



NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

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MASAC RECOMMENDATION ON SIPPET (SURVEY OF INHIBITORS IN PLASMA-PRODUCT- EXPOSED TODDLERS): RESULTS AND RECOMMENDATIONS FOR TREATMENT PRODUCTS FOR PREVIOUSLY UNTREATED PATIENTS WITH HEMOPHILIA A

The following recommendation was approved by the Medical and Scientific Advisory Council (MASAC) on June 17, 2016, and adopted by the NHF Board of Directors on June 28, 2016.

The development of inhibitors (neutralizing antibodies to factor VIII) is the most significant current treatment-associated complication of hemophilia A, affecting up to 30% of previously untreated patients (PUPs) treated with factor VIII (FVIII). (1) Inhibitors to FVIII can occur with both plasma-derived and recombinant FVIII concentrates. The rate of inhibitors observed in PUPs is unacceptably high, therefore clinical trials in this patient population are critically important to efforts to reduce inhibitor formation.

Results were recently published from SIPPET, a study which analyzed data from 251 PUPs with severe hemophilia A who might have received transfusions of blood or blood products but not clotting factor concentrates. (2) The study aim was to assess the frequency of FVIII inhibitor formation in patients treated with plasma-derived FVIII concentrate containing von Willebrand Factor (pdFVIII/VWF) compared to patients treated with recombinant FVIII (rFVIII). In this prospective, randomized, controlled study, 125 PUPs were treated with either first, second, or third generation rFVIII, and 126 PUPs were treated with pdFVIII/VWF.

- The results showed a significant increase in inhibitor development in the rFVIII-treated patients compared to pdFVIII/VWF-treated patients.
- The cumulative incidence of all inhibitors was 26.8% with pdFVIII/VWF and 44.5% with rFVIII; the cumulative incidence of high-titer inhibitors was 18.6% with pdFVIII/VWF and 28.4% with rFVIII.
- The follow-up period was planned to be 3 years or 50 exposure days (EDs: days on which one or more infusions of factor concentrate were received). Not all patients achieved one of these endpoints because of early termination of the study due to publication of another study that implicated one of the rFVIII products used in SIPPET with increased inhibitor development. (3)

Historical Background

Inhibitor development in hemophilia

The development of inhibitors is a complex interplay of host and environmental factors. About half of all inhibitors that form are low titer and clinically insignificant and usually disappear

spontaneously; thus FVIII therapy may be continued. However, the remaining inhibitors are high-titer and persistent, rendering treatment with FVIII products ineffective at preventing or stopping bleeding. These inhibitors require intensive therapy, known as immune tolerance induction (ITI), to eliminate them. About 70% of the patients with high-titer inhibitors can be successfully treated with ITI.

The widespread use of rFVIII beginning in 1992 suggested an increased incidence of inhibitors due, at least in part, to more frequent measurements than what had occurred historically, more intensive treatment frequency and dosing, and the development of more sensitive assays that detected inhibitors below 1.0 Bethesda unit (BU). (1) Focusing on high-titer inhibitors of 5.0 BU and greater, which tend to be clinically relevant and persistent, mitigates these problems and provides a more accurate assessment of inhibitor incidence.

PUP studies and inhibitor development

PUP studies have been published for each new FVIII product introduced to the market in the past 25 years. Taken together, all of these studies have shown rFVIII inhibitor rates to be either similar to or greater than inhibitor rates for pdFVIII products. These studies have all suffered from using highly selected populations and have never included a pdFVIII concurrent comparator arm. Two large Western European prospective observational studies have been performed (RODIN and PedNet), in which a total of 883 PUPs were followed for over 10 years. More than 98% of patients in these studies reached 50 exposure days. 658 PUPs were treated with rFVIII and 225 with pdFVIII. No differences in inhibitor rates were found, even when comparing all pdFVIII/VWF products to all rFVIII products. (3, 4)

MASAC Observations on the SIPPET Study

With this background of conflicting study results on the relative risks of inhibitor development between pdFVIII and rFVIII, the SIPPET study was initiated. The SIPPET study is the only prospective, randomized, controlled trial to date that has attempted to study the risk of inhibitor formation between two classes of FVIII products. As such, this study provides compelling data showing an increased risk for inhibitor development in PUPs treated with rFVIII compared to pdFVIII/VWF.

However, there are clear differences between the SIPPET study and most of the previous studies that showed no or a minimal increase in inhibitor formation with rFVIII.

