

Consensus opinion for the selection and use of therapeutic products for the treatment of haemophilia in Spain

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The period between isolation of HIV in the early 1980s and the development of effective viral inactivation procedures able to eradicate the virus from the blood supply was long and unfortunately many recipients of blood-derived products became infected; this translated into a devastating impact on their quality of life, quality of care as well as on their life expectancy. Some years later, hepatitis C virus infection was identified as another known blood-borne disease complicating the treatment of haemophilia. Nowadays, the potential threat of emerging new pathogens has stressed the need to provide effective but primarily safe products with regard to infectious agents, as well as to regularly update therapeutic guidelines for haemophilia. The aim of the present publication was to review some of the crucial aspects related to the choice of haemostatic concentrates for the treatment of haemophilia and other inherited bleeding disorders, to analyse the current situation in the United States, Canada and European Union countries and to report the most relevant aspects of the Spanish consensus opinion of haemophilia-treating

doctors for the use of therapeutic products for haemophilia recently issued. Essentially, it suggests that a gradual switch to recombinant concentrates may be a beneficial decision for patients with haemophilia and for the National Health Service. *Blood Coagul Fibrinolysis* 19:333–340 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Scientific evidence versus uncertainty

Encouragingly enough effective screening and inactivation procedures developed have virtually eliminated the transmission of currently known pathogens, such as human immunodeficiency virus (HIV), hepatitis B virus or hepatitis C virus (HCV) by infusion of plasma-derived or recombinant clotting factor concentrates. However, we now face the significant threat of the emergence of new, blood-borne infectious diseases, which may be transmitted by nonlipid-enveloped viruses or prions, which are resistant to currently used inactivation methods, although they may be significantly removed by the purification steps. For the safety of the blood supply and blood-derived products, it must be taken into account that new pathogens might continue to emerge and it should be emphasized that the blood supply might be still vulnerable to contamination by currently unknown infectious agents [1–5].

Regarding prion disease, in the UK, four cases of variant Creutzfeldt–Jakob Disease (vCJD), infection associated

with red blood transfusion have been recently reported [6–10]. To date there have been no vCJD cases associated with infusion of plasma products, including those from batches derived from donors who later developed vCJD [11]. Thus, there is no evidence of prion transmission by haemostatic factors, and this risk is theoretically minimized due to the prion reduction by the fractionation and purification procedures [12]. The possibility of detecting prions biochemically in the blood of infected but not clinically sick animals has been recently published; this offers great prospects for early noninvasive diagnosis of transmissible spongiform encephalopathies (TSEs) [13]. However, it is also worth noting that there is no routinely available test to detect vCJD protein in plasma or plasma-derived products at present. Moreover, it has been proven that prions are also resistant to inactivation procedures.

Preliminary data on the risk of transmission of vCJD by plasma-derived products reported by the Food and Drug Administration (FDA) indicate that this risk is probably very low but nonetheless not quite as low as zero [14,15].

Actually isolated cases have been reported in several countries (one in 2005 in Spain) where factor concentrates manufactured with plasma from donors who later died of vCJD have been administered to a range of haemophilic patients. Even if, as indicated above, not a single transmission of the prion was identified [11], this has led to a serious concern among haemophilic patients who claim it as a proof that transmission of infectious agents is a continuous threat for individuals with inherited bleeding disorders who are being or have been treated with plasma-derived products.

A very elegant and clear review on safety issues, risk of pathogen transmission and inactivation efforts as well as lessons to be learnt from the past has been recently published [16].

The precautionary principle

The precautionary attitude is based on the fact that by the time definite evidence of an emerging infectious agent becomes available, it is often too late to prevent transmission to the most susceptible patient subsets [5,15,17]. Thus, proactive decision-making processes regarding the safety of our blood supply cannot rely solely on an evidence-based approach. Rather, we must learn the lessons from the past and, using our current knowledge of disease-causing agents, make an accurate estimate of the potential risks in order to better design effective healthcare policies. The precautionary principle provides important guidelines for public health policy decision-making that are of particular value in times of crisis, such as the emergence of a new pathogen: be open and honest to the public about scientific uncertainty and consider immediate, adaptable policy decisions.

In retrospect, it is clear that many chances to prevent further HIV infection were lost during the early years of the AIDS crisis [15]. Only therapies with the lowest level of risk should be considered for the care of patients with haemophilia [18].

Another issue to be taken into account is that the potential reduction in risk for emerging pathogens may make plasma products much more expensive and induce a potential reduction in the availability of blood and plasma-derived products.

Plasma-derived versus recombinant products in haemophilia

Currently available treatments for haemophilia have varying degrees of exposure and vulnerability to contamination by blood-borne pathogens, which are correlated with the extent to which they include components of human or animal-derived plasma or albumin in the final product or during the manufacturing process [19]. Wherever possible, the degree of vulnerability should be minimized, and therapies having the lowest degrees of exposure to

human-derived or animal-derived proteins should be provided [18].

