



NATIONAL HEMOPHILIA FOUNDATION

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MASAC STATEMENT REGARDING INHIBITOR RISK OF FACTOR VIII CONCENTRATES

The following statement was approved by the Medical and Scientific Advisory Council (MASAC) on April 14, 2013, and adopted by the NHF Board of Directors on May 10, 2013.

Inhibitor development is the single most important complication of clotting factor concentrate usage, especially for patients with severe hemophilia A. Based on the total body of current knowledge and emerging data available at this time, any Factor VIII (FVIII) preparation can be associated with alloantibody inhibitor formation, especially in previously untreated patients (PUPs) with hemophilia.

A recently published article presented the data from the RODIN (Research Of Determinants of Inhibitor development among PUPs with haemophilia) study, a longitudinal observational study of PUPs in Europe and Canada. (1) In this study, 574 PUPs treated with a variety of plasma-derived (pd) and recombinant(r) FVIII clotting factor concentrates were followed for 75 exposure days (ED) or until development of an inhibitor. The overall inhibitor rate was 31%, and 20% of these patients had high-titer inhibitor. Inhibitors developed regardless of the type or class of concentrate, i.e. there was no difference in risk of inhibitor formation between patients treated with pdFVIII versus rFVIII concentrates. Additionally, there was no increased risk of inhibitor development associated with switching between products or associated with the von Willebrand factor content of the products among those treated with pdFVIII. However, in a *post hoc* analysis of data after collection was completed, there was an unexpected finding that the risk of inhibitor formation was higher in children treated with a second-generation, full-length rFVIII product as compared to those treated with a third-generation, full-length rFVIII. The authors stated that this could be a biased finding, a chance finding, or a causal effect. We agree with the authors that further studies are needed to verify these observations and to identify possible biological explanations.

Based on published information (1-3) and on presentations by MASAC members, industry and regulatory representatives at their meeting on April 13, 2013, MASAC concludes that no change in clinical practice is warranted at this time. MASAC will continue to liaise with regulatory agencies as they review these data. Furthermore, MASAC is aware that there are a number of ongoing national and international studies addressing the risk of inhibitor formation for specific factor products. MASAC encourages those investigators who are conducting these studies to publish their findings in a timely manner so that their data can be added to the body of available scientific knowledge regarding risks for inhibitor development in hemophilia.

REFERENCES

1. Gouw SC et al. Factor VIII products and inhibitor development in severe hemophilia A. *New Engl J Med* 2013; 368(3): 231-9.
2. Iorio A, Skinner MW, Makris M. Letter to the Editor: Factor VIII products and inhibitors in severe hemophilia A. *New Engl J Med* 2013; 368(15): 1456-7.
3. Kessler CM, Iorio A. The RODIN (Research Of Determinants of Inhibitor development among PUPs with haemophilia) study: the clinical conundrum from the perspective of haemophilia treaters. *Haemophilia* 2013; DOI: 10.1111/hae.12149. Epub ahead of print.

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