UKHCDO statement in response to SIPPET study

In 2015, the UKHCDO published inhibitor rates for the complete UK cohort of previously untreated patients (PUPs) 2000-20111. All 407 patients received recombinant factor VIII concentrates in line with UK policy. This UK study identified an overall inhibitor rate of 29% with the important subgroup of those with a “high-titre” inhibitor being 14.7%.

The recently published SIPPET study provides additional data for consideration when selecting FVIII concentrate to initiate treatment for a new PUP2. The SIPPET study compares the inhibitor rates for plasma-derived and recombinant classes of FVIII concentrates in an international, randomized-controlled study. Only a minority of the 251 evaluable participants were recruited in Europe. The study identified an increased risk of inhibitor occurrence with recombinant FVIII products. Those treated with recombinant FVIII concentrates had a 44.5% rate of all inhibitors compared to 26.8% in plasma-derived concentrates with the “high-titre” rates being 28.4% in recombinant versus 18.6% in plasma-derived products.

Choosing the first product to initiate treatment in a PUP must balance known and unknown risks. The overall inhibitor rate in the SIPPET is higher than expected for both classes of product, whilst identifying a class benefit of using plasma-derived concentrates. The SIPPET “high-titre” inhibitor rate for plasma derived FVIII (18.6%) approximates to the UKHCDO PUP recombinant data (14.7%). Clinicians should consider these known risks together with the unknown risk of transfusion-transmitted infection (TTI) in plasma-derived products when choosing a concentrate. The TTI risk is very low, but not zero. The final consideration is the availability of Immune Tolerance Induction funding, which is currently secure in the UK.

The context of first-treatment choice for a PUP may be very controlled when a family history of haemophilia is known. Counseling about first treatment and product choice should be initiated in the ante-natal period, enabling parents to consider both known and unknown risks, particularly taking into account their own family’s ethnicity, *F8* mutation and inhibitor history. However, up to 50% of families will have a new diagnosis of haemophilia, most likely in an acute bleed scenario, with no prior family haemophilia history and consequently no known *F8* mutation or inhibitor family history. In such a scenario, clinicians should counsel parents about the importance of the diagnosis and necessity for FVIII treatment as a priority. In an emergency, we recognize there may not be an opportunity to discuss the additional inhibitor risk data of FVIII-concentrate class.

Pragmatically, UK clinicians should counsel parents about the implications of known inhibitor studies if the presenting clinical scenario allows. Recombinant FVIII concentrates remain an acceptable standard of care for PUPs, with plasma-derived concentrates considered on an individualized basis.

1) [Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe hemophilia A, 2000-2011.](http://www.ncbi.nlm.nih.gov/pubmed/25339360)

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2) [A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A.](http://www.ncbi.nlm.nih.gov/pubmed/27223147)

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