Manufacturers of plasma-derived clotting factor concentrates have addressed the issue of emerging infectious agents by developing recombinant products that limit the need for human plasma over the whole production process. Such recombinant products have improved the safety profile of the former plasma-derived products by ensuring that all products used throughout the cell culturing procedure, purification steps as well as stabilization and storage buffers are completely devoid of human plasma [19,20]. All these measures minimize the risk of human viruses transmission through these therapies to virtually negligible.

During the past 15 years the development of recombinant clotting factors was fuelled by safety concerns within the haemophilia community. The need to increase the capacity of supply of clotting factor therapies has made the use of recombinant clotting factors become widely used in the developed world and these products have proved to be highly effective and safe [1,19,21–24].

Type of factor VIII product and inhibitor development

Some studies have suggested that plasma-derived factor VIII (pdFVIII) products induce fewer inhibitors than recombinant factor VIII products. One of these studies using multivariate analysis compared two cohorts of previously untreated patients (PUPs) with severe haemophilia A, 62 patients treated with the same brand of high-purity pdFVIII containing von Willebrand factor (VWF) and 86 patients treated with full-length recombinant FVIII (rFVIII) [24]. The risk of inhibitor development was observed to be higher in patients treated with rFVIII than in patients treated with pdFVIII, regardless of other risk factors. Another study investigated the inhibitor development in 348 children with severe haemophilia A, first exposed to FVIII as neonates [25]. Initial treatment with rFVIII and the presence of a major molecular defect were the most important variables affecting inhibitor development observed.

In contrast, the recently published multicentre retrospective cohort CANAL (Concerted Action on Neutralizing Antibodies in severe Haemophilia A) study, including 316 patients with severe haemophilia A, showed that the risk of inhibitor development was not clearly lower in plasma-derived compared with rFVIII products [26]. Among high-titre inhibitors, the possible reduction in risk was even less pronounced. Plasma-derived products with considerable quantities of VWF carried the same risk for inhibitor development as rFVIII products. Switching between factor VIII products did not increase the risk for inhibitors. Moreover, DiMichele [27] analysing data from several large registries of haemophilia A plus inhibitors has recently concluded that there are no published

data to support the superiority of any single product type for immune tolerance induction (ITI) or a change in practice. However, the European Medicines Agency (EMA) [28] on 31 July 2007 has completed a review of data on rFVIII products on this issue, advising to include a warning in the summary of product characteristics (SPC) for each rFVIII as follows: 'cases of recurrence of inhibitors (low-titre) have been observed after switching from one rFVIII product to another in previously treated patients with more than 100 exposure days who have a history of inhibitor development'.

In summary, the relationship between the type of product and development of inhibitors continues to be controversial and awaits the results of future prospective controlled trials.

Factor IX concentrates: recovery and inhibitor development

A Canadian study showed that the recovery for recombinant FIX (rFIX) for patients with haemophilia B was significantly lower than that for plasma-derived FIX (pdFIX). For both rFIX and pdFIX concentrates, the recovery was lower in patients of 15 years of age or less compared to those more than 15 years of age [29]. Similar data and conclusions were obtained on 66 patients with paired recovery data from rFIX and pdFIX. These data were similar to those obtained in formal clinical trials. In addition, they showed an incidence of inhibitor development similar to that reported for pdFIX. No other serious adverse events, including thrombotic episodes, were reported.

The safety and efficacy of rFIX were evaluated in a 20-centre international trial which was conducted upon previously treated patients with severe or moderate haemophilia B [30]. Mean incremental rFIX recovery was 0.75 IU/dl per IU/kg, 30% lower than expected for pdFIX, although the mean half-life was similar. Again somewhat lower recoveries were seen in patients younger than 15 years of age and in those with no detectable factor IX antigen. A total of 7362 infusions of rFIX were administered. All 1796 haemorrhages were controlled, 80.9% of which required only one rFIX infusion. Effective haemostasis was also achieved in prophylactic and surgical settings. rFIX was not associated with serious adverse events, thrombogenicity or virus transmission.

The conclusion obtained from these and other studies was that rFIX is safe and effective for the treatment of haemophilia B. Despite a lower recovery compared with pdFIX, rFIX controlled haemorrhage in a wide variety of settings and may provide a safety advantage in terms of risk from blood-borne pathogens.

