other data from the United States and the United Kingdom on 1257 PTPs who changed FVIII confirm a low rate of de novo inhibitors (2.14-3.8 cases for 1000 person-years).<sup>51,52</sup>

In contrast with this reassuring scenario on the incidence of inhibitors in PTPs switching from one FVIII source or brand to another, Aledort et al carried out a systematic review to compare the risk in PTPs of inhibitors associated with recombinant FVIII brands containing the full-length molecule with that of a molecule engineered to lack the B-domain.<sup>53</sup> While confirming a small overall incidence of de novo inhibitors, Aledort et al found a 7- to 10-fold higher inhibitor incidence in recipients of B-domainless FVIII. The systematic review triggered a few criticisms, related to the small number of events (de novo inhibitors) and the marked heterogeneity of the studies analyzed.<sup>54,55</sup> Further data on the immunogenicity of B-domainless FVIII in PTPs may soon stem from the analysis of United Kingdom data because the recent

**Table 3. De novo inhibitors occurring in previously treated patients who switched FVIII product in the frame of the Canadian surveillance system**

Giles et al <sup>49</sup>	Rubinger et al <sup>50</sup>
339 inhibitor-free patients	185 inhibitor-free patients
All switched from plasma-derived to a recombinant FVIII product	All switched from a recombinant FVIII to another second-generation recombinant FVIII
Central testing every 12 mo	Central testing every 12 mo
2 y of follow-up	2 y of follow-up
Inhibitor incidence: 14.7 per 1000 person-years	No de novo inhibitor

implementation of a national cost-driven system for factor procurement led a substantial number of patients to switch from full-length to a B-domainless FVIII.

### How we choose

The risk of inhibitors in PTPs who change FVIII is small and, with the exception of the few peculiar cases described in the early 1990s,<sup>41,42</sup> there is no large difference in risk pertaining to different commercial brands, even if the sample size of the available studies does not allow to rule out small differences. Yet, we prefer to avoid changing FVIII source and brand because surveillance, still a cogent goal in the management of hemophilia, becomes easier if patients are continuing on the same product. Patient's opinions and preferences play an important role because they usually become accustomed to a given product in the frame of self-treatment and changes are often not welcome. The future availability of highly engineered variants of coagulation factors with a longer half-life currently undergoing licensing study will entail switching. In our opinion, this is justified only if new products will offer substantial advantages in terms of significantly less frequent intravenous infusions (for instance, from 3 times weekly to no more than once weekly for FVIII, from once or twice weekly to every fortnight for FIX). In addition, the clinical efficacy, safety, and lack of neoantigenicity of these products must be firmly established, not only by the ongoing early studies but also by long-term pharmaco-vigilance programs such as EUHASS. The development of these products emphasizes the need in the field of hemophilia care not only for ongoing surveillance but also for health technology assessment (ie, the comprehensive and multidisciplinary evaluation of the long- and short-term global consequences on healthcare, economy, and ethics of new drugs and technologies). Harmonization of the actual differences existing between the European and United States agencies in the requirements to license different products would greatly help to improve the evaluation of these new products.

## The choice for immune tolerance induction

The use of recombinant or plasma-derived bypassing agents to control bleeding in patients with inhibitors is extremely expensive.<sup>56</sup> Moreover, the achievement of hemostasis at the time of bleeding is not always as optimal as in patients with no inhibitor treated with regular replacement therapy. Hence, an attempt to eradicate inhibitors by means of ITI through the regular, long-term infusion of FVIII (usually at large daily doses) is the primary therapeutic modality, with a high likelihood of success (inhibitor no longer measurable, normal recovery, and half-life of infused FVIII) that varies between 60% and 80%<sup>57</sup> and results in restoration of a normal response to standard replacement therapy. Features of optimal candidates for successful ITI include low historical inhibitor peak, low titer at the time of ITI start, and low anamnestic peak during ITI.<sup>58</sup> Outcomes are usually better in the frame of primary ITI (ie, initiated as soon as a patient develops an inhibitor), but tolerance is also achieved albeit at a smaller rate in patients who try rescue ITI after a primary attempt has failed.

