The Canadian Hemophilia Society statement on the SIPPET study

For many years there has been debate in the medical community about which class of products has the lowest risk of inhibitor development in previously untreated patients (PUPs) with hemophilia A: recombinant factor VIII or plasma-derived factor VIII?

Some studies showed a lower rate of inhibitor development with plasma-derived FVIII; other studies did not. The studies, however, were quite small and retrospective or observational in nature, and so they didn’t provide conclusive results.

The SIPPET study is the first prospective, randomized trial to attempt to answer the question. Prospective means that the study is designed and then subjects are enrolled and data is collected, and is considered stronger evidence than a retrospective study that looks back in time. Randomized means subjects are randomly assigned to each arm of the study to reduce potential bias. SIPPET was coordinated out of the Milan Hemophilia Center in Italy and conducted in 14 countries in Africa, the Americas, Asia and Europe. SIPPET stands for Survey of Inhibitors in Plasma-Product Exposed Toddlers.

The PUPs received either recombinant FVIII—Advate (Baxalta, now a part of Shire), Kogenate FS (Bayer), Recombinate (Baxalta, now a part of Shire) or Xyntha (Pfizer)—or plasma-derived factor VIII containing von Willebrand factor—Alphanate (Grifols), Fandhi (Grifols), Emoclot (Kedrion) or Factane (LFB).

The main finding of the SIPPET study was that in patients receiving plasma-derived FVIII with von Willebrand factor the incidence of inhibitors was 26.7% while the rate in those receiving recombinant FVIII was 44.5%. Thus, the rate of inhibitors in patients using recombinant products was 1.87 times, or 87%, higher, than in patients using plasma-derived FVIII with von Willebrand factor.

The rate of high titer inhibitors was 18.5% among those receiving plasma-derived FVIII and 28.4% among those receiving recombinant. Thus, the rate of high titer inhibitors was 1.69 times, or 69%, higher, in recombinant FVIII than in plasma-derived FVIII with von Willebrand factor.

The Association of Hemophilia Clinic Directors of Canada (AHCDC) Inhibitor Committee has called the SIPPET study “without question the best available experimental data that exists to date with respect to the question of the comparative immunogenicity between recombinant and plasma-derived FVIII concentrates and should not be ignored.” It is not, however, the last word on this issue. International data involving large numbers of PUPs will need to be gathered to conclusively answer this question.

There is wide agreement that the development of an inhibitor, especially a high-titer inhibitor, is the most serious and frequent adverse event in the treatment of hemophilia.

With regard to the implications of the study, the AHCDC Inhibitor Committee made these key points to the physicians of the AHCDC.
1. When choosing a FVIII product for PUPs with severe hemophilia A, Canadian hemophilia treaters should take into consideration the results of the SIPPET study. Given the SIPPET data, plasma-derived products containing von Willebrand factor—Humate P (CSL Behring), Wilate (Octapharma)—should be presented to patients and families as an option for the treatment of PUPs with severe hemophilia. In this regard, selecting the FVIII product remains the decision of individual clinics and families.

2. At this point the results cannot be extrapolated to PUPs with mild or moderate hemophilia as the study was conducted only on patients with severe hemophilia A. Nevertheless, a clinician may choose to manage mild or moderate hemophilia A PUPs in a similar manner to those with severe hemophilia A.

3. The results of the SIPPET study should not lead to reconsideration of treatment regimens of previously treated hemophilia A patients (PTPs).

4. The results cannot at this point be extrapolated to the newer FVIII concentrates (Eloctate, Kovaltry, Nuwiq) as these products were not studied.

CHS Blood Safety and Supply Committee
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