EAHAD
European Association for Haemophilia and Allied Disorders

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EAHAD statement on the publication of the SIPPET study results

Inhibitor development is the most serious complication of haemophilia treatment today and is known to occur in approximately 25% of previously untreated patients (PUPs) with severe haemophilia A. The causes of inhibitor development are multi-factorial and include genotype, family history, ethnicity, and the way haemophilia is treated. There has been a long debate as to whether recombinant clotting factor concentrates are associated with a higher risk of inhibitor development as compared to plasma-derived concentrates.

Recently the results of the first randomized trial, the Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) were published in the New England Journal of Medicine (2016;374:2054-64). These results show a significantly increased risk of inhibitor development with recombinant concentrates as compared to plasma-derived factor VIII (FVIII) products containing von Willebrand factor.

In interpreting the results of this study, a number of factors must be taken into consideration. Firstly, the study conclusions are drawn from a sample of PUPs with severe haemophilia A and under 50 exposure days. The data do not apply to patients with more than 50 exposure days, those with mild or moderate haemophilia A, or to haemophilia B patients. Secondly, it should be noted that although the SIPPET study was a randomized trial, a study design that is considered to be of a higher methodological rigour, observational studies have not consistently reported the same findings with respect to inhibitor development and type of product used. Thirdly, the results of the study do not apply to products not included in the study, in particular new standard or longer-acting products.

Patient safety must be prioritized in the treatment of haemophilia. It is important to note that although plasma-derived concentrates are now considered safe from the risk of infection, there is always an at least theoretical risk of transfusion-transmitted infection with any kind of plasma-derived concentrate. The higher risk of inhibitor development associated with recombinant products, as reported in the SIPPET study results, must be balanced against the lower infection risk associated with these products. When using plasma-derived products in Europe, it is important to confirm that the products have been licensed by European regulators and undergone viral inactivation/elimination by at least two different methods.

Clinicians treating haemophilia should give a balanced view of the various replacement therapy options based on local resources, product availability, and the individual circumstances of the patient. Specifically, where patients who develop inhibitors have no access to immune tolerance therapy (ITI) or bypassing agents, the balance towards initiating replacement therapy in PUPs with plasma-derived products may be preferred, based on the results of the SIPPET study. Nevertheless, in the case of life- or limb-threatening bleeds, the product that is licensed and immediately locally available should be used. Access to a preferred product should not delay the initiation of a treatment that is urgently needed.

Haemophilia treaters should engage parents in the decision-making process, but remain aware that parents will require information and guidance, as they may not have much knowledge of the subject. This discussion may include a review of the nature of plasma-derived and recombinant products, the theoretical risk of infection with plasma derived products, the conflicting results of previous studies on the risk of inhibitors, as well as the new data provided by SIPPET.

Whilst a lower incidence of inhibitors was reported in patients treated with plasma-derived FVIII, the inhibitor incidence in this group of patients was still 25%. In order to monitor on-going inhibitor risk, EAHAD recommends that all severe haemophilia A PUPs should be entered in registries. Also, where available, patients should be encouraged to consider entering clinical trials of new products to assess the inhibitor risk. Finally, clinicians should ensure that products irrespective of their origin are used, when possible, in a way that would minimize the risk of inhibitor development based on current evidence of risk factors for inhibitor development.

EAHAD will continue to closely monitor this important treatment issue and will provide further advice if appropriate.