

EHC Response to the Publication of the SIPPET Study

What is the SIPPET study?

The Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) study is a randomized clinical trial, which compared the incidence of factor VIII inhibitors among young previously untreated patients (PUPs) treated with plasma-derived factor VIII containing von Willebrand factor or recombinant factor VIII. The study was conducted between 2010 and 2014 and recruited patients from 42 haemophilia centres in 14 countries from Africa, Asia, the Americas and Europe. The results have just been published in the *New England Journal of Medicine* (Peyvandi F et al. *N Engl J Med* 2016;374:2054-2064). 251 PUPs completed the study, of whom 125 received plasma-derived FVIII, which contained von Willebrand factor and 126 received recombinant FVIII. Inhibitors developed in 29 of the 125 patients treated with plasma-derived factor VIII (of whom 20 patients had high-titre inhibitors) and in 47 of the 126 patients treated with recombinant factor VIII (of whom 30 patients had high-titre inhibitors). The cumulative incidence of all inhibitors was 26.8 per cent with plasma-derived factor VIII and 44.5 per cent with recombinant factor VIII. The cumulative incidence of high titre inhibitors was 18.6 per cent with plasma-derived factor VIII and 28.4 per cent with recombinant factor VIII. The use of recombinant factor VIII was therefore associated with an 87 per cent higher incidence of inhibitors than plasma-derived factor VIII and was associated with a 69 per cent higher risk of high titre inhibitors than plasma derived FVIII. The study compared the two classes of concentrates (plasma-derived containing von Willebrand factor and recombinant) and no conclusions can be drawn about the risk associated with specific brands.

A randomized study is one in which patients are randomly assigned to one or other treatment arms, which eliminates the possibility of bias. Such studies are recognized as providing the highest level of evidence (level 1). The SIPPET study is the only randomized study, which addresses this specific issue. The finding that patients treated with plasma-derived factor VIII containing von Willebrand factor had a lower incidence of inhibitors compared to those treated with recombinant factor VIII was not entirely unexpected. Several previous observational studies and non-randomized clinical trials had suggested that there might be an increased risk of inhibitor development in PUPs treated with recombinant products. Indeed, the SIPPET study was specifically set up with the aim of providing a definitive answer to longstanding controversy and debate on this issue.

What are the implications for treatment?

It is important to emphasise that this study has implications only for the initial treatment of previously untreated patients (PUPs) with severe haemophilia A up to a total of 50 exposure days (ED). This is generally regarded as the highest risk period for inhibitor development. The number of exposure days does not necessarily equate with the number of infusions of



concentrate as it is the number of days on which treatment is given, which counts and not the number of injections. For example, if a child is given twice daily infusions of factor VIII on three successive days for a muscle bleed or minor surgery, the number of exposure days is three. Most young patients with severe haemophilia who embark on prophylaxis will reach the threshold of 50 ED by the age of two or three years of age. No change of therapy needs to be considered in the case of older children or adults who have received treatment beyond the initial high risk period of 50 exposure days. This study also has no implications at all for patients with haemophilia B (also known as Christmas disease). There has never been any suggestion of a higher risk of inhibitor development with recombinant factor IX and so only PUPs with haemophilia A were enrolled in the SIPPET study.

Inhibitors are antibodies in the blood which inactivate infused factor VIII. Patients with inhibitors do not necessarily bleed more frequently but they are usually resistant to treatment with conventional factor VIII concentrates. Bleeds in patients with inhibitors can usually be treated effectively with alternative agents known as bypassing agents: examples of such products include FEIBA® and NovoSeven®. Inhibitors will disappear permanently in approximately 70 per cent of patients after a prolonged course of regular treatment with high doses of factor VIII known as immune tolerance. In some patients with low levels of inhibitors, the antibodies may disappear spontaneously within a period of weeks or months and without any specific treatment. Treatment of patients with inhibitors can prove very expensive and the use of bypassing agents and immune tolerance therapy may not be feasible options in countries with limited economic resources. In the 2015 EHC survey, only 19 of 37 European countries responding had access to immune tolerance therapy for all people with haemophilia who required it and a further 8 countries had partial access.

