Factor VIII safety: plasma-derived versus recombinant products

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Introduction

It is impossible to understand the importance of safety issues regarding the use of plasma-derived and recombinant clotting factor concentrates without looking back at the evolution of the management of haemophilia over the last 50 years. The treatment of people with haemophilia improved radically following the discovery by Judith Pool in the first half of the 1960s of the possibility of concentrating anti-haemophilic factors by cryoprecipitation of plasma[1,2].

Various techniques for further concentrating and purifying the coagulation factors were introduced such that these factors became increasingly available and easier to infuse[3]. This opened up a whole new world in which people with haemophilia could treat themselves more rapidly thus limiting bleeding into their joints, could treat themselves at home thus decreasing their dependence on the emergency room, could treat themselves prophylactically prior to activities that might cause bleeding, and could travel. This progress in the management of haemophilia has dramatically improved not only the life-expectancy of these patients but also their quality of life.

The past

The expectations of haemophilic patients and their families of a normal life were suddenly shattered in the early 1980s by the report of a new disease among haemophiliacs[4], called acquired immunodeficiency syndrome (AIDS), previously described only in homosexuals[5]. This report clearly indicated that the cause of this life-threatening disease had to be a transmissible agent, subsequently identified as a lentivirus and initially named human T-lymphotropic virus type 3 but now denominated human immunodeficiency virus (HIV)[6]. In the early years of the AIDS epidemic, it was clear that haemophilia patients treated with plasma concentrates prepared from pooled plasma were at an enormously high risk of HIV infection, because there was then no way to screen plasma or plasma donors for HIV. In the period from 1979 to 1985 about 70% patients with severe haemophilia were estimated to have been infected by this deadly virus and thousands of them have died of AIDS.

The first big step forward was made with the characterisation of HIV and then with possibility of identifying HIV carriers in 1984[7]. This was important for the diagnosis and treatment of patients and for selecting donors. The following year the first anti-retroviral agent came out, offering the opportunity to prolong the survival of patients with signs of full-blown AIDS[8].

The first action taken by the manufacturers of concentrates in order to prevent AIDS being transmitted by plasma-derived products was to heat the clotting factor concentrates[9], a procedure initially studied to prevent non-A, non-B hepatitis virus contamination unsuccessfully[10]. Subsequently, virus inactivation methods involving solvents and detergents were shown to be effective in removing HIV and hepatitis viruses from the concentrates[11]. These methods, together with ever more careful screening of donors, have led to an extraordinary improvement in the safety of plasma-derived factor concentrates, as unequivocally indicated by the fact that no blood-borne transmission of hepatitis viruses or HIV has occurred in the last 20 years[12,13]. Nevertheless, the perception of patients and treaters of the potential risk of blood-borne virus transmission still remains high. This perception was reinforced by the recent discovery that the infectious agent of the variant Creutzfeld-Jacob disease can be transmitted

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by blood[14], despite assertions that any infectivity present might be reduced during the process of plasma fractionation.

In the meanwhile, two groups, one in Boston and one in San Francisco, cloned the gene for factor VIII (FVIII)[15-17], in 1984, enabling the production of recombinant forms of FVIII by genetic engineering[18]. Three years later, the first infusion of recombinant FVIII was given[19] in the USA.

The present

Since 1988 the use of recombinant products has progressively increased, so that in some European countries, such as the United Kingdom, Sweden and The Netherlands, they have almost completely replaced the plasma-derived products. Correspondingly, the use of clotting factor concentrates has doubled or more: this phenomenon is probably due to the by the increased availability and quality of recombinant coagulation factors and the broad implementation of prophylactic treatment regimens[20].

With the increasing use of recombinant products, an increased number of patients with anti-FVIII inhibitors has been observed[21], so that inhibitors have become the most pressing, unresolved problem in patients with severe haemophilia A.

The primary issue is: has the inhibitor development rate truly increased? In fact, the increase of inhibitors could be due to more frequent testing or simply greater awareness; another possible explanation is that previous studies underestimated the incidence. On the other hand, there might really be a higher incidence due to greater immunogenicity of recombinant FVIII concentrates.

Inhibitor development is the most challenging complication of haemophilia treatment and the economic burden of its management is the highest of that for any chronic disease[22]. It is important to know whether plasma-derived and recombinant products are associated with a different risk of inhibitor development in previously untreated patients or not. Unfortunately, no randomised clinical trials are available to provide the evidence we need.

