The Impact of Factor VIII/von Willebrand Factor Concentrate in Inhibitor Development and Management of Patients with Hemophilia A with Inhibitors

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Abstract

The development of inhibitor antibodies that bind to active sites on the factor VIII (FVIII) molecule and neutralize its function and/or accelerate its clearance is the most serious adverse event and safety issue associated with the treatment of hemophilia A. Inhibitor development complicates hemostasis management and increases morbidity and the cost of treatment because bleeding episodes do not respond to standard replacement therapy. Risk factors for inhibitor development include genetic and non-genetic factors. Immunogenicity of the type of product used for replacement therapy may also play a role. Within the category of human-derived products, the presence of von Willebrand factor (vWF) bound to FVIII (vWF/FVIII products) may reduce its immunogenicity. The challenge for inhibitors is to reduce their incidence and, when present, to facilitate their eradication. Factor-bypassing agents have been used to treat acute bleeds in patients who have inhibitors. Immune tolerance induction (ITI) therapy is an alternative approach whose goal is to create tolerance to inhibitors and return patients to their native state. The use of ITI therapy has raised many questions, including the optimal regimen and cost. The basic science data on reduced immunogenicity of vWF/FVIII-containing products and their success in achieving ITI have given us an incentive to continue to explore this approach to both primary and secondary ITI.

Keywords

Inhibitor development, factor VIII/von Willebrand factor (FVIII/vWF) products, vWF/FVIII products, hemophilia A with inhibitors, immune tolerance induction (ITI), immune tolerance, immunogenicity, inhibitor antibodies

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Factor VIII (FVIII) and von Willebrand factor (vWF) are glycoproteins that circulate in plasma in a tightly bound complex. Structural defects or deficiencies in either glycoprotein are responsible for the development of the most common inherited bleeding disorders: hemophilia A and von Willebrand disease (vWD). These diseases manifest spontaneous bleeding in the severe form of each disease. In milder phenotypes of these disorders, bleeding occurs less often and is more often associated with trauma or surgery. In these situations, the disorder may go undetected for prolonged periods of time. The immunogenicity of replacement products for both of these diseases can lead to antibody formation, which is one of the more common and serious complications of treatment. In hemophilia, inhibitors can occur at any time, but more often develop early in therapy just a few days after exposure to factor concentrate. Inhibitor incidence has been estimated to be as high as 52% in patients with hemophilia A, and once these inhibitors occur they are often present throughout the patient's life unless eradicated. Severity of disease, ethnicity, age of the patient, genetic mutation, clinical factors, and type of product used in therapy are some of the factors that are thought to affect both the incidence of inhibitors in hemophilia A and the response of these inhibitors to therapy. Inhibitors following treatment of vWD are rare. The challenge for inhibitors is to reduce their incidence and, when present, to facilitate their eradication. Factor-bypassing products have been used to treat bleeding episodes in patients with inhibitors. However, these products are less effective than FVIII concentrates compared with their efficacy in patients without inhibitors. With factor-bypassing products, one cannot predict hemostasis; also, they are expensive. Patients treated on demand with factor-bypassing products have a poorer hemostatic response to these agents and thus have a higher morbidity from their bleeds, with chronic synovitis and earlier onset of degenerative arthritis and long-term joint arthropathy. Immune tolerance induction (ITI) therapy is an alternative approach whose goal is to create tolerance to inhibitors and return patients to their native state.

Risk Factors for Inhibitor Development

Genetic Risk Factors

The incidence of inhibitors in hemophilia patients seems to be related not only to the specific gene mutation but also to family genetic risk

factors. The development of inhibitors in patients with hemophilia A has been noted in 48% of patients with a family history of inhibitors compared with 15% of cases with no family history of inhibitors.[1] In an analysis of 249 families with hemophilia A, a concordance of 78.3% was calculated between siblings for the presence of inhibitors.[2] Inhibitor incidence in severe hemophilia A is two times higher in African-American patients than in Caucasian patients.[3,4] These propensities are believed to be influenced by both the FVIII genotype and the genetic characteristics of the immune system.

Non-genetic Factors

In addition to the genetic risk factors, there are also clinical factors that may influence the incidence of inhibitor development in patients with hemophilia A. There are conflicting data as to whether administration of factor concentrate at an early age increases the risk for inhibitors.[5,6] Intensive replacement therapy in patients with mild to moderate hemophilia,[7] continuous infusion with replacement therapy during surgery,[8,9] premature birth, lack of breast-feeding, FVIII treatment during infections, surgical procedures, use of prophylaxis prior to inhibitor development, and central nervous system bleeding have all been reported to be associated with increased inhibitor incidence. In-depth, long-term studies are needed to determine definitive correlations between these potential risk factors and the development of inhibitors.

Prevention of inhibitors would be more efficacious from both a quality of life and a cost perspective than waiting for them to develop and then attempting immune tolerance induction.

Immunogenicity of Product

The role of the type of product used for therapy—recombinant FVIII (rFVIII) versus human-derived products (HDP)—in terms of relative immunogenicity has received much attention. Within the category of HDP, the presence of vWF may well reduce its immunogenicity. Prevention of inhibitors would be more efficacious from both a quality of life and a cost perspective than waiting for them to develop and then attempting ITI. Therefore, it is important that studies are undertaken to determine whether FVIII/vWF concentrate has a lower incidence of inhibitor development than rFVIII concentrate. Data have suggested that the risk for inhibitor development is lower when FVIII/vWF concentrate is used, although this has not been confirmed.

