inside blood commentary

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THROMBOSIS AND HEMOSTASIS

Comment on Cannavò et al, page 1245

Moving from parked to neutral(izing)

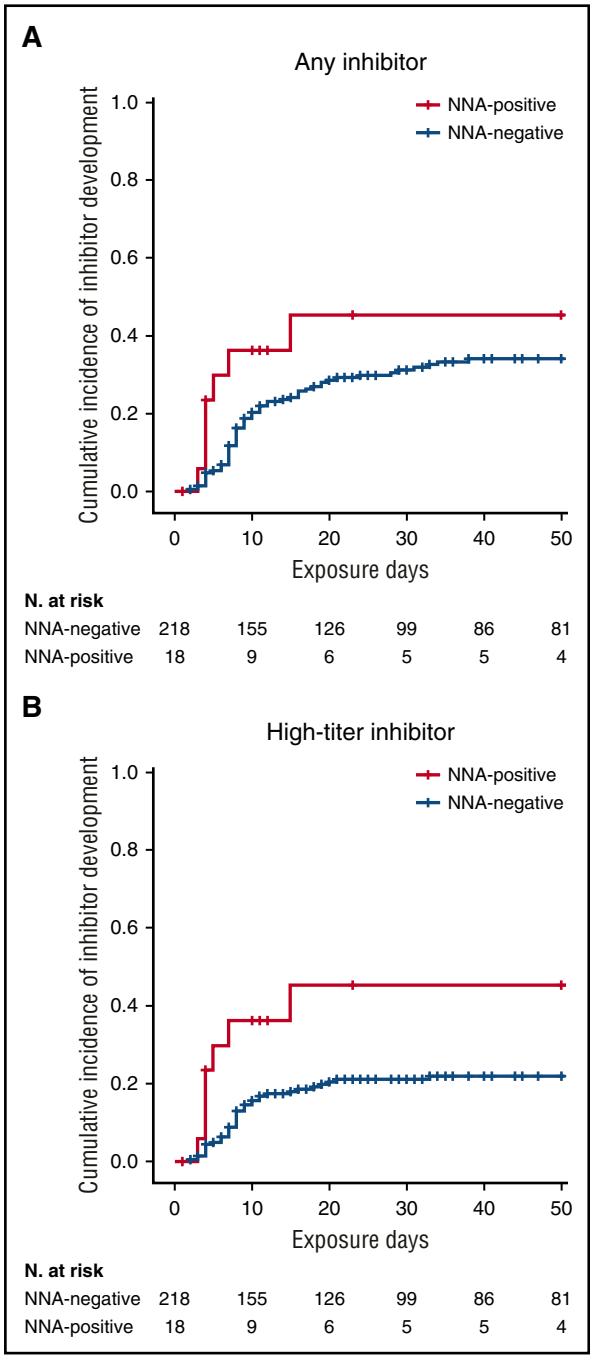
Christine L. Kempton EMORY UNIVERSITY

In this issue of *Blood*, Cannavò et al report on a cohort of children with severe hemophilia A. They found that anti-factor VIII (FVIII) nonneutralizing antibodies (NNAs) were present prior to exposure to FVIII concentrates, and that the presence of these NNAs was associated with subsequent development of high-titer inhibitory anti-FVIII antibodies (inhibitor).[1]

The development of an inhibitor is a major complication of severe hemophilia A occurring in up to one-third of patients. Presently, with widespread early initiation of routine FVIII infusions to prevent bleeding events, young persons with severe hemophilia A can live full and productive lives. When an inhibitor is present, FVIII infusions are no longer effective and alternative therapies such as bypassing agents are less effective than FVIII for both treatment and prevention of bleeding. Fortunately, a significant proportion of young patients are able to eradicate the inhibitor through the use of immune tolerance induction therapy, which consists of several months of repeated exposure to FVIII. In those who do not receive, or fail immune tolerance induction, the inhibitor remains, increasing the likelihood of significant disability by the time young adulthood is reached. In the past decade, significant advances have been made toward the understanding of risk factors for inhibitor development including race, genetics, intensive exposure, surgery at first exposure, and product type.[2-5] Unfortunately, knowledge of these risk factors has yet to translate to a capacity to avoid inhibitor development even in those who are high risk. In an ideal world, we would be able to predict an individual patient's risk for inhibitor development prior to any FVIII exposure with sufficient accuracy to institute appropriate therapy to prevent the development of a clinically relevant inhibitor.

