How I treat

How we treat a hemophilia A patient with a factor VIII inhibitor

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The most significant complication of treatment in patients with hemophilia A is the development of alloantibodies that inhibit factor VIII activity. In the presence of inhibitory antibodies, replacement of the missing clotting factor by infusion of factor VIII becomes less effective. Once replacement therapy is ineffective, acute management of bleeding requires agents that bypass factor VIII activity. Long-term management consists of eradicating the inhibitor through immune tolerance. Despite success in the treatment of acute bleeding and inhibitor eradication, there remains an inability to predict or prevent inhibitor formation. Ideally, prediction and ultimately prevention will come with an improved understanding of how patient-specific and treatment-related factors work together to influence anti–factor VIII antibody production. (Blood. 2009;113: 11-17)

Introduction

Hemophilia A (HA) is an X-linked congenital bleeding disorder resulting from a deficiency of factor VIII (fVIII). Therapy to prevent or treat bleeding is replacement of fVIII. The availability of purified plasma-derived and recombinant fVIII products has led to dramatic improvements in the health and well-being of many affected by HA. However, as a consequence of treatment patients with HA may develop inhibitory IgG antibodies to fVIII, termed inhibitors. Inhibitors bind fVIII and prevent its hemostatic action. When this occurs, treatment becomes more costly and morbidity increases. Inhibitor formation, occurring in up to 36% of patients with severe HA,[1,2] is currently one of the most significant complications affecting patients with HA.

Despite understanding several well-established risk factors for inhibitor development (Table 1), why some patients develop an inhibitor and others do not remains unclear. This lack of clarity is likely a consequence of the complex interplay between host genetic factors and the circumstances that surround the delivery of fVIII. In this review we will discuss the detection of inhibitors, the current understanding of why inhibitors develop, and management of patients with inhibitors during acute bleeding and long-term inhibitor eradication. Our discussion will focus on HA.

How are inhibitors detected?

Inhibitors should be suspected when there is a lack of response to fVIII infusion as a result of poor recovery, shortened half-life, or inadequate clinical response. When an inhibitor is suspected, testing using a Bethesda inhibitor assay (BIA) should be performed. It is also generally accepted that inhibitor screening should occur before invasive procedures and at regular intervals during the initial 50 treatment days as this is the highest risk period for inhibitor development.[1] After a patient has received factor for 150 treatment days, the rate of inhibitor development is substantially reduced.[3] Although rates of detection are low with routine surveillance in those with greater than 150 treatment days, we recommend annual testing to facilitate postmarketing surveillance by the Centers for Disease Control and Prevention Universal Data Collection (UDC) Project and other national surveillance programs.[4]

The BIA consists of incubating a 1:1 mixture of a dilution of the patient's plasma with undiluted normal plasma for 2 hours, followed by assay of residual fVIII activity.[5] The control incubation consists of a 1:1 mixture of the buffer diluent and undiluted normal plasma. The inhibitor titer is the reciprocal of the dilution of inhibitor plasma that neutralizes 50% of fVIII activity in the normal plasma. Inhibitor titers that are less than 5 BU/mL are considered low titer, whereas those that are equal to or greater than 5 BU/mL are considered high titer. A low-responding inhibitor is one in which the titer remains less than 5 BU/mL despite repeated fVIII infusions and, once it is equal to or greater than 5 BU/mL at any time, it is considered high responding.[6] In the absence of fVIII exposure, high-responding inhibitors may decrease and may even become undetectable. Classically, when these patients are re-exposed to fVIII, their titer will increase over 4 to 7 days. This response is called anamnesis and is a hallmark of a high-responding inhibitor. However, we have rarely observed patients with historically high-responding inhibitors but who have had an undetectable titer for years who do not have anamnesis upon re-exposure to fVIII. Low-titer inhibitors comprise 25% to 50% of observed inhibitors and approximately 10% of these are considered transient, disappearing over weeks to months despite continued treatment with fVIII.[7-10]

Why do inhibitors develop?

Why some patients develop inhibitors is poorly understood. The inability to predict inhibitor development may reflect the complexity of interactions involved in an immunologic response to a foreign protein. Tolerance allows the differentiation of self from nonself, and in the absence of sufficient protein to produce tolerance, patients with hemophilia will recognize infused clotting factor as nonself. The propensity to develop an inhibitor is likely influenced by congenital or acquired variances at

Table 1. Hypothesized risk factors for inhibitor development

Patient-related	Treatment-related
Race	Number of fVIII exposure days
Family history	Age at first exposure to fVIII concentrates
fVIII mutation	Type of fVIII concentrate used
MHC class	Concurrent infection/inflammatory state
Polymorphisms of immune-response genes (IL10, TNF, CTLA4)	Intensive exposure to fVIII concentrates

multiple steps in this cellular immune cascade that begins with antigen uptake by antigen presenting cells and ends with antibody production (Figure 1).

