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INHIBITORS IN HEMOPHILIA: A PRIMER

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Treatment of Hemophilia Monographs
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Introduction

Throughout life, persons with hemophilia battle the complications of both the disease and its treatment. One of the most serious of these problems is the development of an inhibitor. An inhibitor is a type of antibody; the function of antibodies in the body is to try to destroy substances they do not recognize. In a person with hemophilia A or B, inhibitors directed against either factor VIII or IX may be created by the body following treatment to replenish the missing factor. The antibody attaches to the factor VIII or IX and neutralizes—or inhibits—its ability to stop bleeding.

An inhibitor is usually detected in one of two ways. Although the person with hemophilia may have no symptoms, the inhibitor may be discovered during routine screening performed during a comprehensive clinic visit. Alternatively, an inhibitor may be suspected when, suddenly and unexpectedly, bleeding does not stop as quickly as it should in response to treatment with factor.

The presence of an inhibitor is usually confirmed using a specific blood test called the Bethesda inhibitor assay. The assay is now often performed using the Nijmegen modification of the original method to improve test accuracy. The amount of antibody can be measured using this test, and is reported as a number of Bethesda units, or a Bethesda titer. The higher the number of Bethesda units (or, the higher the Bethesda titer) the more inhibitor is present.

When an antibody is detected, it is usually classified as either high- or low-responding, depending on how a person's immune system is stimulated upon repeated exposure to factor VIII or IX. If the immune system reacts briskly and strongly, the amount of inhibitor directed against factor VIII or IX can rise quickly to very high levels (reflected in a titer of at least 5 Bethesda units). Without further exposure to the factor, the inhibitor titer may drop to a low level, but this process could take months or years to occur. An inhibitor with these characteristics is generally called high-responding. Alternatively, the immune system may be stimulated in a way such that its response to factor exposure is slower and weaker, and the inhibitor titer will remain low (usually under 5 Bethesda units). This type of inhibitor is generally characterized as low-responding. The characteristics of an inhibitor can change over time and, at times, inhibitors have been noted to be transient, i.e., to disappear spontaneously within several weeks or months without immune tolerance (see below).

Incidence and Nature of Inhibitors

Based on studies from around the world, it is estimated that the incidence of antibody development in persons with severe (less than 1% factor) or moderately severe (1% to 5% factor) hemophilia A is between 20% and 33%. Among persons with hemophilia B, inhibitors are much less frequent, affecting only 1-6%. However, the development of factor IX inhibitors can be associated with a mild or severe allergic reaction during factor IX administration.

The risk of developing an inhibitor does not remain the same during the lifetime of a person with hemophilia. Historically, the majority of inhibitors have been reported to develop during childhood, at an average age of 12 years. However, in studies conducted during the past 20 years primarily on persons with severe hemophilia A, inhibitor development occurred at an average age of between 1 and 2 years, and after an average of 9-12 treatments. Inhibitor risk is greatest during the first 50 exposures to recombinant (genetically engineered) factor VIII. Although the risk greatly diminishes after 200 treatment days, a low rate of new inhibitor development has been documented through the sixth decade of life.

Historically, with the use of products derived from human plasma, about 80% of inhibitors were of the high-responding type and very few spontaneously disappeared. However, in more recent studies, possibly due to closer surveillance, more low-responder and transient factor VIII antibodies have been observed.

Inhibitor development is not common among persons with mild disease (factor levels of greater than 5%), but it can occur. This is especially true when the individual carries a predisposing alteration (mutation) in the factor VIII gene. Unfortunately, similar information on the nature of factor IX inhibitors is less available due to the low prevalence of this problem in the hemophilia B population.

Lastly, it is known that inhibitors are made against only certain parts of the factor VIII protein. Interestingly, this is true regardless of whether the inhibitor develops in response to recombinant or plasma-derived factor VIII, as well as whether it is high- or low-responding in nature. Researchers are already using this information to attempt to design factor VIII products with a diminished potential to stimulate inhibitor development. The factor IX protein has yet to undergo similar study.

Who Will Develop an Inhibitor and Why?