Type of product and costs

Recombinant FVIII and FIX concentrates are today more expensive than plasma-derived products (around 1.69-fold

in Spain). This is not an exception because the improvement of many medical therapies has carried out an important cost increase. In haemophilia, the cost–efficiency benefit of recombinant concentrates compared to plasma-derived products is difficult to evaluate in terms of risk from blood-borne pathogens

The situation in the United States, Canada and European Union

The majority of patients with haemophilia have been switched from plasma-derived to recombinant therapies since the licensing of the first rFVIII concentrate in 1992 [31–37]. Since April 2005, all haemophiliacs in the UK have been treated exclusively with recombinant products. The situation in this country was forced by the comparatively high prevalence of vCJD in the general population. Most Canadian haemophilia patients were started on rFVIII concentrate in 1994. This decision was made by the Canadian Blood Agency following the advice of the Association of Haemophilia Clinic Directors of Canada who considered rFVIII to be the safest replacement therapy available at that moment. Despite improvements in infectious safety achieved with recombinant concentrates, there are some 'safety gaps' that still remain unfilled because of the addition of human or animal proteins during product processing and final formulation of these products. The UK Department of Health began a progressive replacement of plasma-derived factor therapies and encouraged the use of recombinant therapies not containing any human or animal protein additives as first line choice for adults with haemophilia A and B; children under the age of 16 had previously been switched to recombinant products following a 1998 provision [33–35]. These measures were taken as a precaution against potential transmission of vCJD through blood products. These guidelines point out the proactive measures which some organizations are taking to protect their patients from blood-borne infectious agents.

In the case of Canada, government health agencies made the proactive decision in 1994 to switch patients to recombinant therapies before further evidence of an imminent threat to the blood supply is reported and despite concerns of increased costs and the potential for increased inhibitor formation.

The situation in Spain: the position of the Scientific Committee of the Royal Foundation Victoria Eugenia

Background of haemophilia in Spain

There is a currently ongoing epidemiological study and registry for haemophilia A and B (Spanish Society on Thrombosis and Haemostasis, SETH) whose results are not available yet. Although more precise results from this study are awaited, some data on the current situation regarding an estimation of the actual number of patients

Table 1 Prevalence of haemophilia A and B (patients/men)

Global ^a	1/7500
The United States ^a	1/7518
Canada ^a	1/6250
United Kingdom ^a	1/5140
The United States + Canada + Japan + Western Europe ^a	1/6211 ^b , 1/8475 ^c , 1/12 195 ^d
Spain (estimate)	1/6709
Population (men) in Spain (2007)	22 340 000
Estimated number of	
Haemophilia A and B patients	3330
Haemophilia A (85.7%)	2853
Haemophilia B (14.3%)	477

^a Estimate according to Stonebraker *et al.* [38]. ^b 90 percentiles. ^c 50 percentiles. ^d 10 percentiles.

and clotting factor concentrate use in Spain compared to other countries are shown in Tables 1 and 2 and Figs 1 and 2.

An interesting analysis and comparison of FVIII usage among various countries in 2004 [38,39] showed that the probability-weighted average for an unrestricted FVIII demand model (assuming an unlimited supply situation) was 6.9 units per patient. FVIII consumption rates in Luxembourg (7.7 IU/capita) were the highest of the 30 countries compared. Such rates were 6.8, 5.2 and 4.8 IU/capita in Sweden, Germany and the Netherlands, respectively. That study concluded that 2004 FVIII usage in Spain was below 3 IU/capita in 2004. By using several economic indexes, it was concluded that FVIII consumption in Spain was higher than expected, which is, to some extent, an indication of a higher priority given to haemophilia healthcare in our country. It should be emphasized that according to the data provided by the Spanish Ministry of Health (Agencia Española de Medicamentos y Productos Sanitarios), the 2004 FVIII usage was 4.27 IU/capita in 2004 (Fig. 1).

More recently, the 2006 WFH Global Survey (69 countries) has reported that usage related to the gross national product [GNP or gross national income (GNI)] per capita, in countries above US\$10 000 per capita income, is about 4.46 IU/capita for FVIII and 0.78 IU/capita for FIX. These data suggest that in Spain [GNP per capita: \$27 570 (World Bank)] it is a little lower than expected (Fig. 1). Furthermore, the proportion of rFVIII/pdFVIII compared with other EU countries was low in 2003, with both Spain and Finland being the lowest

Table 2 Haemophilia A severity distribution (%) estimate

	Haemophilia A severity ^a (%)		
	Severe (%)	Moderate (%)	Mild (%)
10th percentile	34	15	51
50th percentile	43	26	31
90th percentile	63	18.5	15.5

^a Estimate according to Stonebraker *et al.* [38].

reported users of rFVIII (Fig. 2). This proportion showed a slowly progressive increase in these figures up to 2006.

No reliable data revealing the incidence of inhibitors in haemophilia in Spain are available at present, but it does not appear to be different to that previously described. A 2001 study from the Spanish Registry on ITI showed that in 26 out of 38 cases (68%) the inhibitor was eradicated [40].

