Injecting humans with human proteins is generally innocuous, but clinicians and investigators have long known that repeated administration of virtually any human protein almost always results in an immune response that often complicates treatment. Such is the case in the administration of insulin, gamma globulin, albumin, or factor VIII.

The development of factor VIII (FVIII) inhibitors has been, next to HIV and hepatitis, the most serious complication of hemophilia therapy. Although the recent production of highly purified and genetically engineered FVIII products has dramatically decreased or even eliminated the risk of these infections, the development of inhibitors remains a major therapeutic challenge. Because affected patients, usually children, are rendered resistant to conventional replacement therapy, control of hemostasis becomes difficult, resulting in substantial morbidity.

Inhibitors are IgG antibodies, mostly of the IgG4 subclass, that react with FVIII and interfere with its pro-coagulant function. They are present in up to 20% of patients with severe hemophilia A (1–3), and recent surveys estimate that the cumulative risk of inhibitor development may be as high as 30% by the age of six (4–7). Clinically, patients with inhibitors are classified into high and low responders according to the strength of the anamnestic response they experience when they are re-exposed to FVIII. The goals of therapy in these patients are to control severe acute bleeding and to eradicate the inhibitor.

One approach to dealing with the production of antibodies to “self” is the administration of high doses of the “offending” material, generally intravenously, with the hope of inducing some form of tolerance, such that further administration of therapeutic amounts of protein are practical again. The induction of tolerance as a method to suppress and/or eliminate FVIII inhibitors was first reported in 1977 by Brackmann and Gormsen, who advocated the use of large doses of FVIII in association with activated prothrombin complex concentrates (APCCs) (8). Despite considerable success, the almost prohibitive cost of this therapy led to the design of alternative approaches, including lower dosages of FVIII, immunosuppressive drugs, high doses of IVIG, or combinations of the above (for reviews see references 9 and 10). A recent survey from the International Haemophilia Registry involving 40 centers from the USA, Canada, Europe, and Japan, evaluated tolerance induction among patients treated with different dosages of FVIII. This study showed that two variables were independently associated with the highest probability of success: the use of high dose protocols, and the presence of low levels of inhibitors at the time of enrollment. Additionally, the survey confirmed that, once achieved, tolerance to FVIII is long-lasting: only one out of 107 patients relapsed, and the longest documented tolerant patient was inhibitor-free for 16 years (11).

It has been known for some time that hemophilia patients maintain detectable levels of circulating antibodies to FVIII once tolerance is achieved (12). However, since the sera of tolerant patients lack coagulation inhibitory activity and display normal rates of elimination of FVIII, these anti-FVIII antibodies were thought to be different from those found in pretolerant sera. Either, a decrease in affinity for FVIII, and/or a switch toward the recognition of FVIII epitopes different from those located within the functionally active sites of the molecule could explain this phenomenon.

In this issue of The Journal, Gilles et al. confirm the presence of anti-FVIII antibodies in the sera of hemophilia patients before, during, and after the administration of high doses of FVIII. Interestingly, these authors report that the epitope specificity and functional characteristics of these antibodies remain unchanged in the tolerant compared to the pretolerant sera (13). They also show that clinical recovery, or achievement of tolerance, is associated with the development of anti-inhibitors (idiotypes), i.e., antibodies that react with variable region determinants expressed on anti-FVIII antibodies and neutralize their FVIII inhibitory capacity.

The existence of a suppressor or neutralizing idiotypic network encompassing FVIII and anti-FVIII antibodies was reported by Sultan et al. in 1987. These authors studied the sera of nonhemophilic patients with FVIII inhibitors generated in the context of an autoimmune disease and found detectable levels of anti-idiotypic antibodies at the time of clinical recovery. Interestingly, none of the patient’s sera shared cross-reactive idiotypes, suggesting individual variation in either the FVIII epitopes responsible for triggering the autoimmune response and/or the repertoire of variable region genes encoding anti-FVIII antibodies (14). The previous observation by the same authors that pooled human IVIG contained anti-idiotypic specificities was then used to explain the beneficial effect achieved with this modality of therapy in autoimmune patients (15). Alloresponses triggered by FVIII replacement therapy in hemophilia patients, however, are only partially controlled by infusing high doses of IVIG alone. Additionally, these patients are rendered “clinically tolerant” while boosting their immune systems with high doses of alloantigen. The observation by Gilles et al. that “tolerant” hemophilia patients continue to secrete anti-FVIII antibodies similar to those from the pretolerant state reminds us that the immune system is not programmed to silence and/or delete B cells responsible for reacting against non-self, even if, as in these patients, these cells secrete censurable antibodies.

Several questions remain to be addressed. The role of an anti-idiotypic network in the neutralization of anti-FVIII antibodies needs to be validated, for example, by studying patients that fail to respond to the desensitization approach. Finally, the variety of inhibitor-recognized epitopes in FVIII (16–18) makes it less likely that we will be able to generate clinically relevant anti-idiotypic reagents to treat these patients. Manipulating the immune system with immune complexes containing FVIII and autologous antibodies, as proposed by Gilles et al., may be a solution. Randomized clinical trials will be necessary, though, to help clinicians reach conclusions.
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References