What patients are at risk for inhibitor development?

Genetic risk factors

The best characterized risk factor is the type of fVIII mutation that underlies hemophilia. Mutations that are associated with a high prevalence of inhibitors include null mutations, large deletions, nonsense mutations, and intron 22 inversions (Table 2).[11]

The type of fVIII mutation may also influence the titer of inhibitor. Oldenburg et al[12] found that 68.8% of those with large deletions had high-titer inhibitors compared with only 21.2% with missense mutations, and 30% to 40% with all other mutation types.

Despite the strong influence of fVIII genotype on inhibitor development, it is not adequately predictive for clinical purposes.[13-15] Studies investigating the role of major histocompatibility complex (MHC) class II alleles in inhibitor development have suggested a weak association (Table 3).[16-20] Astermark et al[21-23] evaluated the effect of polymorphisms in immune response genes on inhibitor development (Table 3). The association of these polymorphisms with inhibitor formation strongly suggests that, in addition to a lack of self-tolerance to fVIII, individual variation in the immune response to foreign antigen influences the risk of developing an inhibitor in patients with severe HA. The interplay between molecular defect and immune response genes has been discussed.[24]
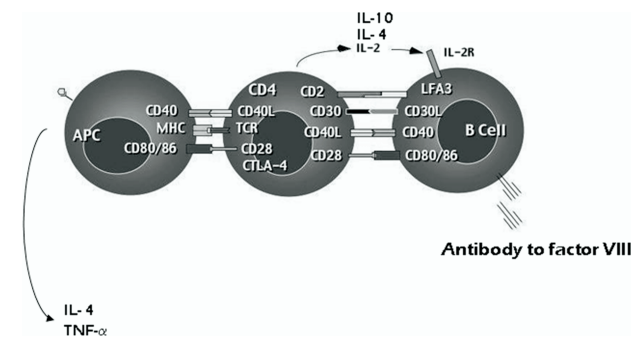

Figure 1. MHC class II cellular immune cascade. Exogenous peptide antigens such as fVIII are processed through MHC class II mechanisms. Antigen-presenting cells take fVIII into endocytic vesicles where it is bound to an MHC class II molecule. Bound peptides are then presented on the surface of the cell to specific T-cell receptors (TCR) on CD4+ T lymphocytes. In response to antigen presentation, T lymphocytes elaborate cytokines and up-regulate several surface molecules. These surface molecules interact with corresponding proteins on B lymphocytes, leading to maturation of B cells and antibody formation. APC indicates antigen-presenting cell; CD4, CD4+ T lymphocyte; B cell, B lymphocyte; MHC, major histocompatibility complex; TCR, T-cell receptor; CD, cluster of differentiation; IL, interleukin. Copyright G.C. White II.

Table 2. FVIII mutations and inhibitor prevalence in all severities of hemophilia A[69,70]

Mutation	Relative incidence, %	Inhibitor prevalence, %
Large deletions	3.0	41
Multidomain		88
Single domain		25
Nonsense mutations	9.3	31
Light chain		40
Heavy chain		17
Intron-22 inversion	35.7	21
Small deletions	10.2	16
Missense	38.2	5
C1/C2 domain		10
Non-C1/C2 domain		3
Splice site	2.4	17

Relative incidence is given for each mutation type and subtype, along with the prevalence of inhibitor development in patients with that mutation type or subtype.

Treatment-related risk factors

Although the influence of both fVIII and immune response genes is compelling, treatment-related variables may also play a role, as evidenced by the discordance in inhibitor development between monozygotic twins.[14]

In 3 small cohort studies, the rate of inhibitor development was greater in those who received their first fVIII infusion before 6 months of age.[25-27] However, in a larger cohort, the effect of age disappeared after adjustment for confounding variables.[28] Thus, age at first infusion is likely a surrogate for severity of disease leading to the requirement for early intensive therapy. Accordingly, necessary treatment should not be altered to avoid fVIII infusions at a young age.

It has been proposed that inhibitor development can be influenced by the circumstances in which fVIII is used (Table 4). In a cohort of previously untreated patients (PUPs), 65% of those in which surgery was the first indication for fVIII developed an inhibitor compared with approximately 23% in those with other indications for first treatment.[15] In those who received 5 or more consecutive days of fVIII at the time of their first exposure, 56% developed an inhibitor, compared with 19% in the group that received fewer than 3 consecutive days of fVIII. However, this was not adjusted for the indication for treatment. In contrast, those who received regular prophylaxis (at least once weekly) had a reduced risk of inhibitor development.