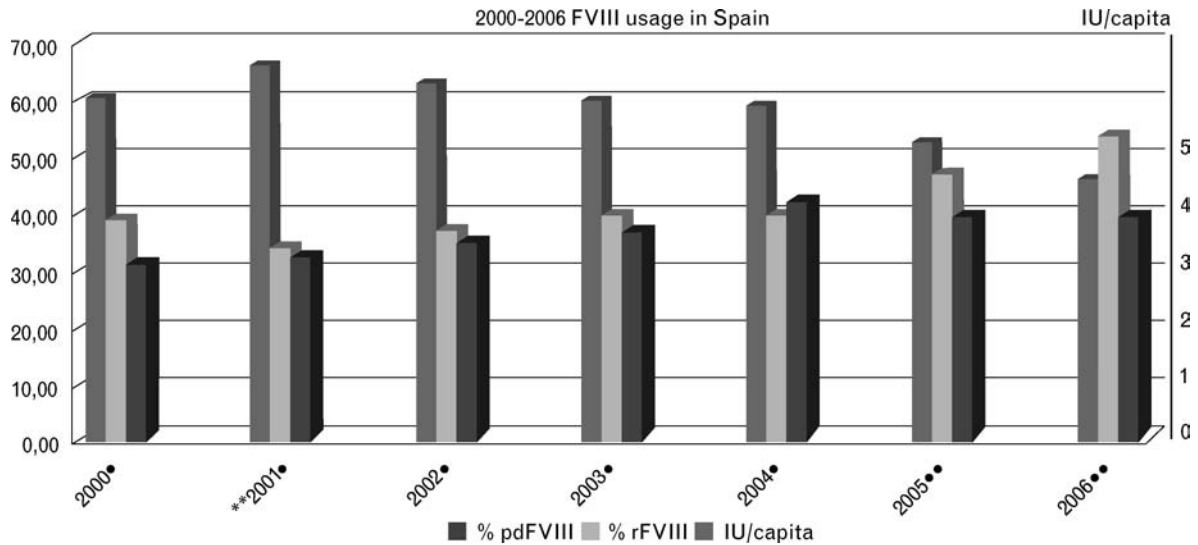
As far as HIV and HCV infection status is concerned, there are few published data yet (from some regional haemophilia-treating centres), awaiting again the results from the registry mentioned above become available. In 1992, the HIV seroprevalence in a cohort of 435 haemophiliacs from a large Spanish haemophilia-treating centre was 59%; all such cases resulted from the administration of human plasma-derived replacement therapy before inactivation methods were introduced and requested [41]. A 2004 study from the same centre showed that among 383 cohort members, overall AIDS incidence was 9.7 per 100 person-years, peaking in 1992–1993 and dropping by 87% in 1998–2001 compared with rates reported before 1988 [42]. Overall mortality was 7.5 per 100 person-years; rates reported were highest from 1992 to 1997 and fell by 66% in 1998–2001 compared with those from before 1988. Important reductions in HIV disease progression to AIDS and death have been observed from 1998 to 2001, and this can be attributed to highly active antiretroviral therapy.

The HCV seroprevalence among haemophilia patients was 71% (60–80%, depending on the test used) in 1995 [43]; these data are in agreement with those reported in other countries. HCV infection has accounted for an increasing proportion of deaths in recent years, mainly associated with chronic liver disease, which is a growing health concern among haemophilic patients overall.

A 2007 study of the Spanish Ministry of Health cumulative data since 1981 shows that a total of 809 patients, considered as recipients of blood derivatives (those receiving blood transfusions are considered in another group), had AIDS, most of them being haemophiliacs [44]. Furthermore, recent data related to patients with inherited bleeding disorders (mainly with haemophilia A and B) from an HIV and HCV Registry of the Spanish Ministry of Health, built up with an indemnification purpose, show that 882 out of 2222 patients with HCV and 1002 out of 1539 with HIV have already died.

In a prospective Dutch cohort study on the mortality and cause of death (1992–2001), in 977 patients with haemophilia A and B, data show that HIV and hepatitis C still largely influence mortality and the effects of hepatitis C will be present for many years to come [45].

