Factor VIII products in haemophilia A: one size fits all?

Pier Mannuccio Mannucci1; Isabella Garagiola2
1Scientific Direction, IRCCS Ca’ Granda Maggiore Policlinico Hospital, Milan, Italy; 2Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Ca’ Granda Maggiore Policlinico Hospital, Milan, Italy

The development of alloantibodies (inhibitors) that inactivate the coagulant activity of factor VIII (FVIII) is the major problem for the management of persons with severe haemophilia A (1). This complication occurs in approximately one third of boys previously untreated and hence first exposed to FVIII-containing products (2, 3). The risk of inhibitors is maximal during the first 20 treatments (i.e. days of exposure to FVIII) and is much smaller after this period has elapsed (4). The development of inhibitors is a multifactorial event (2, 3). Beside the severity of haemophilia, the most certain risk factors are the type of FVIII gene mutation and other genetic factors such as a family history of inhibitor, some polymorphisms in immunoregulatory genes and an African heritage. Another well-established factor is the exposure of patients at risk to intensive replacement therapy needed for major surgery or to stop severe bleeding (3). Being a multifactorial event, inhibitor development cannot be controlled by means of a single approach. Obviously patient genetics cannot be modified, nor it is easy to avoid intensive exposure to FVIII warranted for surgery and major bleeding. However, it is theoretically possible to decrease the inhibitor cumulative incidence by acting upon modifiable risk factors. One option is the choice of the regimen of replacement therapy. According to some data (5) regular prophylactic administration of FVIII helps to decrease inhibitor onset. Another approach to reduce inhibitors that recently generated a heated debate and a number of articles is based upon the choice of the source of FVIII products to be used in at risk previously untreated patients (PUPs): plasma-derived (pd) or recombinant (r) DNA technology (6, 7)? There is some biological plausibility that pd FVIII may be less immunogenic than rFVIII. Being extracted from human plasma these products are more native than FVIII produced by recombinant DNA technology from mammalian cell lines, which causes post-translational modifications in the FVIII molecule (8–10). Another factor that makes biologically plausible that pd FVIII products may be less immunogenic is their high content of the chaperone protein von Willebrand factor (VWF), that may reduce immunogenicity through FVIII epitope masking and protection from endocytosis by antigen-presenting cells (11, 12). Moreover, pd FVIII contains human proteins other than FVIII that may have immunomodulatory properties (13).

With this background of biological plausibility, the hypothesis of less inhibitors with pd FVIII is supported clinically by a number of observational studies (14), which have cumulatively found a lower cumulative incidence of inhibitors in PUPs with severe haemophilia A treated exclusively with pd FVIII: 14.5% vs 31% for rFVIII (Figure 1). However, this impressive difference is equivocal, because all the studies had limitations related to non-homogenous populations in terms of disease severity, gene mutation type, ethnicity and therapy regimen. Poor homogeneity also pertains to study designs (retrospective vs prospective, frequency of inhibitor testing and length of the observation period). A possible approach to this dilemma is offered in this issue of Thrombosis and Haemostasis by Marcucci et al. (15), who did a meta-analysis based upon individual patient data stemming from some of the reports listed in the Figure 1. Among a total of 761 PUPs with severe or moderate haemophilia, 27% developed an inhibitor: 40% of those treated with rFVIII, 22% with pd FVIII (15). Even though these different inhibitor rates apparently confirm a higher immunogenicity for rFVIII, the effect of the FVIII source was found to be mainly due to confounders (15). Marcucci et al. (15) conclude that their own meta-analytic findings stemming from observational studies are inconclusive and prompt the performance of randomized trials, i.e. the basis of evidence-based medicine. SIPPET (Study on Inhibitors in Plasma-Product Exposed Toddlers) is an investigator-driven, worldwide, prospective, open-label clinical trial designed to establish in 300 PUPs or minimally treated patients with severe haemophilia A whether or not there is a different inhibitor incidence between patients randomised to the class of pd FVIII products containing VWF or that of rFVIII not containing VWF (16). SIPPET has recently completed the recruitment of the planned 300 cases in five continents, and the absence of futility in the frame of a planned interim analysis means that the original hypothesis of an at least two-fold lower incidence of inhibitors in patients randomised to pd-, VWF-containing products is still viable and valid.