The publication of this important study will clearly now generate discussion around the world among physicians involved in haemophilia care and related professional organizations. There are a number of possible treatment options for PUPs and the EHC does not anticipate that there will be universal agreement on the way forward. The SIPPET study focused purely on the risk of inhibitor development but other factors also need to be weighed in the balance when making a decision regarding the treatment of PUPs. Freedom from the risk of transmission of blood-borne pathogens has always been the major attraction of recombinant products. Whilst there is no risk of transmission of viruses such as HIV or hepatitis C with modern plasma-derived concentrates, there is no guarantee that viruses, which may emerge in future years, or other agents such as prions, will not be transmitted.

Many physicians are likely to recommend the use of a plasma-derived factor VIII concentrate, which contains von Willebrand factor (VWF) for the initial 50 or so exposure days, before switching to a brand of recombinant factor VIII. This is a very reasonable option, based on the results of the SIPPET study. It is certainly the most sensible option in countries with limited economic resources where the development of an inhibitor in a young patient could have very serious adverse consequences. This approach can only help to minimise the risk of inhibitor development and does not abolish it altogether: as reported above, about one in every four patients who receive plasma-derived factor VIII concentrate can be expected to develop an inhibitor. When selecting a plasma-derived product, it must be borne in mind that the SIPPET study specifically examined the impact of plasma-derived products, which contain von Willebrand factor as well as factor VIII. The study does not provide any evidence of a similar

beneficial effect with high-purity plasma-derived factor VIII concentrates, which contain only factor VIII.

On the other hand, some clinicians will take the view that freedom from the risk of pathogen transmission is a more important consideration and opt to continue treating new PUPs with recombinant factor VIII. A hybrid approach, which has also been advocated, involves the use of plasma-derived products for the initial treatment of the small minority of PUPs perceived to be at increased risk of inhibitor development, whilst continuing to treat all other PUPs with recombinant products. Risk factors for inhibitor development, which have already been identified from previous studies include certain genotypes (the underlying genetic abnormalities, which cause haemophilia), close family history of inhibitor development (such as an older brother) and Afro-Caribbean ethnicity.

We hope that National Member Organisations will be consulted and be involved in the development of national guidelines on this issue and also that individual physicians will discuss with the parents of young PUPs the key issues.

What are the implications for clinical trials?

A number of novel recombinant factor VIII products have been developed in recent years, including some with an extended half-life. Some of these have already been licensed for clinical use by regulatory agencies, after submission of satisfactory data on safety and efficacy in adults and adolescents with haemophilia. However, clinical trials of these agents in PUPs have begun only fairly recently and it is important to consider the implications of the SIPPET findings in relation to recruitment to these ongoing clinical studies. The EHC feels that it is important that such studies in PUPs should continue and the results of the SIPPET study should not deter parents from enrolling their children in such studies. It is possible that some of these novel products may actually prove to be less immunogenic than conventional products. Given the limited numbers of PUPs, it would be highly desirable for as many as possible to be enrolled in formal prospective clinical trials and/or pharmacovigilance studies.

Summary:

Options for the treatment of PUPS with FVIII deficiency should be carefully considered by the key haemophilia clinicians in each country. Clinicians should collectively consider the views of the national haemophilia patient organisation on this issue in addition to carefully discussing the various options with parents of children with haemophilia who are previously untreated.

In countries where recombinant FVIII is the standard treatment, options for treatment of PUPs include:

- Continued treatment with recombinant FVIII
- Treatment of PUPs with plasma derived FVIII containing VWF
- Treatment of PUPs with plasma derived FVIII containing VWF for the first 50 exposure days followed by treatment with recombinant FVIII
- Use of plasma derived FVIII containing VWF for the initial 50 exposure days only in PUPs perceived to be at significantly increased risk of inhibitor development