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LETTERS TO THE EDITOR

Risks of inhibitors from recombinant factor VIII: a quarter of a century to reach the conclusion

T. BURNOUF* and P. F. W. STRENGERS†
*Graduate Institute of Biomedical Materials and Tissue Engineering, College of Biomedical Engineering, Taipei Medical University, Taipei, Taiwan; and †International Plasma Fractionation Association, Amsterdam, The Netherlands

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The first recombinant factor VIII (rFVIII) for substitutive therapy of hemophilia A was licensed 25 years ago. Several rFVIII products now dominate the hemophilia market in high-income countries, with the benefit of leaving larger quantities of the more affordable plasma-derived FVIII (pdFVIII) available to treat hemophilic patients in low–medium-income countries. Interestingly, a recently published randomized multicenter clinical study provided a definite demonstration that rFVIII is almost twice as likely as pdFVIII containing von Willebrand factor (VWF) to induce anti-FVIII inhibitory antibodies, a very serious adverse drug reaction, in previously untreated severe hemophilia A patients [1]. Anti-FVIII inhibitor development in hemophilic patients is a very challenging clinical complication of hemophilia A treatment. It requires the implementation of specialized and costly therapeutic strategies to overcome the anticoagulant effect of the FVIII inhibitor.

Understanding why more than 25 years of clinical studies and routine use of rFVIII have been needed to confirm the early evidence of higher immunogenic risks of rFVIII needs to be scrutinized retrospectively, as it can serve as an interesting case study for future decision-making on therapeutic strategies in hemophilia treatment. From the 1990s, the introduction and widespread use of rFVIII in wealthy countries was definitely stimulated by the many devastating viral transmissions that were associated with the distribution and clinical use of non-virally inactivated pdFVIII produced from blood plasma donations that were not screened or were insufficiently screened for bloodborne infections. Until the mid-1980s to late 1980s, the plasma fractionation industry, largely lacking a scientific background and medical knowledge, and insufficiently regulated, had not developed the viral inactivation methodologies needed for pdFVIII. At that time, health decision-makers, regulatory authorities, and clinicians in wealthy countries, abruptly facing the viral risks of pdFVIII, speeded up the licensing and use of rFVIII, thereby ignoring legitimate concerns about immunogenicity. Cumulative incidence rates of > 30% for inhibitor development found in initial clinical trials of rFVIII [2] were tentatively explained by thorough follow-up of patients and the use of improved Bethesda assays capable of better detecting transient inhibitors. Former studies showing low incidence rates of inhibitors in patients treated with pdFVIII fractions were questioned and criticized. It was eventually claimed that the occurrence of inhibitors was somehow part of the natural history of any hemophilia treatment, and that either the clinical seriousness of inhibitors was overstated, or that they could be well controlled with immune tolerance protocols. Suggestions were even made that pdFVIII immunogenicity had been historically underestimated [3]. These claims were reinforced by suggestions that cryoprecipitate itself, the first plasma fraction used for hemophilia A substitutive therapy, could induce the development of many inhibitors. Occasional inhibitor outbreaks found in hemophilic populations that received highly purified, pasteurised and/or 'over-heat-treated' pdFVIII [4,5] further led to the belief and claims that pdFVIII and rFVIII actually had similar immunogenicity [2,6]. To further complicate the issue, the interpretation of several clinical evaluations using rFVIII was biased by the inclusion of patients with FVIII baseline levels of > 1%, a critical threshold in inhibitor development, contributing to leveling out of the immunogenic risks. Studies emphasized the genetic profile of patients – rather than the product used – as being the critical factor for inhibitor development [2].

Correspondence: Thierry Burnouf, Graduate Institute of Biomedical Materials and Tissue Engineering, College of Biomedical Engineering, Taipei Medical University, 250 Wu-Shin Street, 11031 Taipei, Taiwan.
Tel.: +886 2 2736 1661 Ext 5201; fax: +886 2 2737 4113.
E-mail: thburnouf@gmail.com

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Some clinical studies did provide evidence of increased risks of inhibitor development associated with rFVIII as compared with pdFVIII containing VWF [7], but, still, scientific uncertainties persisted for years. In addition, calls by some clinicians for the performance of randomized controlled double-blind clinical studies of rFVIII and virally safe pdFVIII were increasingly discouraged by a lack of funding and practical difficulties in recruiting a meaningful number of hemophilia A patients willing to receive pdFVIII, as they perceived rFVIII as being inherently virally safer, although virally safe pdFVIII was available. As a result, the recently reported clinical study [1] proving higher immunogenicity of rFVIII had to be organized in countries with limited access to rFVIII, and where hemophilia A patients and their care-takers were willing to be enrolled and receive pdFVIII.

It is clear that both rFVIII and pdFVIII are needed now, and will be needed for years to come, to provide enough and affordable quality products for the treatment of hemophilia A patients. Improved serologic and biotechnological plasma screening methods and dedicated robust virus-inactivating and virus-removing production methods have prevented the transmission of both known and emerging transfusion-transmitted infections via pdFVIII for > 20 years worldwide [8]. Many countries are still facing continuous global shortages of these products, which are on the Model list of Essential Medicines of the World Health Organization, thereby highlighting the crucial importance of ensuring appropriate supply at the national level. The new findings [1] highlight that, more than ever, the advantages and limits of currently marketed FVIII products should be considered wisely to ensure optimal safety of treatment and care for the hemophilia A population at the global level.

Addendum

T. Burnouf wrote the first draft. P. Strengers made several suggestions. Both authors approved the final version.

Disclosure of Conflict of Interests

P. Strengers acts as the president of the International Plasma Fractionation Association (not-for-profit plasma fractionators). T. Burnouf states that he has no conflict of interest.

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