In addition to neutralizing anti-FVIII antibodies, NNAs are present in healthy individuals and patients with hemophilia A with and without inhibitors.[6] Their clinical importance in the development of either tolerance or inhibitors is unclear, as most studies have used a cross-sectional design evaluating older children or adults. Understanding the pattern of inhibitor development and relevance of NNAs prior to inhibitor onset is challenging, requiring clinical and laboratory analysis of young infants prior to receiving any FVIII concentrates and monitoring until either an inhibitor develops or the risk period is over (>50 FVIII exposure days). The samples collected as part of the recently published SIPPET study have provided a unique opportunity to do just that.[5] The SIPPET study was a randomized clinical trial comparing the incidence of inhibitor development between plasma-derived and recombinant FVIII products in children with severe hemophilia A who were naive to FVIII and only minimally exposed (<5 exposure days) to blood components. The study demonstrated a significantly lower incidence of inhibitors in children who received plasma-derived FVIII compared with recombinant FVIII (26.8% vs 44.5%). The current study by Cannavò et al investigated whether anti-FVIII NNAs present prior to exposure to FVIII are associated with inhibitor development. Among the 237 patients enrolled in the SIPPET study, 7.6% had NNAs present at study entry, which was prior to any FVIII exposure. The cumulative incidence of developing an inhibitor was modestly greater in those with NNAs compared with those without (45.4% and 34%) and was associated with a nearly threefold to sixfold higher hazard of developing an inhibitor (see figure). Additionally, inhibitors in those with preceding NNAs were more likely to be high titer and not transient. The authors evaluated in bivariable analysis whether age, exposure to blood products, the presence of FVIII antigen, and nonnull mutations influenced the proportion of patients with NNAs. They found that the proportion of children with NNAs increased with age. Interestingly, the odds of having NNAs was lower in those who had received a blood product prior to enrollment, whereas the presence of a nonnull FVIII mutation and family history of inhibitor were also associated with higher odds of having NNAs. Adjusting the association between NNA and inhibitor development for age, mutation, family history of inhibitor, and all other studied variables either did not effect or increased the strength of the association.

Unfortunately, as is often the case when studying rare complications of rare diseases, the sample size of this study is small and the ability to draw firm conclusions is limited by wide confidence intervals that either overlap or contain the null hazard ratio of 1.0. Despite the limitations posed by sample size, the increased hazard of developing an inhibitor when an NNA is present appears to be robust and consistent after adjustment for 1 or 2 variables. Larger studies are needed to replicate the finding and to simultaneously adjust for multiple variables to exclude confounding effects. Even if this finding is confirmed with



Survival curves for inhibitor development ([A] any inhibitor; [B] high-titer inhibitor) according to the presence or absence of NNAs. See Figure 1 in the article by Cannavò et al that begins on page 1245.

similar effect size, the presence of NNAs alone does not hold sufficient predictive power to be used in isolation for clinical prediction, but holds promise to accurately risk stratify patients prior to any FVIII exposure if combined with other genetic data (eg, FVIII mutation, immune-modifying genes, and blood type) and family history of inhibitor. Now, we just need a treatment that is effective at reducing inhibitor development. The present strategy of avoiding surgery at first exposure, instituting prophylaxis early, and potentially using plasma-derived products at the start of treatment are insufficient. Novel approaches are needed to make this morbid and costly complication of historical interest only.

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