Plasma-derived versus recombinant Factor VIII concentrates for the treatment of haemophilia A: recombinant is better

Massimo Franchini

[1]*Servizio di Immunoematologia e Trasfusione, Azienda Ospedaliero-Universitaria di Parma, Italy*

The introduction of coagulation factor replacement therapy over the past half century has greatly contributed to the improvement in care of people with haemophilia A. After the epidemic resulting from the transmission of blood-borne viruses (hepatitis B virus, hepatitis C virus and human immunodeficiency virus) in the late 1970s and early 1980s caused by the use of non–virally inactivated clotting factor concentrates derived from plasma, the need for safer haemophilia treatments became crucial to the haemophilia community[1,2]. Thus, the development of recombinant factor VIII products, first introduced in the late 1980s[3], has revolutionised the care of people with haemophilia A. The unlimited production of recombinant FVIII products has theoretically provided an opportunity to overcome the potentially limited availability of plasma-derived FVIII concentrates, and the perceived increased safety of the replacement therapy associated with the introduction of recombinant FVIII products dramatically improved the quality of life of patients with haemophilia A and their families and enabled regular infusion of factor concentrate replacement therapy to prevent bleeding and resultant joint damage (i.e., primary prophylaxis), home treatment, and, ultimately, a near-normal lifestyle and life expectancy[4-7].

On the other hand, the improvement of viral inactivation methods and methods used to screen viruses in blood donation facilities and plasma pools also greatly improved the safety of plasma-derived products. In the past 14 years, there have been no confirmed cases of blood-borne transmission of hepatitis viruses or human immunodeficiency virus associated with the use of plasma-derived FVIII products[8]. However, because of the uncertainty regarding as-yet-unknown pathogens and the potential impact of prion disease in the haemophilia population reliant on blood derivatives[9], there was a strong push in Western countries to treat children with haemophilia with only recombinant FVIII products. Furthermore, the process of manufacturing recombinant FVIII products has further evolved during the last few years to minimise the risk of pathogen transmission with the improvement of protein purification techniques and viral inactivation steps and the avoidance of human or animal proteins at any stage of their manufacture[10].

Because of the widespread prophylactic use of recombinant FVIII products, the most serious and challenging complication of replacement therapy has become the development of inhibitors against coagulation FVIII. Inhibitory alloantibodies develop in approximately 20% to 30% of patients with severe haemophilia A and render the FVIII treatment ineffective, precluding the access of haemophiliacs to a safe and effective standard of care and predisposing them to an unacceptably high risk of morbidity and mortality[11].

The research in this area has mainly focused on identifying risk factors that contribute to inhibitor development by studying previously untreated patients (PUPs)[12]. These studies have revealed the importance of genetic risk factors (e.g., ethnicity, *F8* gene mutations, major histocompatibility complex genotype, polymorphisms of immune-response genes [interleukin-10, tumour necrosis factor-a, cytotoxic T-lymphocyte antigen-4]) and environmental risk factors (e.g., number of days of exposure to FVIII, age at first exposure to FVIII concentrate, type of FVIII concentrate administered and modality of treatment) in the development of inhibitors[13-22]. This research confirms that inhibitor formation in haemophilia is a complex multifactorial process.

The role of FVIII replacement therapy in the development of inhibitors has been explored in a number of observational multicentre PUP studies

Blood Transfus 2010;8:292-6 DOI 10.2450/2010.0067-10

during the last two decades. Some investigators postulated that patients receiving plasma-derived FVIII concentrates might have a lower inhibitor incidence because of the protective effect of von Willebrand factor (vWF), which would mask the epitope sites of inhibitors on the FVIII molecule or would prevent FVIII endocytosis by dendritic cells[23]. Several criticisms can be raised against the *in vitro* studies providing evidence supporting the former mechanism because of the difficulty of reproducing the physiological *in vivo* conditions (in which circulating vWF levels are much higher than FVIII levels and vWF immediately binds exogenous FVIII molecules) in a laboratory[24], and contradictory studies have been recently published on the latter mechanism[25,26]. Dasgupta and colleagues observed that pre-incubation of vWF with FVIII reduced the uptake and presentation of FVIII by dendritic cells compared with pre-incubation with FVIII alone[25]. Pfistershammer and colleagues demonstrated that neither an immunogenic response from allogeneic or autologous T cells nor the modulation of the release of cytokines by human dendritic cells is stimulated by FVIII, thrombin-activated FVIII, vWF, or a complex of FVIII and vWF[26]. Clinical studies have also yielded conflicting results[23]. Unfortunately, no randomised trials have been conducted so far in this setting, and only a few comparative studies have been published, with no significant results.