- The SIPPET study included ethnicities which differ from those for which we have the most data (i.e. Caucasian), as the majority of its patients came from Egypt, India, and Iran. The risk of inhibitor development in these populations relative to European and North American populations is unknown.
- A large proportion of patients had gene mutations known to be associated with increased inhibitor risk (e.g. null mutations).
- Not all patients achieved 50 ED, the historical benchmark by which time the majority of inhibitors are seen to form.
- About half of the patients were on on-demand therapy (episodic), and some received as few as 1-4 treatments per year, which is quite different than the prophylactic treatment regimens used in the U.S.

- A cutoff of 0.4 BU was used for inhibitor detection; most other recent studies use 0.6 BU, while older studies used 1.0 BU. A lower BU cutoff will result in a greater number of inhibitors being detected.
- Third-generation and extended half-life products are currently used by the majority of patients in the U.S. Since only 16% of SIPPET patients in the rFVIII arm were treated with a third-generation product, SIPPET results using predominantly first and second generation products should not be extrapolated to these newer products.
- SIPPET does not address what to do after 50 EDs. Inhibitors may still occur beyond 50 EDs, and it would be difficult to determine if they were the result of any treatment changes or part of the natural history of inhibitors.

Plasma-derived products continue to carry the theoretical risk of viral transmission. HIV and hepatitis viruses are no longer risks due to extensive viral screening, inactivation, and elimination procedures. However, many new pathogens have emerged in the three decades since HIV and hepatitis viruses contaminated plasma-derived clotting factors. Zika, bird flu, SARS, and numerous other emerging viruses are eliminated by current pathogen removal and inactivation methods. However, some pathogens such as parvovirus B19 are less susceptible to heat and solvent-detergent inactivation methods, are small enough to pass through nanofiltration devices (5), and therefore are surrogate markers for future viruses of very small size. Thus, there remains a small risk that a new pathogen will emerge that is transmissible by blood, that will not be detected quickly by testing and screening, and that will not be cleared in the manufacturing process of plasma-derived clotting factors to eliminate the risk of transmission.

Thus there are many differences between the SIPPET study, previous inhibitor detection studies in PUPs, and clinical practice in the U.S. We do not yet fully understand the applicability of the SIPPET findings to the U.S. population. Also, the risk of inhibitor development must be weighed against the risk of a pathogenic infectious agent being transmitted by pdFVIII/VWF. PdFVIII/VWF products are, by definition, intermediate, not high, purity plasma products, meaning that they contain many other proteins in addition to FVIII and VWF. The three pdFVIII/VWF products licensed in the U.S. are Alphanate (used by only 7% of pdFVIII/VWF group in SIPPET) and Humate P and Koate DVI (not utilized in SIPPET). Thus it is difficult to make a blanket recommendation about which product to use in a given patient. Patients and families must discuss these issues with their treating provider.

MASAC Recommendations

Based on currently available evidence, MASAC makes the following recommendations:

1. Individuals with greater than 50 exposure days to any recombinant product (i.e. Previously Treated Patients or PTPs) should consider remaining on their current product, since multiple clinical studies have shown that their risk for inhibitor development with any FVIII product is markedly diminished after 50 EDs.
2. Individuals with more than zero and less than 50 exposure days should consider staying on their current recombinant FVIII product, since the differences between SIPPET and numerous other studies may not warrant switching patients who have already initiated a treatment regimen.
3. Newly diagnosed individuals and their caregivers should consider the new data from the SIPPET study in the context of all the accumulated data on inhibitor formation in PUPs and the pathogen safety risk/benefit of the two product classes and consider the following options:
 - a. Initiate therapy with a pdFVIII/VWF product in all PUPs.
 - b. Initiate therapy with a rFVIII product as previously recommended by MASAC (6).
 - c. Initiate therapy with a newer rFVIII product.
4. Regardless of which option is chosen, all PUPs should be enrolled in the ATHN data collection system or a clinical trial to assess outcomes.
5. For all classes of treatment products, the risk for inhibitor formation in PUPs is unacceptably high. All efforts by government, HTC's, patient advocates, and industry should be directed at reducing the risk of inhibitor formation.

References

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5. Soucie JM et al. Evidence for the transmission of parvovirus B19 in patients with bleeding disorders treated with plasma-derived factor concentrates in the era of nucleic acid test screening. *Transfusion.* 2013; 53(6): 1217-25.
6. MASAC Recommendation regarding the use of recombinant clotting factor products with respect to pathogen transmission. *MASAC Document #169*, 2006.

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