Fig. 1



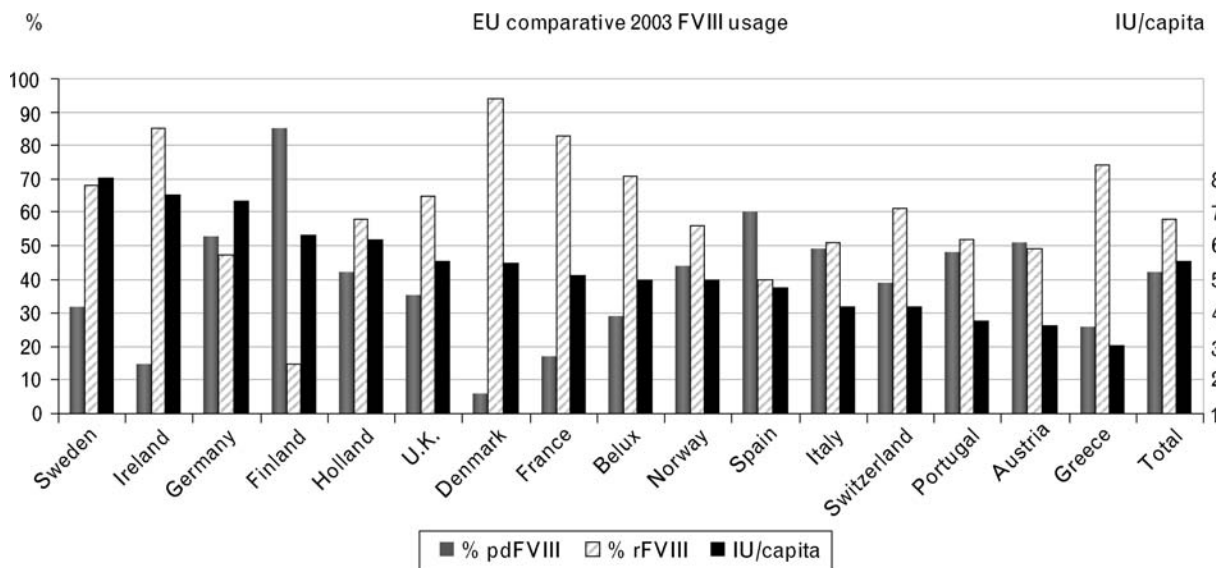
Factor VIII (FVIII) use in Spain between 2000 and 2006 in IU/capita and percentage of plasma-derived factor VIII and of recombinant factor VIII are shown. According to data from • Agencia Española del Medicamento y Productos Sanitarios (Spanish Ministry of Health), •• Pharmaceutical industry estimates. ** FVIII supply shortage.

The fact must be emphasized that in the past 20 years, as inactivation procedures for plasma-derived products have been available, there has not been a single new case of HIV or HCV.

Role and position of the Scientific Committee of the Royal Foundation Victoria Eugenia

Between 1994 and 1998 this committee issued several guidelines to provide haemophilia-treating physicians

Fig. 2



Comparison factor VIII (FVIII) use reported in European Union countries in 2003 as total FVIII/capita; the percentages of plasma-derived FVIII (pdFVIII) and recombinant FVIII (rFVIII) are presented. Finland and Spain had the lowest rFVIII/pdFVIII ratios. According to pharmaceutical industry estimates.

throughout the country with clear consensus guidelines for the appropriate choice of factor replacement products [46–49]. However, still at present a significant heterogeneity in the type of factor concentrates used (recombinant versus plasma derived) can be found in Spain. The main factors involved in this heterogeneity are the uncertainty mentioned above: the absence of homogeneous criteria for the choice of replacement products and also the shift of Spanish healthcare management to an autonomic scenario in which different therapeutic resources are set by the different autonomic administrations.

Aware of this heterogeneity and of the importance of currently known and potentially emerging new pathogens, the Scientific Committee of the Royal Foundation Victoria Eugenia (SC-RVEF), comprising representatives of the largest haemophilia-treating centres in Spain, elaborates and presents in this position paper some guidance for the updating of the guidelines mentioned above [46–49] aimed to advise the health authorities and physicians directly in charge of haemophilia care about the basic and most relevant issues in this respect. Essentially this guidance is based on that previously published by the UK Haemophilia Centre Directors Organisation [34], updated in some aspects and adapted to the Spanish-specific clinical, epidemiological, political and economic characteristics.

In summary, these guidelines include the need to inform the patients and to obtain their informed consent with regard to the choice of factor concentrate made, attending physician, therapeutic regimen implemented, point of care and ancillary as well as comprehensive care services. In addition, it stresses the importance of avoiding exposure to concentrates (especially plasma-derived) whenever possible and replacing them by antifibrinolytic drugs and desmopressin, the latter in responding cases as previously proven by the administration of a trial dose.

In order to select the optimal replacement therapy, it is crucial to discuss all therapeutic alternatives available as well as the potential benefits and complications of all of them including inhibitor development, potentially emerging pathogens, patient convenience, consistency and reliability of supply, relative cost–benefit ratios and patient preference.

Selecting the appropriate product for each patient can be a tough task. For this reason, clinicians should consider all the following criteria: safety and efficacy; potential for inhibitor development; convenience; consistency of supply; reputation of the manufacturing company; and cost–benefit ratio. The patient preference should be taken into account also, as long as some patients are reluctant to switch to a recombinant product.