### Background

The choice of the FVIII product to be used during ITI is a formidable challenge, mainly because of the huge costs owing to the large amounts of factor that must be infused daily or at alternate days, for several months or even years. The most common choice

is, at least in the frame of primary ITI, to continue with the same brand and source of FVIII administered at the time of inhibitor development. On the other hand, when rescue ITI is attempted, there is an obvious thrust to change the source of FVIII associated with failure. However, some findings indicate that plasma-derived FVIII products rich in VWF may increase the likelihood of success even in the frame of primary ITI. Data from German hemophilia centers<sup>58</sup> showed that the overall success rate of ITI declined from 87% to 91% to 54% to 29% in the early 1990s after the choice of conducting ITI with high-purity FVIII obtained from human plasma by monoclonal antibodies or by recombinant DNA technology instead of intermediate purity products containing large amounts of VWF and other proteins.<sup>58</sup> Most importantly, as many as 80% and 82% of the patients were again successfully tolerized with the return to the use of VWF-rich FVIII.<sup>58</sup> These data are intriguing, but not conclusive, because the duration of ITI (a critical aspect for a successful outcome) was much shorter when recombinant/monoclonal FVIII products were used, perhaps affecting the rate of inhibitor eradication. Subsequent studies supported the efficacy of ITI regimens based on VWF-containing plasma-derived FVIII, particularly in patients with poor prognostic factors and resistant to previous tolerization with VWF-poor FVIII.<sup>59-63</sup>

### How we choose

In primary ITI, we continue with the product used at the time of inhibitor occurrence (which, in Western Europe and United States, is mainly recombinant FVIII). This choice is accompanied by a high rate of successful ITI, as recently established by a randomized clinical trial.<sup>57</sup> The small body weights of children, who represent the majority of the patient population undergoing ITI, allow to mitigate the overall impact of costs, which would however be much smaller if plasma-derived FVIII were chosen. The situation is very different when rescue ITI is attempted in older boys of higher body weight, as well as in some selected adults. In this context, the favorable clinical results obtained using VWF-rich plasma-derived products<sup>58</sup> and their lower costs prompt us to prefer VWF-containing FVIII from human plasma. A more evidence-based choice of FVIII in ITI in patients with poor prognosis will hopefully stem from the results of 2 ongoing prospective studies.<sup>64</sup> In the Rescue Immune Tolerance Study (RESIST), naive patients with severe hemophilia A and inhibitor who never attempted ITI are randomly assigned to a large daily dose of plasma-derived VWF-rich or recombinant FVIII, whereas in the RESIST-experienced study patients who previously failed ITI with VWF-poor FVIII attempt a de novo tolerization with VWF-rich products.<sup>64</sup>

## The choices in developing countries

The unfortunate reality is that persons with hemophilia who live in low-income countries (at least two-thirds of those in the whole world) receive no treatment at all. Thus, in these countries, the most cogent problem is not choice but availability.<sup>65,66</sup> In addition, in many middle-income countries, the available treatment is often far from satisfying the choices mentioned for high-income countries.<sup>65,66</sup> These formidable problems are being tackled by an international consumer organization such as the World Federation of Hemophilia by means of various programs described in their Web site. Two huge countries, such as China and India, that together are inhabited by more than one-third of the whole world population, fail to offer at the moment to persons with hemophilia

the quality of care that both their rapidly expanding economies and high degree of technology should be able to afford. The limited degree of development of blood transfusion services makes difficult to envisage that plasma-derived coagulation factor production is the strategy of choice. Perhaps China and India should choose to exploit upfront recombinant DNA technology, as witnessed by the fact that the first human experiment of gene therapy in hemophilia B was attempted in China.<sup>67</sup> In addition, in many middle-income countries, the main problem is factor availability, because of the high cost of hemophilia therapy and priorities given in the frame of healthcare budgets to other more frequent communicable and noncommunicable diseases. When enough priority is given to hemophilia to initiate a modern program of care delivery, there are different options that should be chosen according to the local situations. In some instances, the most convenient approach is to purchase commercial products, perhaps implementing a national procurement scheme that allows to minimize costs. In other instances, particularly when blood transfusion services are sufficiently developed to produce enough plasma but facilities for its fractionation are absent or limited, a good option is that of contracting with industrial manufacturers the production from national plasma of coagulation factors for replacement therapy. Yet the total availability of factors may not be sufficient to implement on a large-scale programs of regular prophylaxis or treatment of patients with inhibitors with bypassing agents and ITI. Interesting attempts are being developed in a few developing countries to validate the usefulness of low-dose prophylaxis and ITI regimens in the frame of limited factor availability.<sup>65</sup>