In vitro data from Berntorp[10,11] demonstrated that vWF-containing products had less affinity with antifactor VIII antibodies. Others have corroborated these findings. The question of *in vivo* immunogenicity of HDP versus recombinant products has led to further laboratory and clinical studies. The work of Kaveri et al.[12,13] in France has repeatedly demonstrated that recombinant products have a greater affinity for antigen-presenting cells—dendritic cells—compared with vWF containing HDP. In addition, they demonstrated that antibody formation was more rigorous with recombinant products as measured by interleukin (IL)-10 formation than with vWF containing HDP. These findings were extended to demonstrate that vWF itself could modify and reduce the immunogenicity of rFVIII by pre-incubating them together in the *in vitro* system.

These observations were recently confirmed by a large clinical study by Goudemand and collaborators in France.[14] Using prospective and retrospective data, they demonstrated that previously untreated patients (PUPs) had an adjusted relative risk for inhibitor development with rFVIII versus pdVIII of 2.4 for all inhibitors and 2.6 for high-titer inhibitors. Furthermore, long-term studies are needed to evaluate the risks of the plasma-derived products and recombinant therapy.

Another research area that needs to be addressed is the importance of genetic and/or environmental risk factors that can influence the incidence of inhibitors in patients with hemophilia A. The confirmation of pre-existing risk factors for inhibitors could then identify certain hemophilia A patients whose initial factor therapy could be modified to prevent inhibitor development, thereby avoiding the need for ITI.

Inhibitor Eradication

The first report of tolerization of high-titer inhibitors in hemophilia A patients was presented by the Bonn Group, who used a high dose of FVIII: 100IU/kg given twice daily.[15] The optimum dosing regimen for ITI has yet to be determined, although an international ITI study is ongoing to answer the questions, in particular examining high- versus low-dose regimens.

Large registries of ITI patients have identified several factors that seem to affect treatment outcomes of patients with ITI.[16] ITI has been shown to be more effective in patients with a titer of fewer than 10 Bethesda units (BU) at onset of treatment and those who have not had a historical inhibitor peak of greater than 200BU. The interval between the diagnosis of the inhibitor and the initiation of ITI and the factor VIII dose used in ITI likely also play a role in the success of ITI.[17,18]

Choice of Factor Product

In 1996, Kreuz et al. published a report describing the effectiveness of monoclonal/recombinant FVIII concentrate versus plasma-derived vWF/FVIII concentrate in ITI.[19] In the study, four patients with hemophilia A experiencing no response from ITI with recombinant/monoclonal therapy were switched to ITI utilizing a vWF/FVIII concentrate. All responded well, with eradication of their inhibitors. Following this result, high-dose vWF/FVIII concentrate was administered to 21 patients with hemophilia A inhibitor patients from 1979 to 1993 with a 91% success rate and an average time to tolerance of four months.[19] This was compared with a 29% tolerance success rate for 14 hemophilia A patients treated with high-dose recombinant therapy between 1993 and 2001.[20] Similarly, a success rate of 91% in 51 hemophilia A inhibitor patients administered with high-dose vWF/FVIII concentrate was noted, in contrast to a success rate of 53% over an 11-year period in 14 hemophilia A patients treated with the rFVIII.[21] Furthermore, eight high-titer hemophilia A patients treated on a high-dose FVIII/vWF regime achieved tolerance of 85%

within eight to 12 months.[22] Recent data from Italy and Spain also suggest that the FVIII/vWF concentrate is successful in inhibitor patients with poor prognostic factors. Patients with one or more of the poor prognostic signs for treatment with ITI still had a positive outcome to FVIII/vWF concentrate treatment.[23]

These early clinical studies supported by *in vitro* data have led to an explosion of interest in HDP-containing vWF/FVIII in ITI. There has been concern over the safety of these products since the recognition of transfusion-transmitted viral diseases such as hepatitis A, B, and C, parvovirus, and HIV. With current donor-screening techniques and polymerase chain reaction (PCR) testing of viruses, these products have a stellar safety record without viral transmission since 1987.

The literature is now replete with small anecdotes, as well as larger cohorts of patients, demonstrating that HDP-containing vWF may well be a rescue product for ITI failures, and may even be effective as a first line of defense.[24] A new study associated with the international ITI study—REScue Immunotolerance STudy (RESIST)—will prospectively study this potential use.[25] In addition, it will be able to evaluate this regimen as a primary therapeutic approach to ITI. Concerns such as efficacy, time to achieve tolerance, and relative costs of this versus recombinant products will be evaluated.

Whether ITI is carried out in countries with total coverage provided by the government or in those with pluralistic third-party payer programs such as in the US, high- or low-dose ITI is costly.[26] Choosing the optimal patient, ideal regimen, and appropriate product is critical to assure tolerance in the shortest period of time, with the fewest complications, and with the use of the smallest amount of factor product. As prospective studies are undertaken, guidelines for ITI will be developed. These guidelines will subsequently make therapeutic choices simpler for healthcare providers treating hemophilia patients with inhibitors.

Conclusion

Inhibitor formation remains one of the greatest challenges for hemophilia patients and their healthcare providers. The eradication of these inhibitors using ITI is effective therapy, but its use has raised many questions, including the optimal regimen and cost. The basic science data on reduced immunogenicity of FVIII/vWF-containing products, and their success in achieving ITI, have given us the incentive to continue to explore this approach to both primary and secondary ITI. ■

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