Safety and efficacy are, just like for most therapies, the most important criteria for product choice; this choice is in the case of haemophilia substantially complicated by fear of inhibitor development. Convenience is also of great importance for patients, particularly for those on prophylaxis, because they may receive infusions up to three times a week. As shown by the shortage in factor concentrate supply due to manufacturing and documentation problems, which occurred worldwide in 2001, availability and consistency of this supply are also important. As the efficacy of the different therapies available is generally equivalent and many safety issues remain unproved, cost–benefit ratios still play a role in a patient's choice of therapy.

Registered products should be preferred to those used on a compassionate basis, whereas nonregistered products should be included in clinical trials. Patients switching treatment should be enrolled in pharmacovigilance follow-up protocols for inhibitor development and pathogen transmission. Treating patients with a single concentrate is highly recommendable if usefulness of these vigilance protocols is to be of real use.

Plasma-derived versus recombinant products

Recombinant concentrates of FVIII and FIX should be regarded as the treatment of choice. Changes from plasma to recombinant concentrates should be gradually carried out at each centre (e.g. a period of 3 years might be considered standard).

In patients with haemophilia who develop with high-response inhibitors, recombinant factor VIIa should be preferred to activated prothrombin complex concentrates overall for the treatment of bleeding episodes, unless lack of clinical efficacy of such products is observed in particular cases.

ITI should be started in patients with inhibitors as early as possible following diagnosis. Treating physicians are highly encouraged to enrol such patients in the international ITI study whenever possible. Should enrolment not be possible, the concentrate responsible for inhibitor development will be the one prescribed for ITI. In cases of initial unresponsiveness to ITI, a prolonged treatment using a VWF-rich FVIII concentrate should be attempted.

Understandably enough, haemophiliacs for whom a particular therapeutic approach and product have proved successful are usually unwilling to change treatment. Even though alternative treatments might have proved to be safer, patients are still often reluctant to switch to different products. Concerns may include a perceived potential to increase the risk for inhibitor development, cost or reduced clinical efficacy. Additionally, many patients prefer to delay exposure to newly approved

therapies until wider experience on safety and efficacy issues has been gained with the treatment of larger numbers of patients.

Continued surveillance on blood supply and its derivatives nation and worldwide is critical as long as infectious disease is a potential threat which cannot be excluded on the basis of experience accumulated in the past in this field. The need for ongoing vigilance in order to maintain safety and purity of the blood supply also remains unchanged. Continuous surveillance for inhibitor development in patients with haemophilia is also mandatory. Given that many haemophiliacs are still treated with plasma-derived factor concentrates any problem arising in relation to the blood supply (whether emerging pathogen-related or of any other type) will likely target the haemophilia community first.

The SC-RVEF considers it to be a matter of major importance to emphasize that plasma products are safe at present, as demonstrated by widespread licensing of such products by different health authorities. Moreover, we have to learn from the past that due to occasional shortage of recombinant concentrates there may exist a need (often temporary) to reshift patients from recombinant back to plasma-derived products. In addition, it is unwise to raise unnecessary fear in patients who can only receive plasma-derived products, such as those for whom recombinant products are not available owing to the type of disorder (this is the case of von Willebrand disease) or due to economic reasons.

In Spain, specific actions in this matter have been focused on the proposal made by our committee to the Ministry of Health for the development of specific regulations for the progressive increase of use of recombinant product treatment in a short period of time, the setting up of a bank of samples for pharmacovigilance purposes and the development of a patient's information programme on the potential risks of every treatment. In this setting, a formal informed consent by the patient must be required. Switching from plasma-derived to recombinant factor concentrates, as recommended in these guidelines, is consistent with Farrugia's [50] view, who states that 'the future use of plasma derivatives, at least in the developed world, will probably follow a different path to the one seen so far, and a sound understanding for the pathophysiology of the medical indications for plasma therapies should contribute to a continuing role for these medicines in modern therapeutics'. Recently, the local health authorities from the Autonomous Communities of Galicia, Valencia and the Basque Country, in agreement with these guidelines, have approved the switching to the recombinant products.