In a prospective, comparative study of PUPs with moderate to severe haemophilia A, Kreuz and colleagues detected inhibitors in 18 of 51 (35%) patients treated with plasma-derived FVIII and 4 of 21 (19%) patients treated with recombinant FVIII[27]. In the subgroup of patients with severe haemophilia, inhibitors developed in 46% of the patients treated with plasma-derived FVIII and in 36% of those treated with recombinant FVIII concentrate. No difference was observed in the development of high-titre inhibitors between patients with severe haemophilia treated with plasma-derived FVIII (13/35 [37%]) and those treated with recombinant FVIII (4/11 [36%]). Another prospective study, conducted by Mauser-Bunschoten and colleagues, compared the incidence of inhibitors in 59 PUPs with severe haemophilia A who were initially treated with cryoprecipitate or intermediate purified FVIII concentrates with the incidence of inhibitors in 22 patients treated exclusively with monoclonally purified FVIII and recombinant FVIII products[28]. The inhibitor incidence rate was almost the same between the two groups (24% versus 23%, respectively).

Data from a retrospective evaluation of 148 PUPs with severe haemophilia A were recently published by Goudemand and colleagues[29]. Sixty-two patients were treated exclusively with plasma-derived FVIII concentrates and 86 exclusively with recombinant FVIII products. No statistically significant difference between the two treatments was found for the cohort of high responders (p=0.157), but there was a significant difference when comparing patients with high-titre inhibitors and/or immune tolerance induction (ITI; p=0.045). According to a Cox multivariate analysis excluding other risk co-factors (i.e., *F8* gene mutation, ethnicity, family history of inhibitor, age at first infusion), recombinant FVIII was found to be an independent risk factor for inhibitor development, carrying approximately a 2.4- to 3.2-fold higher risk than plasma-derived FVIII concentrates.

In a retrospective cohort study of 348 children with severe haemophilia A, Chalmers and colleagues[30] found that high-titre inhibitors developed in 15% and 10% of patients treated with recombinant FVIII and plasma-derived FVIII products, respectively, without statistical significance (p=0.173). The significance appeared only using pooled data without any stratification, showing that inhibitors developed more frequently in patients initially treated with recombinant FVIII than in those treated with plasma-derived FVIII concentrates (27% versus 14%, respectively; p=0.009). A multicentre retrospective cohort study of 316 PUPs from the Concerted Action on Neutralizing Antibodies in Severe Hemophilia A trial was conducted to explore the relationship of FVIII product type and switching between FVIII products with inhibitor formation[31]. The risk of inhibitors (overall and high-titre inhibitors) was not lower in the plasma-derived FVIII patients than in those treated with recombinant FVIII (relative risk [RR] for all inhibitors, 0.8; 95% CI, 0.5–1.3; p=0.34; RR for high-titre inhibitors, 0.9; 95% CI, 0.8–2.5; p=0.72). Switching between FVIII products did not increase the risk of inhibitors (RR, 1.1; 95% CI, 0.6–1.8).

The Paediatric Committee of the German, Austrian, and Swiss Society for Thrombosis and

Haemostasis Research conducted a multicentre study to observe inhibitor development in PUPs[32]. A total of 324 PUPs with haemophilia A or B have been recruited since 1993. Of the 183 PUPs studied, 88 received plasma-derived FVIII and 95 received recombinant FVIII. Twenty-one percent of patients who received plasma-derived FVIII developed inhibitors, compared with 36% who received recombinant FVIII (p=0.08).

Overall, the existing data on the impact of the type of FVIII product on inhibitor incidence in PUPs with haemophilia A are conflicting. For instance, a low inhibitor incidence rate (approximately 10%) was found in some prospective studies using plasma-derived FVIII concentrates[16,33]; however, an equally low incidence was detected by other prospective studies with recombinant FVIII products, especially the second generation recombinant products[34,35]. In addition, the great majority of the studies found an overlapping incidence rate of high-titre inhibitors between plasma-derived FVIII and recombinant FVIII groups.