Inhibitor development occurs more frequently in individuals with certain inherited predispositions. As already mentioned, persons with hemophilia A are much more likely to develop inhibitors than those with hemophilia B. The incidence of inhibitors is highest among those with severe or moderately severe hemophilia. Inhibitors do occur more often than predicted in individuals with severe hemophilia A and a family history of antibodies to factor VIII. Ethnic origin also plays a role. For example, hemophilia A individuals with African ancestry are more likely than Caucasians to develop inhibitors to factor VIII. All these observations suggest that hemophilia genetics may be important. We now understand that among the several hundred mutations that have so far been described in the factor VIII and factor IX genes, some have been found to have a greater association with inhibitor development than others**.** Individuals with large, complete or multiple factor VIII or IX gene deletion mutations appear to be particularly vulnerable.

An individual's immune system also plays an important role in the body's reaction to factor VIII or IX. To date, characteristics of the interaction between T and B cells, as well as several immune signaling proteins, have been identified as being potentially important in factor VIII inhibitor development. Researchers are actively studying the hemophilia and non-hemophilic genes, the immune system, as well as their interactions for more answers.

On the other hand, issues related to the therapy itself may influence factor VIII inhibitor development. Potentially important treatment situations that may adversely influence inhibitor development in some individuals with severe hemophilia A include surgical prophylaxis and other high-intensity factor VIII exposure (duration and total dose). Conversely, routine prophylaxis may lower the risk of later antibody development. The influence of product type, i.e., recombinant vs. plasma-derived, is still controversial. These issues are being actively researched as well.

It would appear that the risk of inhibitor development in severe hemophilia A is complex and multi-factorial. Currently, due to its relative rarity, there is little information about how treatment-related circumstances might affect inhibitor development in hemophilia B.

Treatment of Bleeding in the Presence of Inhibitors

The treatment of hemophilic bleeding in a person with an inhibitor can be a challenging experience. In persons with low-responding inhibitors and low Bethesda titers, therapy with either factor VIII or IX replacement products is frequently possible. In these cases, there is usually good control of both minor and more serious bleeds, although higher doses of the factor and/or more frequent (or continuous) factor infusions may be required to overcome the antibody. However, when there is a large amount of antibody in the system, as reflected in a high Bethesda titer, specific treatment with factor VIII or IX is usually not possible because the inhibitor neutralizes even large factor doses. In rare instances, when high levels of inhibitor exist but there is life-threatening bleeding that can only be treated with specific factor therapy, much of the antibody can be removed from the body through a process called plasmapheresis or immune adsorption. This is only a temporary measure, however, since giving the factor will then stimulate the body to make large amounts of new antibody within several days. For most bleeding episodes, the person with hemophilia and a high-responding inhibitor will have to rely on alternative treatment (bypass therapy) selected and dosed on the basis of circumstances such as inhibitor characteristics, nature and severity of the bleed, age and treatment response pattern of the individual, whether or not

the person is eligible for or on immune tolerance (see below) and, for many individuals, access to the various therapeutic products.

For both hemophilia A and B, the choice of products within the global hemophilia community include prothrombin complex concentrates (PCCs), an activated prothrombin complex concentrate (APCC), and recombinant activated factor VII (rFVIIa).

APCC and PCCs are plasma-derived and virally attenuated, and contain activated clotting factors that stimulate the formation of a clot and stop bleeding, thus bypassing the specific requirement for factor VIII or IX. Used in the treatment of inhibitor bleeding since the late 1970s, APCC has been found to be effective for 60-90% of musculoskeletal bleeds as well as for major and minor surgery prophylaxis. Doses of 50-100 units/kg are generally infused every 8-24 hours, depending on the severity of the bleed.

However, there are several drawbacks that limit the use of—and satisfaction with—this treatment. This type of therapy is short-acting by its very nature, and when given too frequently may paradoxically cause either more bleeding or excess clotting. This clotting problem can be made worse if antifibrinolytic drugs (Amicar® or Cyclokapron®) are used along with APCC or PCCs Furthermore, because these products contain small amounts of factor VIII and larger amounts of factor IX, they too can stimulate new antibody production to both factor VIII in hemophilia A and factor IX in hemophilia B.

rFVIIa also bypasses the requirement for factor VIII or IX in persons with hemophilia A or B and inhibitors. Studies have shown rFVIIa to be effective in the prevention and treatment of joint hemorrhage, the treatment of life-threatening bleeding, as well as in the prevention of surgical bleeding. Because this product is also short-acting, multiple doses of
90 µg/kg or more infused every 2-6 hours may be required to stop bleeding. Single doses of 270 µg/kg have also been reported to be effective in the prevention and treatment of joint hemorrhage. However, optimum dosing is still being evaluated.

