

# **Recombinant Factor VIII Concentrates Associated with Increased Risk of Inhibitor Development in Severe Hemophilia A: Perspectives on the Results of the SIPPET Trial**

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## **Background**

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Hemophilia A is an X-linked condition caused by deficiency in clotting factor VIII (FVIII). Treatment with intravenous FVIII concentrate can limit the debilitating bleeding-related joint damage that was prevalent in patients with hemophilia A decades ago. Because plasma-derived factor VIII (pdFVIII) products were contaminated by HIV and hepatitis in the late 1970s and early 1980s, recombinant factor VIII (rFVIII) products have become the primary treatment for hemophilia A in developed countries. Improved processing of pdFVIII products, including thorough plasma donor screening and viral inactivation methods, have effectively decreased the risk of viral transmission through plasma-derived products, and the last case of viral transmission from a factor product was in 1987. The standard of care for treatment of severe hemophilia A in children in developed countries is prophylactic treatment with FVIII intravenously every other day, which has been shown to reduce joint damage (Manco-Johnson et al, NEJM 2007).

The development and treatment of inhibitors, FVIII neutralizing alloantibodies that quickly eliminate FVIII from circulation, is a significant problem in hemophilia treatment, making treatment and prevention of bleeding difficult and expensive. Inhibitors develop in around one-third of children with severe hemophilia, usually within the first 50 FVIII doses (DiMichele, *Pediatr Blood Cancer* 2013). The recently published results of SIPPET (Survey of Inhibitors in Plasma-Product Exposed Toddlers), sheds light on a significant risk factor for inhibitor development (Peyvandi et al, NEJM 2016). The international open-label study enrolled 264 previously untreated <6 year old children with severe hemophilia A and randomized to treatment with either rFVIII or Von Willebrand Factor (VWF)-containing pdFVIII. Subjects treated with rFVIII products had an 87% higher risk of developing inhibitors than those treated with VWF-containing pdFVIII products.

In practice, the results of the SIPPET trial are balanced by continued fear within the hemophilia community of viral transmission through plasma-derived factor products. This is especially difficult for families with multiple members with hemophilia who have suffered and died from HIV or hepatitis. Furthermore, with the development of recombinant long-acting factor products, the perceived benefit of less frequent infusions may outweigh the risk of inhibitor development for some families. In addition, the optimal duration of treatment with pdFVIII products has not been prospectively evaluated. Should VWF-containing pdFVIII be used throughout a patient's life, or simply during the first 50 doses that are known to carry the highest risk of inhibitor development?

Because of the SIPPET trial, we can now confidently say that infusion of plasma-derived factor VIII confers a lower risk of inhibitor development than recombinant factor VIII in previously untreated children with severe hemophilia A. The specific effects of SIPPET on clinical care remain in question.

## **Perspective 1**

Guy Young, MD, FAAP

As described in the article, the results of the SIPPET study definitively prove that rFVIII confer an increased risk for inhibitors when compared to pdFVIII. Yet, it is unlikely and perhaps “wrong” to simply put all previously untreated patients (PUPs) on pdFVIII going forward. Thus, what is the clinician to do? There are 3 basic points of view as follows and in no particular order. First, one can simply dismiss the results feeling that in a time of advancing technology, moving to pdFVIII seems anachronistic. The other extreme is to take the results at face value and to place all PUPs on pdFVIII. If one were to take the middle ground, one could consider putting PUPs at particular high risk for inhibitors based on genotype, family history and ethnicity and place them on pdFVIII and leaving rFVIII for those at lower risk. There are arguments for and against each of these approaches. Against the first is that ignoring the results would likely lead to a higher inhibitor rate in that clinician’s practice and there is no doubt that inhibitors are the most serious complication of factor therapy. In opposition to placing all PUPs on pdFVIII is the fact that for those at lower risk (or in fact all patients), a minority will develop an inhibitor and most of those can be tolerized. While the middle approach seems reasonable, one could argue that if a clinician believes in the results, shouldn’t they apply that potential benefit to all of their patients?

A few additional caveats need to be mentioned. The SIPPET study (due to the time it was initiated) did not include extended half-life (EHL) FVIII concentrates and there exists in vitro and animal data that hints at the notion that these products could cause fewer inhibitors, data that can only be confirmed once the PUP studies for these products are completed. Regardless, the SIPPET study doesn’t address the issue of these newer factors. Another important caveat for those who intend to use pdFVIII products in PUPs is the issue of how long one must continue these products. Is it reasonable, as some have suggested, to use pdFVIII for the first 50 exposure days and then when the risk for inhibitor development has essentially passed, switch to a rFVIII product? Clearly, no data exist to answer this question, however I caution against believing in the absence of data that such a strategy would protect patients from getting inhibitors. Whether or not a clinical trial to answer this question can be done remains to be seen, however it does seem to be the next logical step. Lastly, what of the non-factor replacement products such as emicizumab (a.k.a. ACE910) and others? Will the future of inhibitor prevention include not even exposing patients to factor VIII replacement at all? Impossible to know at this time but something to at least begin thinking about.

## **Perspective 2**

Michael Wang, MD

SIPPET is one of a scarce number of clinical trials in hemophilia that have been conducted as a prospective randomized controlled study, and as such its findings deserve careful examination. This is to acknowledge an important clinical trial in hemophilia while recognizing the limitations faced by the study investigators; it was not designed or executed in a way that would answer all questions surrounding inhibitor development in PUPs in relation to product choice, plasma-derived versus recombinant FVIII. The finding that PUPs receiving pdFVIII had fewer inhibitors to FVIII develop than those treated with rFVIII had been suspected and reported through alternative analyses and clinical experience (Mannucci, Haemophilia 2011); therefore, the findings were not entirely surprising and cannot be ignored. Inhibitors are one of the most morbid and costly

complications of hemophilia treatment (Valentino, Haemophilia 2012), so preventing even a fraction of inhibitors would be a successful therapeutic intervention. Implementing SIPPET findings into clinical practice will be a challenge. There will always be a limited supply of pdFVIII world-wide. pdFVIII products may be in greater demand in developed countries, leaving resource limited countries with the burden of not only more expensive recombinant products, but also a potentially larger burden of inhibitor patients. This is magnified when looking at high-titer inhibitors where the burden of illness is the greatest. Preventing one high-titer inhibitor is an important clinical outcome in any clinical setting. The reality is that not every PUP will be able to start infusing with pdFVIII. A strategy where other risk factors such as family history, genotype (if available) and ethnicity may need to be used. Collection of outcomes data following this tailored approach will be vital to continue improving our understanding of inhibitor development risk, and will further guide us in our use of FVIII products.

Another issue is that we do not know the inhibitor incidence of extended half-life (EHL) rFVIII products in PUPs. It seems prudent at this point to use them only in the context of PUP trials where safety and data can be carefully gathered. A third issue is the duration of pdFVIII exposure that best attenuates inhibitor development is not known. Fifty doses is a duration of exposure used clinically that has also been used safely for clinical trials of EHL products without increased inhibitor incidence in either pdFVIII or rFVIII previously treated patients. Finally, after completing pdFVIII many patients will choose an EHL product, and the risk of this switch is also unknown although an ongoing trial, ATHN 2, hopes to help answer this question. Despite ongoing development of novel hemostatic agents that may dramatically decrease the exposure to FVIII, it cannot be completely eliminated from the treatment of a severe hemophilia patient; therefore, mitigating inhibitor development will continue to be an important clinical pursuit.

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