Despite the heterogeneity among the various studies, attempts have been made, through systematic review and meta-analysis, to compare the incidence of inhibitor development in patients with haemophilia A who were treated with FVIII/vWF or recombinant FVIII products. In 2003, Wight and Paisley published a systematic review investigating the association of FVIII product type with inhibitor formation[36]. Fifty relevant retrospective or prospective studies were identified in the literature. A comparison of data from 13 studies in PUPs found that patients treated with plasma-derived FVIII had a lower cumulative incidence of inhibitors than those treated with recombinant FVIII. In patients treated with plasma-derived FVIII, the cumulative inhibitor incidence ranged from 0% to 12.4% (weighted mean, 6.8%) for all inhibitors and from 0% to 2.5% (weighted mean, 1.4%) for high responders (>5 Bethesda units). In comparison, patients treated with recombinant FVIII had cumulative inhibitor rates between 36% and 38.7% (weighted mean, 37.5%) for all patients; for high responders, the inhibitor incidence ranged from 11.3-18% (weighted mean, 15.1%). This review has been criticised for its comparison of trials with very different study designs (e.g., prospective/retrospective, frequency and method of inhibitor testing, length of follow-up) and study populations (e.g., ethnicity, type of gene mutation, definition of disease severity, age at first exposure to FVIII)[37], making it impossible to draw any reasonable conclusion based on the comparison of inhibitor incidence of the different products across studies. In addition, pooling all plasma-derived FVIII and all recombinant FVIII products is problematic because there are great differences between drugs of the same type. The amount of vWF varies among commercial plasma-derived FVIII formulations, and important differences also exist among recombinant FVIII products (e.g., antigen content). The more recent meta-analysis by Iorio and colleagues[38] identified 2094 patients from 24 retrospective and prospective studies, 420 of whom developed inhibitors. Six percent of patients treated with plasma-derived FVIII developed high-titre inhibitors while 19.4% of those treated with recombinant FVIII products did so (p=0.195); the pooled incidence inhibitor rate was 14.3% for plasma-derived FVIII concentrates and 27.4% for recombinant FVIII products (p<0.001, multivariate analysis).

The use of recombinant FVIII as haemophilia replacement therapy has increased due to the good safety profile of these products, driving the conversion of many previous treated patients from plasma-derived FVIII to recombinant FVIII.

Giles *et al.* reported that no increase in the incidence of inhibitor development was found in 478 previously treated patients followed up for 1 year after switching from plasma-derived FVIII to recombinant FVIII. Overall, the incidence of true inhibitor development (i.e., negative for inhibitors before conversion to recombinant FVIII and positive after conversion) in previously treated patients with haemophilia A was 2% to 3% over 2 years. This is similar to the incidence in patients treated with plasma-derived FVIII[39].

In addition, there is no consensus on the preferred FVIII product for achieving inhibitor eradication during ITI. No conclusive evidence demonstrates that using plasma-derived FVIII rich in vWF will improve the likelihood of successful tolerisation; the only data suggesting that high-content vWF factor concentrates play a role in the outcome of ITI regimens are derived from small *in vitro* studies[40,41], small case series[42,43] and retrospective studies[44,45], and small, uncontrolled studies[46].

Meta-analysis of data from the IITR, NAITR and PROFIT trials found no association between ITI outcome and treatment product (the distribution of success and failure was equivalent: 70% success, 30% failure)[47]. The International Workshop on Immune Tolerance Induction declared, by consensus recommendation, that ITI is successful using FVIII products with and without vWF (level 2B recommendation)[47]. Moreover, the International Immune Tolerance Induction Study was interrupted prematurely last year because intercurrent bleeding was significantly higher in the low-dose arm than in the high-dose arm regardless of the product used[48].

In conclusion, the published data document that inhibitor development in patients with haemophilia A and the outcome of ITI are not influenced by the type of FVIII product. Thus, because of the low risk of pathogen transmission associated with recombinant FVIII and in accordance with current evidence-based guidelines, recombinant FVIII products should be considered the treatment of choice for patients with haemophilia A. Furthermore, the increased use of recombinant FVIII products over the next few years may lead to decreased costs, rendering the comparison with plasma-derived FVIII concentrates more favourable from an economic point of view.