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References

- 1 Stanley S. The need for continuing vigilance: addressing the threat for transmission of blood-borne infectious disease. *Semin Hematol* 2006; **43** (Suppl 3):S17–S22.
- 2 Pipe S. Consideration in hemophilia therapy selection. *Semin Hematol* 2006; **43** (Suppl 3):S1–S3.
- 3 Busch MP, Kleinman SH, Nemo GJ. Current and emerging infectious risks of blood transfusions. *JAMA* 2003; **289**:959–962.
- 4 Dodd RY. Emerging infections, transfusion safety, and epidemiology. *N Engl J Med* 2003; **349**:1205–1206.
- 5 Farrugia A. Safety and supply of haemophilia products: worldwide perspectives. *Haemophilia* 2004; **10**:327–333.
- 6 Ironside JW. Variant Creutzfeldt–Jakob disease: risk of transmission by blood transfusion and blood therapies. *Haemophilia* 2006; **12** (Suppl 1): 8–15.
- 7 Ironside JW, Head MW. Variant Creutzfeldt–Jakob disease: risk of transmission by blood and blood products. *Haemophilia* 2004; **10**:64–69.
- 8 Llewelyn CA, Hewitt PE, Knight RS, Amar K, Cousens S, Mackenzie J. Possible transmission of variant Creutzfeldt–Jakob disease by blood transfusion. *Lancet* 2004; **363**:417–421.
- 9 Peden AH, Head MW, Ritchie DL, Bell JE, Ironside JW. Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. *Lancet* 2004; **364**:527–529.
- 10 Fourth case of transfusion-associated variant-CJD infection. <http://www.hpa.org.uk/hpr/archives/2007/news2007/news0307.htm>.
- 11 Hewitt PE, Llewelyn CA, Mackenzie J, Will RG. Creutzfeldt–Jakob disease and blood transfusion: results of the UK Transfusion Medicine epidemiological review study. *Vox Sang* 2006; **91**:221–230.
- 12 Foster PR, Welch AG, McLean C, Griffin BD, Hardy JC, Bartley A, *et al.* Studies on the removal of abnormal prion protein by processes used in the manufacture of human plasma products. *Vox Sang* 2000; **78**:86–95.
- 13 Saa P, Castilla J, Soto C. Presymptomatic detection of prions in blood. *Science* 2006; **313**:92–94.
- 14 Centers for Disease Control and Prevention. CDC's Universal Data Collection project: blood safety. 2006; Published online at <http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4271b1-index.htm>.
- 15 Evatt B. Infectious disease in the blood supply and the public health response. *Semin Hematol* 2006; **43** (Suppl 3):S4–S9.
- 16 Pipe S. The physician's role in selecting a factor replacement therapy. *Haemophilia* 2006; **12** (Suppl 1):21–25.
- 17 Stoto M. The precautionary principle and emerging biologic risks: lessons from human immunodeficiency virus in blood products. *Semin Hematol* 2006; **43** (Suppl 3):S10–S12.
- 18 Dolan G. Clinical implications of emerging pathogens in haemophilia: the variant Creutzfeldt–Jakob disease experience. *Haemophilia* 2006; **12** (Suppl 1):16–20.
- 19 Ludlam CA, Powderly WG, Bozzette S, Diamond M, Koerper MA, Kulkarni R, *et al.* Clinical perspectives of emerging pathogens in bleeding disorders. *Lancet* 2006; **367**:252–261.
- 20 Farrugia A. Evolving perspectives in product safety for haemophilia. *Haemophilia* 2002; **8**:236–243.
- 21 Aledort LM. Making a therapeutic choice: human versus recombinant fractions – can we do it? *Haemophilia* 2001; **7** (Suppl 1):1–3.
- 22 Mannucci PM. The choice of plasma-derived clotting factor concentrates. *Baillieres Clin Haematol* 1996; **9**:273–290.
- 23 Mantovani LG, Monzini MS, Mannucci PM, Scalone L, Villa M, Gringeri A. Differences between patients, physicians and pharmacists preferences for treatment products in haemophilia: a discrete choice experiment. *Haemophilia* 2005; **11**:589–597.
- 24 Goudemand J, Rothschild C, Demiguel V, Vinciguerratt C, Lambert T, Chambost H, *et al.* Influence of the type of factor VIII concentrate on the incidence of factor VIII inhibitors in previously untreated patients with severe hemophilia A. *Blood* 2006; **107**:46–51.
- 25 Chalmers EA, Brown SA, Keeling D, Liesner R, Richards M, Stirling D, *et al.* Early factor VIII exposure and subsequent inhibitor development in children with severe haemophilia A. *Haemophilia* 2007; **13**:149–155.
- 26 Gouw SC, van der Bom JG, van den Berg HM. Treatment-related risk factors of inhibitor development in previously untreated patients with hemophilia A: the CANAL cohort study. *Blood* 2007; **109**:4693–4697.