A first, very accurate and systematic review on the epidemiology of inhibitors in haemophilia A was carried out by the School of Health and Related Research of the University of Sheffield, UK[23]. This review evaluated the role of the different FVIII products on the risk of inhibitor development. The cumulative risk in previously untreated patients treated with different plasma-derived products of low or intermediate purity was reported to range from 20.3[24] to 33.0%[25,26]. By contrast, for patients treated with a single plasma-derived concentrate, the cumulative risk ranged from 0[27] to 12.4%[28]. The cumulative risk for patients treated with a single recombinant product was reported to range from 36.0[29] to 38.7%[30]. More recent surveys found that the incidence of inhibitors ranged from 16.7[31] to 32%[32] in patients treated with a second generation recombinant FVIII product.

The analysis of concentrate immunogenicity is complicated by several factors: first, the different modality of inhibitor testing; second, the heterogeneity of study populations, not only because of the varied severity of the FVIII defects among the patients enrolled, but also because of the different risk factors that might play a role in inhibitor development, such as ethnicity, type of gene mutation and age at first treatment[33]; and third, the multiplicity of FVIII products used. Some confusion is also introduced when intermediate and high purity products are considered together, since these differ in some ways, in particular with respect to their content of von Willebrand factor (VWF). In fact, since 1995, the presence of VWF has been suggested to play a role in the immunogenicity of FVIII concentrates[34-36].

Experience with VWF-containing FVIII concentrates, not yet fully published, in Norway and UK, seems to mirror the findings in already published cohorts. A French study compared a cohort of previously untreated patients with severe haemophilia A given a single, high-purity plasma-derived FVIII concentrate containing von Willebrand factor or first-generation full-length recombinant FVIII concentrates and found a 2.4 higher risk of inhibitor development in patients treated with a recombinant FVIII concentrate than in patients treated with a plasma-derived VWF-containing FVIII[37]. On the other hand, a retrospective international cohort study[38] showed no difference in the rate of inhibitor development with the two different sources of FVIII, at variance with another cohort study carried out in UK[39] which found that VWF-containing FVIII products were less immunogenic than recombinant products.

Very recently, a meta-analysis based on a

systematic review examined the incidence rates of inhibitor development in previously untreated patients with haemophilia A treated with either plasma-derived FVIII concentrates or with recombinant FVIII concentrates and explored the influence of both study and patient characteristics[40]. Meta-regression and analysis-of-variance (ANOVA) were applied to data from 1,167 patients treated with plasma-derived FVIII and 927 patients treated with recombinant FVIII in 24 studies. The pooled incidence rate of inhibitor development was 14.3% (C.I. 10.4-19.4) for plasma-derived FVIII and 27.4% (C.I. 23.6-31.5) for recombinant FVIII; the incidence rate of high responding inhibitor was 9.3% (6.2-13.7) for plasma-derived FVIII and 17.4% (14.2-21.2) for recombinant FVIII. Using the multi-way ANOVA study design, study period, testing frequency and median follow-up were found to explain most of the variability, while the source of FVIII concentrate lost statistical significance. Thus, it is still unclear whether the plasma-derived concentrate is better than the recombinant concentrate[41,42].

Conclusions

The management of people with haemophilia A has improved enormously over the last 50 years: the average life expectancy of a child with haemophilia is now almost 70 years and his quality of life is greatly meliorated. There has been progressive improvement of virus-inactivation methods in plasma products and the introduction of methods used to screen for the presence of viruses in blood donations and plasma pools has led to an impressive increase in the safety of plasma-derived factor concentrates. Indeed, there have been no new cases of product-transmitted hepatitis viruses or HIV infection in the last 20 years. The availability of safe replacement therapy has allowed primary prophylaxis treatment for children and adolescents and, in some countries, adults.

Nevertheless, the management of people with haemophilia is still evolving. The most challenging complication of current therapy, the development of FVIII inhibitors, is still a major issue to be resolved. It is essential to determine whether recombinant and plasma-derived FVIII products have different immunogenicity, since inhibitors hamper effective and prompt treatment of bleeding events and their prevention and lead to a high risk of morbidity and mortality.

This was the reason for designing the Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) (http://www.clinicaltrials.gov, study NCT 01064284; EUDRACT n. 2009-011186-88), which is currently underway. This survey is an international, multicentre, prospective, controlled, randomised, open-label clinical trial on inhibitor frequency in previously untreated patients or patients with minimal treatment with blood components when exposed to plasma-derived, VWF-containing FVIII concentrates or to recombinant FVIII concentrates. Patients meeting the enrolment criteria will be consecutively enrolled at each participating centre, randomised to treatment exclusively with a single plasma-derived, VWF-containing or recombinant FVIII product, and followed up until inhibitor development or until 50 exposure days or 3 years from enrolment have elapsed, whichever comes first. Approximately 300 patients will be enrolled from up to 78 centres in 14 countries in four continents.

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