References

1) Franchini M, Coppola A, Molinari AC, et al. Forum on: the role of recombinant factor VIII in children with severe haemophilia A. Haemophilia 2009; **15**: 578-86.
2) Mannucci PM, Tuddenham EG. The hemophilias - from royal genes to gene therapy. N Engl J Med 2001; **344**: 1773-9.
3) White GC 2nd, McMillan CW, Kingdon HS, Shoemaker CB. Use of recombinant antihemophilic factor in the treatment of two patients with classic hemophilia. N Engl J Med 1989; **320**: 166-70.
4) Coppola A, Franchini M, Tagliaferri A. Prophylaxis in people with haemophilia. Thromb Haemost 2009; **101**: 674-81.
5) Franchini M, Lippi G. Recombinant factor VIII concentrates. Semin Thromb Hemost 2010; **36**: 493-7.
6) Tagliaferri A, Rivolta GF, Iorio A, et al. Mortality and causes of death in Italian persons with haemophilia, 1990-2007. Haemophilia 2010; **16**: 437-46.
7) Leissinger CA. Prophylaxis in haemophilia patients with inhibitors. Haemophilia 2006; **12**(Suppl 6): 67-73.
8) Mannucci PM. Back to the future: a recent history of haemophilia treatment. Haemophilia 2008; **14**(Suppl 3): 10-8.
9) Llewelyn CA, Hewitt PE, Knight RS, et al. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. Lancet 2004; **363**: 417-21.
10) Pipe SW. Recombinant clotting factors. Thromb Haemost 2008; **99**: 840-50.
11) Gringeri A, Mantovani LG, Scalone L, Mannucci PM. Cost of care and quality of life for patients with hemophilia complicated by inhibitors: the COCIS Study Group. Blood 2003; **102**: 2358-63.
12) Gomperts ED. The need for previously untreated patient population studies in understanding the development of factor VIII inhibitors. Haemophilia 2006; **12**: 573-8.
13) Astermark J. Overview of inhibitors. Semin Hematol 2006; **43** (2 Suppl 4):S3-7.
14) Briet E, Rosendaal FR, Kreuz W, et al. High titer inhibitors in severe haemophilia A. A meta-analysis based on eight long-term follow-up studies concerning inhibitors associated with crude or intermediate purity factor VIII products. Thromb Haemost 1994; **72**: 162-4.
15) Chambost H. Assessing risk factors: prevention of inhibitors in haemophilia. Haemophilia 2010; **16**(Suppl 2): 10-5.
16) Ettingshausen CE, Kreuz W. Recombinant vs. plasma-derived products, especially those with intact VWF, regarding inhibitor development. Haemophilia 2006; **12**(Suppl 6): 102-6.
17) Goodeve A. The incidence of inhibitor development according to specific mutations -and treatment? Blood Coagul Fibrinolysis 2003; **14**(Suppl 1): S17-21.
18) Hay CR. The epidemiology of factor VIII inhibitors. Haemophilia 2006; **12**(Suppl 6): 23-9.
19) Oldenburg J, Pavlova A. Genetic risk factors for inhibitors to factors VIII and IX. Haemophilia 2006; **12**(Suppl 6): 15-22.
20) Scharrer I, Bray GL, Neutzling O. Incidence of inhibitors in haemophilia A patients - a review of recent studies of recombinant and plasma-derived factor VIII concentrates. Haemophilia 1999; **5**: 145-54.
21) Scharrer I, Neutzling O. Incidence of inhibitors in haemophiliacs. A review of the literature. Blood Coagul Fibrinolysis 1993; **4**: 753-8.
22) Scharrer I, Neutzling O, Schwaab R, et al. Experiences with recombinant factor VIII products: development of inhibitors and immune tolerance therapy. Ann Hematol 1998; **76**(Suppl 1): A1-6.
23) Franchini M, Lippi G. VWF-containing FVIII concentrates and inhibitors in hemophilia A: a critical literature review. Thromb Haemost 2010.
24) Verbruggen B, van Heerde W, Budde U. Methodological shortcomings in assessment of factor VIII concentrate inhibition. Haemophilia 2007; **13**: 680-1.
25) Dasgupta S, Repesse Y, Bayry J, et al. VWF protects FVIII from endocytosis by dendritic cells and subsequent presentation to immune effectors. Blood 2007; **109**: 610-2.
26) Pfistershammer K, Stockl J, Siekmann J, et al. Recombinant factor VIII and factor VIII-von Willebrand factor complex do not present danger signals for human dendritic cells. Thromb Haemost 2006; **96**: 309-16.