The differential influence of the indication for fVIII concentrates (prophylaxis vs surgery) may reflect how the environment can influence antigen presentation to T cells. Injury or inflammation at the time of fVIII exposure has been hypothesized to send "danger" signals. In the danger model, distressed cells send alarm signals that activate antigen-presenting cells (APCs), further amplifying immunologic responses.[29] Although the danger model may apply to the overall result of the CANAL study,[15] approximately 20% of subjects still developed an inhibitor in the absence of circumstances that could be associated with these danger signals,

Table 3. Non-fVIII genes associated with inhibitor formation

Gene	Reference	Severe hemophilia A OR (95% CI)	All hemophilia A OR (95% CI)
DQA0102	20	2.7 (1.2-5.9)	
IL10 allele 134	22	5.4 (2.1-9.5)	4.4 (2.1-13.7)
TNF-a −308 A/A genotype	21	19.2 (2.4-156.5)	4.0 (2.1-13.7)
CTLA4 −318 T allele	23	0.3 (0.1-0.8)	

Table 4. Treatment-related risk factors for inhibitor development

Risk factor	Relative risk	95% CI
Age at first infusion < 6 months of age vs > 12 or 18 months	1.8[28]	0.7-4.7
	1.7[27]	1.3-1.9
Surgery at first infusion vs treatment of a bleed at first infusion > 5 days of treatment at first infusion vs < 2 days	2.6[28]	1.3-5.1
	3.3[28]	2.1-5.3
Prophylaxis vs no prophylaxis	0.4[28]	0.2-0.8
	0.2*[71]	0.06-0.5
Plasma-derived product vs recombinant product	2.4[27]	1.0-5.8
	0.8[32]	0.5-1.3

*Odds ratio.

whereas still others did not develop an inhibitor despite the presence of danger signals.

Some have questioned whether the method of delivery of fVIII concentrates influences inhibitor formation. In a retrospective study of patients with mild HA who had received 6 or more consecutive days of factor, inhibitors developed more frequently in patients receiving continuous infusions compared with bolus injections (57% vs 0%).[30] In another retrospective study, after approximately 250 cumulative episodes of treatment with fVIII by continuous infusion, 10 patients developed an inhibitor, 5 of which had nonsevere disease.[31] Although these studies are interesting, given their study designs it is difficult to base practice on their findings. At this time, we continue to prefer continuous infusion for major surgery because it avoids trough fVIII levels that may place the patient at immediate risk of bleeding. Furthermore, desmopressin should be used when appropriate in those patients with mild HA who have a confirmed response after desmopressin challenge to limit exogenous fVIII exposure.

It has also been suggested that the type of product may influence inhibitor development (Table 4). In a retrospective cohort of 148 PUPs with severe HA, after adjustment for mutation, ethnicity, family history, and age at first infusion, recombinant fVIII concentrates appeared to convey a small risk of inhibitor formation.[27] However, there was no adjustment for the impact of prophylactic therapy or surgery at the time of first infusion, which may further influence the strength of the association. In a cohort of 316 subjects, Gouw et al found that there was no association between the type of product used and inhibitor development.[32] In addition, since the rate of nontransient inhibitor development in prospective trials of new recombinant products was similar to studies using plasma-derived products[33,34]; and inhibitor formation is rare in previously treated patients who are switched to recombinant products[33,35,36]; we believe the overall weight of the data suggests that there is no association between the type of fVIII product and inhibitor formation. Thus, we do not consider the risk of inhibitor formation when selecting a fVIII product to use for an individual patient.

These studies designed to associate treatment conditions with inhibitor development are interesting, but until the genetic factors that underlie inhibitor development are better understood and can be used to properly stratify patients, the association between how fVIII is delivered and inhibitor formation will be hard to define.

How do we treat patients with an inhibitor?

Treatment of acute bleeding

When an inhibitor is first detected, if it is low titer, patients may continue to respond to fVIII replacement with minimal change in the fVIII dose. Such low-titer inhibitors can be observed, as some will resolve spontaneously. Above approximately 5 BU/mL, an inhibitor renders fVIII replacement ineffective and treatment of bleeding episodes requires "bypassing" the deficient clotting factor. Currently available agents include recombinant activated factor VII (rfVIIa; Novoseven; NovoNordisk, Bagsvaerd, Denmark), and FEIBA VH (Baxter, Deerfield, IL). rfVIIa is produced using baby hamster kidney (BHK) cells expressing the cloned human factor VII gene. A new formulation of rfVIIa, Novoseven RT, contains sucrose and L-methionine to allow extended storage at room temperature before reconstitution. rfVIIa facilitates hemostasis by activating factor X directly on the platelet surface thereby bypassing the tenase complex.[37] The half-life is 2.3 hours in adults but potentially shorter in children.[38] Attempts to protein engineer rfVIIa to have a longer circulation time are currently underway.[39,40] FEIBA VH is a vapor-heated concentrate of plasma-derived vitamin K–dependent clotting factors (factors II, VII, IX, and X and others) in both zymogen and active forms. The mechanism of action is multifactorial, though prothrombin and factor X are thought to be critical components.[41] rfVIIa and FEIBA VH have similar efficacy and rates of thrombosis; however, in a prospective randomized comparison of rfVIIa and FEIBA VH, approximately 30% of subjects responded more favorably to one product or the other 6 and 12 hours after treatment.[42] To better tailor treatment in individual patients some have looked to thromboelastography and endogenous thrombin potential. Unfortunately, clinical studies linking these tests with clinical outcomes are lacking[7,43]; therefore, treatment with rfVIIa and FEIBA VH must be adjusted according to clinical outcomes rather than laboratory testing results.