Although episodes of excess blood clotting as described for APCC have been reported with the intensive use of rFVIIa, these appear uncommon enough to safely allow for frequent dosing, as well as for concomitant treatment with antifibrinolytic drugs when required. Since this product is recombinant and contains no factor VIII or IX, re-stimulation of the antibody to factor VIII or IX should theoretically be less problematic than with the use of the plasma-derived products. Consequently it is frequently the bypass therapy of choice for children awaiting a decline in inhibitor titer before starting immune tolerance. For the same reason, this product is the hemostatic treatment of choice for bleeding in the face of factor IX inhibitors with accompanying allergic reactions. A clinical study comparing the effectiveness of APCC and rFVIIa demonstrated a trend toward equivalent effectiveness in the treatment of joint bleeding. At this time, both types of bypass agents have a role in the management of hemophilic bleeding in the presence of high-titer inhibitors.

Immune Tolerance: Treatment of Inhibitors

Although there are several therapeutic options for hemophilic bleeding in persons with an inhibitor, there are none that can guarantee the same good outcome as specific factor VIII or IX treatment. Consequently, persons with inhibitors frequently suffer from many more orthopedic and life-threatening complications from hemophilia and have greater disability in their day-to-day lives than those who do not have an inhibitor.

Therefore, for most of these individuals, the eradication of the inhibitor is the best option. The only currently available method to accomplish this is a process called immune tolerance. Immune tolerance induction (ITI) is comprised of regular (daily or several times weekly) infusions of variable doses of factor VIII or IX administered for a period of weeks to years in an effort to tolerize the immune system to factor VIII or IX, i.e., to train the immune system to better accept treatment with the missing clotting factor without producing further antibodies. ITI, although time-consuming and costly, is effective in 70-85% of ITI for factor VIII inhibitors, based on 30 years of experience with its use. However, a lower success rate of about 30% is often seen with factor IX antibodies. Successful ITI is defined by both the absence of residual antibody (a negative Bethesda titer), and a return to normal factor pharmacokinetics (i.e., normal behaviour of factor in the body).

Information collected through the international, German, and North American registries of immune tolerance allow a better understanding of

the characteristics of both the inhibitor and ITI that are more likely to be associated with successful outcomes in both hemophilia A and B. These have been best described for ITI in hemophilia A and include primarily low historical peak inhibitor titer, pre-ITI titer of less than 10 Bethesda units, and lower peak titer during tolerance. Age at the start of ITI, interruption in therapy, as well as the length of time between when an inhibitor occurs and when tolerance is started may all also be important in predicting success.

The impact of factor VIII dose and product type on ITI outcome remains unclear. In the absence of information suggesting otherwise, the major consensus opinion is that ITI should be performed using the product on which the inhibitor developed. A plasma-derived factor VIII containing von Willebrand factor may be preferentially used in some circumstances.

The question surrounding optimum dose will hopefully be clarified in the near future by an international study currently underway of children with high-responding factor VIII inhibitors and favourable risk parameters. It is hoped that low-dose ITI regimens, if proven effective, will increase global access to this inhibitor eradication strategy. In the absence of more definitive data to the contrary, there is broad worldwide consensus that factor VIII inhibitor patients who are at higher risk for failure should be treated with daily higher dose ITI regimens.

Unfortunately, much less is known about the predictors of successful ITI in hemophilia B. Most factor IX inhibitors occur in individuals with large or complete deletions of the factor IX gene and their development is often associated with severe allergic reactions. This unexplained and unusual immunological reaction usually precludes the successful completion of ITI and often leads to a kidney complication (nephrotic syndrome) that is almost never seen in hemophilia A. For these reasons, it is advised that ITI in such cases be performed with extreme caution and close surveillance for this problem, or not at all.

Finally, as researchers further understand how the immune system recognizes and responds to clotting factor, targeted immune modulation may ultimately become the therapeutic strategy of choice. Several such strategies are now being used in some patients with factor VIII and IX inhibitors but their overall effectiveness and safety are as yet unknown. The effectiveness and safety of one such drug, rituximab, for factor VIII inhibitors is under investigation. However, much more research must be done on how the immune system develops and eradicates these antibodies before optimum interventions can be designed.

Inhibitors: The Future

Despite the very serious nature of this hemophilia complication, there are reasons for a person with an inhibitor to be optimistic. Never has there been more interest in the problem of inhibitor development on the part both of the researcher and the physician. An intensive and cooperative research effort will eventually yield the knowledge required to treat this problem more effectively and, most importantly, to prevent it altogether.

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