27) Kreuz W, Ettingshausen CE, Zyschka A, et al. Inhibitor development in previously untreated patients with hemophilia A: a prospective long-term follow-up comparing plasma-derived and recombinant products. Semin Thromb Hemost 2002; **28**: 285-90.
28) Mauser-Bunschoten EP, van der Bom JG, Bongers M, et al. Purity of factor VIII product and incidence of inhibitors in previously untreated patients with haemophilia A. Haemophilia 2001; **7**: 364-8.
29) Goudemand J, Rothschild C, Demiguel V, 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.
30) Chalmers EA, Brown SA, Keeling D, et al. Early factor VIII exposure and subsequent inhibitor development in children with severe haemophilia A. Haemophilia 2007; **13**: 149-55.
31) Gouw SC, van der Bom JG, Auerswald G, et al. Recombinant versus plasma-derived factor VIII products and the development of inhibitors in previously untreated patients with severe hemophilia A: the CANAL cohort study. Blood 2007; **109**: 4693-7.
32) Kreuz W, Auerswald G, Budde U, et al. Inhibitor incidence in previously untreated patients (PUPs) with hemophilia A and B. A prospective multicenter study of the pediatric study group of the German, Swiss and Austrian Society of Thrombosis and Hemostasis (GTH). The GTH-PUP-Study Group. In: Scharrer I, Schramm W, eds. 35th Hemophilia Symposium. New York, NY: Springer Berlin Heidelberg; 2006:34-7.
33) Addiego JE Jr, Gomperts E, Liu SL, et al. Treatment of hemophilia A with a highly purified factor VIII concentrate prepared by anti-FVIIIc immunoaffinity chromatography. Thromb Haemost 1992; 67: 19-27.
34) Kreuz W, Gill JC, Rothschild C, et al. Full-length sucrose-formulated recombinant factor VIII for treatment of previously untreated or minimally treated young children with severe haemophilia A: results of an international clinical investigation. Thromb Haemost 2005; **93**: 457-67.
35) Musso R, Santagostino E, Faradji A, et al. Safety and efficacy of sucrose-formulated full-length recombinant factor VIII: experience in the standard clinical setting. Thromb Haemost 2008; **99**: 52-8.
36) Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. Haemophilia 2003; **9**: 418-35.
37) Scharrer I, Ehrlich HJ. Reported inhibitor incidence in FVIII PUP studies: comparing apples with oranges? Haemophilia 2004; **10**: 197-8.
38) Iorio A, Halimeh S, Holzhauer S, et al. Rate of inhibitor development in previously-untreated hemophilia a patients treated with plasma-derived or recombinant factor VIII concentrates. A systematic review. J Thromb Haemost 2010:[Epub ahead of print].
39) 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**: 139-48.
40) Berntorp E, Nilsson IM. Immune tolerance and the immune modulation protocol. Vox Sang 1996; **70**(Suppl 1): 36-41.
41) Sukhu K, Keeling DM, Giangrande PL. Variation in inhibitor reactivity in acquired haemophilia A with different concentrates. Clin Lab Haematol 2000; **22**: 287-90.
42) Auerswald G, Spranger T, Brackmann HH. The role of plasma-derived factor VIII/von Willebrand factor concentrates in the treatment of hemophilia A patients. Haematologica 2003; **88**: EREP05.
43) Orsini F, Rotschild C, Beurrier P, et al. Immune tolerance induction with highly purified plasma-derived factor VIII containing von Willebrand factor in hemophilia A patients with high-responding inhibitors. Haematologica. 2005; **90**: 1288-90.
44) Greninger DA, Saint-Remy JM, Jacquemin M, et al. The use of factor VIII/von Willebrand factor concentrate for immune tolerance induction in haemophilia A patients with high-titre inhibitors: association of clinical outcome with inhibitor epitope profile. Haemophilia 2007; **14**: 295-302.
45) Kurth MA, Dimichele D, Sexauer C, et al. Immune tolerance therapy utilizing factor VIII/von Willebrand factor concentrate in haemophilia A patients with high titre factor VIII inhibitors. Haemophilia 2007; **14**: 50-55.
46) Gringeri A, Musso R, Mazzucconi MG, et al. Immune tolerance induction with a high purity von Willebrand factor/VIII complex concentrate in haemophilia A patients with inhibitors at high risk of a poor response. Haemophilia 2007; **13**: 373-9.
47) Dimichele DM, Hoots WK, Pipe SW, et al. International workshop on immune tolerance induction: consensus recommendations. Haemophilia 2007; **13**(Suppl 1): 1-22.
48) Dimichele DM, Goldberg I, Foulkes M, on behalf of the International Immune Tolerance Study Group. International prospective randomized immune tolerance (ITI) study: preliminary results of therapeutic efficacy and safety [abstract 07S03]. Haemophilia 2010; **16**(Suppl 4): 29.

Correspondence: Massimo Franchini
Immunohematology and Transfusion Center
Department of Laboratory and Pathology Medicine
University Hospital of Parma, Parma Italy
email: mfranchini@ao.pr.it