- 27 DiMichele D. Immune tolerance therapy for factor VIII inhibitors: moving from empiricism to an evidence-based approach. *J Thromb Haemost* 2007; **5 (Suppl 1)**:143–150.
- 28 Public statement. Review of recombinant Factor VIII products and inhibitor development. EMEA/310225/2007Corr. <http://www.emea.europa.eu/pdfs/human/press/pus/31022507en.pdf>.
- 29 Poon M-C, Lillicrap D, Hensman C, Card R, Scully M-F. Recombinant factor IX recovery and inhibitor safety: a Canadian postlicensure surveillance study. *Thromb Haemost* 2002; **87**:431–435.
- 30 Roth DA, Kessler CM, Pasi KJ, Rup B, Courter SG, Tubridy KL, Recombinant Factor IX Study Group. Human recombinant factor IX: safety and efficacy studies in hemophilia B patients previously treated with plasma-derived factor IX concentrates. *Blood* 2001; **98**:3600–3606.
- 31 Giles AR, Rivard GE, Teitel J, Walker I. Surveillance for factor VIII inhibitor development in the Canadian hemophilia A population following the widespread introduction of recombinant factor VIII replacement therapy. *Transfus Sci* 1998; **19**:139–148.
- 32 Association of Hemophilia Clinic Directors of Canada. Clinical practice guidelines: hemophilia and von Willebrand's disease: 2. Management (Edition 2, Update 2). 7 July 1999. Published online at <http://www.ahcdc.ca/vWDMManagement.html>. [Accessed April 2005].
- 33 United Kingdom Haemophilia Centre Doctors' Organisation on behalf of The Department of Health Forward Planning and Monitoring Group. Rollout of recombinant products for all adult haemophilia patients in England: Report of 2003/2004. 2004. Published online at <http://www.dh.gov.uk/assetRoot/04/09/00/63/04090063.pdf>.
- 34 United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO). Guidelines on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. *Haemophilia* 2003; **9**:1–23.
- 35 Giangrande P, Haemophilia B. Christmas disease. *Expert Opin Pharmacother* 2005; **6**:1517–1524.
- 36 Chambost H, Ljung R. Changing pattern of care of boys with haemophilia in western European centres. *Haemophilia* 2005; **11**:92–99.
- 37 Mauser-Bunschoten EP, Roosendaal G, van den Berg HM. Product choice and haemophilia treatment in the Netherlands. *Haemophilia* 2001; **1**:96–98.
- 38 Stonebraker JS, Amand RE, Bauman MV, Nagle AJ, Larson PJ. Modelling haemophilia epidemiology and treatment modalities to estimate the unconstrained factor VIII demand. *Haemophilia* 2004; **10**:18–26.
- 39 Stonebraker JS, Amand RE, Nagle AJ. A country-by-country comparison of FVIII concentrate consumption and economic capacity for the global haemophilia community. *Haemophilia* 2003; **9**:245–250.
- 40 Haya S, López MF, Aznar JA, Batlle J, Spanish Immune Tolerance Group. Immune tolerance treatment in haemophilia patients with inhibitors: the Spanish Registry. *Haemophilia* 2001; **7**:154–159.
- 41 Martínez MM, Ortega F, Pinilla J. AIDS and hemophilia: experience in the La Paz Hemophilia Center. *Haemostasis* 1992; **22**:281–292.
- 42 Quintana M, del Amo J, Barrasa A, Pérez-Hoyos S, Ferreros I, Hernández F, et al. Progression of HIV infection and mortality by hepatitis C infection in patients with haemophilia over 20 years. *Haemophilia* 2003; **9**:605–612.
- 43 Aguilar C, Lucia JF. Hepatitis C and hemophilia. *Med Clin (Barc)* 1995; **105**:139–141.
- 44 Ministry of Health. HIV/AIDS epidemiological surveillance in Spain. National register of AIDS cases. Update to June 2007. http://www.isciii.es/htdocs/centros/epidemiologia/epi_sida.jsp.
- 45 Plug I, Van Der Bom JG, Peters M, Mauser-Bunschoten EP, De Goede-Bolder A, Heijnen L, et al. Mortality and causes of death in patients with hemophilia, 1999–2001: a prospective cohort study. *J Thromb Haemost* 2006; **4**:510–516.
- 46 Arrieta R, Aznar JA, Magallón M, Padilla A, Serrano MA, Tusell J, et al. Therapy with plasma derived concentrates in haemophilia A. *Sangre* 1994; **39**:157–162.
- 47 Arrieta R, Aznar JA, Magallón M, Padilla A, Serrano MA, Tusell et al. Guidelines on the choice of plasma derived prothrombin and factor IX concentrates in haemophilia B. *Sangre* 1994; **39**:315–322.
- 48 Alonso C, Arrieta R, Aznar JA, Gómez JL, Magallón M, Medarde A, et al. Guidelines on the choice of factor VIII and IX concentrates. *Sangre* 1997; **42**:437–444.
- 49 Alonso C, Aznar JA, Batlle J, Magallón M, Moreno M, Serrano MA, et al. Guidelines on the choice of concentrates in haemophilia therapy. *Sangre* 1998; **43**:451–452.
- 50 Farrugia A, Robert P. Plasma protein therapies: current and future perspectives. *Best Pract Res Clin Haematol* 2006; **19**:243–258.