The design of SIPPET was originally based on the unequivocal assumption that all FVIII products were equally efficacious and broadly equivalent pertaining to their capacity to control bleeding (16). However, the study also assumed that in the frame of the two classes of FVIII products (plasma derived or recombinant) to which patients were randomised there was no different risk of immunogenicity between the various commercial brands chosen to represent each FVIII class. A striking challenge to
Figure 1: Top: Cumulative incidence of factor VIII (FVIII) alloantibodies (inhibitors) in previously untreated boys with severe haemophilia A treated exclusively with plasma-derived (pd) or recombinant (r) FVIII products. Updated from references 6 and 14. Bottom: Cumulative incidence of inhibitors in previously untreated boys with severe haemophilia A, treated exclusively with various commercial brands of recombinant FVIII. Drawn from references 17, 20-22.
this paradigm did first stem from an observational study (RODIN) carried out in 574 PUPs with severe haemophilia A originating from the PedNet prospective registry, which unexpectedly found that two commercial brands of rFVIII (Kogenate Bayer/ Helixate NexGen) were associated with an approximately 60% higher rate of inhibitors than another rFVIII taken as reference (Advate) (17). The main biological difference between these brands of rFVIII is that the former is produced from baby hamster kidney cells, the latter by Chinese hamster ovary cells. The surprising data of RODIN fuelled a number of critiques mainly based upon the limitations inherent in an observational registry (18, 19). The climax of the debate was reached when two additional retrospective observational studies stemming from France and UK substantially confirmed that Kogenate/Helixate were associated with an approximately 60% higher inhibitor rate in PUPs (20, 21). The last installment of the saga is reported in this issue of Thrombosis and Haemostasis by Fischer et al. (22), who, analysing the data originating from a European Surveillance Registry (EUHASS), observed that in 417 PUPs there was no class or brand-related difference between the various rFVIII products employed in 68 European Centres. These data are summarised graphically in Figure 1 (bottom).

Here are my candid comments of practising clinician on this issue, potentially so important for persons with haemophilia. Three to one studies that support a difference in the choice between pd FVIII and rFVIII products are more likely to explain the differences. In conclusion, pertaining to the choice among rFVIII, Kogenate/Helixate should be avoided for the time being in PUPs with severe haemophilia A, because when in doubt we should abstain, owing to the presence of valid alternatives. However, there is no ground to switch to other products those patients who did not develop inhibitors with these products within the critical period of 20–50 days of treatment. It is very unlikely that a randomised clinical trial comparing the various rFVIII will be done, considering the extreme rarity of the needed cases: a PUP is born yearly among 3–5 million people in the general population of every country! Moreover, such a trial should be investigator-driven, but it is unlikely that independent funds will ever become available, unless regulatory authorities such as the FDA and EMA decide to take the initiative to fund it. Per- taining to the choice between pd and rFVIII, both sources of FVIII are now needed by the haemophilia community and will be needed for many years to come. While higher pathogen safety is the main perceived advantage of rFVIII, lower immunogenicity is the main perceived advantage of pd FVIII. On the other hand, there is not enough pd FVIII to meet the current (and future) patient needs, and the long-acting FVIII products which are now licensed or in the development pipeline are all based on recombinant DNA technology. The choice made by patients fully informed on the few available facts and the many perceptions should be the main criterion.

Conflicts of interest
P. M. Mannucci has received speaker fees for participation at educational meetings organised by Bayer, Baxter, Grifols, Kedrion Biopharma, Novo Nordisk and Pfizer. No conflict of interest is declared for I. Garagiola

References

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