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## Conclusive remarks

This article has no pretention of providing evidence-based recommendations, but rather opinion of experts from a large hemophilia center with nearly 50 years of clinical experience. In general, the current management of patients with hemophilia is seldom based on the results of randomized clinical trials comparing competing treatments. Nonrandomized prospective cohort studies are also relatively scanty. Our choices are not substantially different from the most widely adopted current practice for treatment, which in turn is often based on expert opinions and hence on low levels of evidence. Our rationale is that all the available FVIII products are able to achieve a satisfactory hemostasis when bleeding needs to be controlled or prevented. Moreover, the record of safety in terms of pathogen transmission has been impeccable since the late 1980s to early 1990s. However, one should not forget that both plasma-derived and recombinant coagulation factors are biologic products, so that zero risk is unrealistic and continuous surveillance should not be discontinued. For instance, contamination of the cell culture system used to produce recombinant proteins may potentially take place, as suggested by the finding of a calicivirus of the type vesivirus 2117 in the bioreactors used for the production of imiglucerase, the therapeutic copy of the natural enzyme deficient in Gaucher disease (press release in 2009 of the European Medicines Agency). By the same token, there may be emerging transmissible pathogens specially resistant to the robust and multiple inactivation methods currently used in the manufacture of plasma-derived and recombinant FVIII products. Hence, an important trigger of our present choices is the unresolved problem of FVIII inhibitor risk. We are fully cognizant that no optimal choice of product will completely abate this multifactorial event and that there is as yet no definite evidence that plasma-derived FVIII is less

immunogenic than recombinant FVIII. The completion of the randomized SIPPET study and of prospective cohort studies and registries, such as RODIN, PEDNET, GTH and EUHASS, will perhaps provide an unequivocal answer to this issue.

Our preferences and choices are also strongly governed by the cost of factor for replacement therapy. Patients with hemophilia have enjoyed so far, at least in high income countries, the benefits of a treatment that allowed them to reach the same life expectancy of their normal male peers. However, the current global economic crisis is triggering containment and rationing of healthcare costs, which are inevitably going to impinge on an expensive treatment, such as that of hemophilia. Hence, the community of stakeholders (doctors, patients, and FVIII manufacturers) should strive to optimize the costs of therapy without jeopardizing efficacy and safety. To this end, a bidding designed to lead to cost containment was first developed in New York more than 30 years ago.<sup>68</sup> More recently, a new approach meant to control the cost of recombinant FVIII was started in the United Kingdom in 2006 by the Department of Health (responsible for allotting the budget to hemophilia care centers), with the full involvement of stakeholders. Before the recent implementation of this procurement scheme, the price of recombinant FVIII in the United Kingdom was approximately twice that of plasma-derived products. The clinical rationale of the United Kingdom tender was that all the 4 brands of recombinant FVIII commercially available in the country are biosimilar and interchangeable in terms of efficacy and safety. The tendering process involved an electronic reverse e-auction in which each interested manufacturer could bid repeatedly over the course of an hour in a blinded competitive process designed to yield a reduction in price. The final score was based not only on price (the major but not the only criterion) but also on efficacy, supply security, factor distribution facilities, and ease of administration. Market shares were ultimately allocated according to a composite product score, thus retaining in the United Kingdom the existing plurality of products, mitigating the risk of supply interruption, maintaining some degree of prescription freedom, and minimizing the number of patients who had to switch FVIII brand. The net result of the program is that the price of recombinant FVIII did decrease stepwise by approximately 50%. Most importantly, as a result of the implementation of this national procurement scheme and the resulting savings, the Department of Health has not cut the budget that it does allocate to hemophilia, notwithstanding the current economic constraints. We are aware that it may not be realistic to implement the United Kingdom scheme unchanged in many other countries. Yet, this initiative stands as milestone of an example of the effective contribution of stakeholders to reduce the cost of a rare disease without adversely affecting the quality of care. Moreover, it highlights the need for policy makers, politicians, patients, and healthcare providers to join up to make hard choices within a socially responsible, cost-effective, and sustainable framework.

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## Authorship

Contribution: P.M.M. wrote the first draft of the manuscript; and M.E.M. and E.S. contributed to writing the manuscript and critically revised the final manuscript.

Conflict-of-interest disclosure: P.M.M. has served on the speaker bureau for Baxter, Bayer, Biotest, Grifols, Kedrion, Novo Nordisk, and Pfizer and has taken part in advisory boards summoned by these

pharmaceutical companies. M.E.M. has served on the speaker bureau for Baxter, Bayer, Grifols, Kedrion, Novo Nordisk, Pfizer, and CSL Behring and has taken part in advisory boards summoned by Bayer and CSL Behring. E.S. has served on the speaker bureau for Baxter, Bayer, Biotest, Grifols, Kedrion, Novo Nordisk, and CSL Behring, has taken part in advisory boards summoned by these companies, and has received unrestricted research grant for Novo Nordisk and Pfizer.

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