Since rfVIIa is a recombinant product and has no potential for anamnesis to fVIII (small amounts of fVIII can be found in FEIBA VH),[44] we favor the initial use of rfVIIa as a bypassing agent for acute management of bleeding episodes in patients with inhibitors that no longer respond to fVIII. For typical joint bleeds we begin treatment with standard doses, 90 to 120 mcg/kg rounded up to the nearest vial size, given every 2 to 3 hours. This approach in a prospective clinical investigation was effective in 92% of treated bleeds after a mean of 2.2 injections.[45] Target joints are more difficult to treat; therefore, based on a randomized trial that demonstrated equivalent efficacy and safety of a single dose of 270 mcg/kg and 3 doses of 90 mcg/kg,[46] it is reasonable to use 270 mcg/kg for treatment of target joint bleeds. In addition, a single high dose may be preferred to standard dosing in patients with poor venous access. But since a single treatment may be effective in up to 40% of patients when initiated early and for bleeding in nontarget joints, we do not use the high dose in all patients.[47] In the setting of limb or life-threatening bleeding, we begin treatment using at least 120 mcg/kg every 2 hours. Higher initial doses (up to 300 mcg/kg rfVIIa) have also been used in this setting with no

untoward effect and should be considered if an adequate clinical response is not achieved using 120 mcg/kg. Once hemostasis is achieved, treatment can be tapered by extending the interval between doses or reducing the dose if high doses are used.

When patients fail to respond to rfVIIa, FEIBA VH should be tried as a single agent.[42] FEIBA VH can be used at doses of 50 to 100 U/kg given every 8 to 12 hours, but should not exceed 200 U/kg per day. Lower doses (50-75 U/kg) are used for routine joint bleeds, whereas higher doses (100 U/kg) are given for severe limb or life-threatening bleeding. The use of alternating rfVIIa and FEIBA VH in patients refractory to either alone has been reported to be effective,[48] but should be done under careful supervision with attention paid to dose, frequency, and thrombin activation because of the risk for thrombosis.

Alternative approaches for acute bleeding management include porcine fVIII, high-dose human fVIII, and antibody removal by immunoadsorption or plasmapheresis followed by fVIII infusion. Since inhibitors have variable and limited cross reactivity with porcine fVIII, it can be used as a replacement clotting factor. Currently, porcine fVIII is not available in the United States; however recombinant porcine fVIII is in development. High-dose fVIII can also overcome inhibitors in those with a titer less than 5 BU/mL, but may lead to anamnesis in those with a high responding inhibitor. However, under life-threatening circumstances, the benefit of a therapeutic fVIII level, although short-lived, outweighs the subsequent risk of anamnesis. Dosing algorithms in this setting have little scientific basis and have not been validated. In the absence of a rational and validated approach, we use the following formula to estimate the amount of fVIII needed as a loading dose to neutralize the inhibitor [body weight (kg) × 80 × [(1-hematocrit) × antibody titer (BU/mL)] and add an additional 50 IU/kg above the calculated loading dose to achieve a measurable fVIII activity. fVIII levels should be measured 15 minutes after completion of the bolus, and adjustment to reach target levels is necessary because there is substantial individual variation.

As with those with HA without an inhibitor, management of bleeding requires a multidisciplinary approach. After joint or muscle bleeding, physical therapy to facilitate maintenance of range of motion and strength is imperative.

Perioperative management of hemophiliacs with inhibitors

Because of an inability to reliably achieve and monitor hemostasis, surgery in patients with hemophilia A complicated by a high-responding inhibitor should be undertaken with caution. Although there are no comparative clinical studies, both rfVIIa and FEIBA VH can be used for the management of hemostasis in the surgical setting. When choosing which product to use for an individual patient, the product that leads to the best treatment response for acute bleeding is the product to use at the time of surgery. rFVIIa can be used either as continuous infusion or bolus injection. In clinical studies, no differences have been found between these 2 approaches, though the studies were small and underpowered.[49] In the absence of clinical data to guide decision making, we prefer to use bolus dosing as it is our opinion that the burst of thrombin generation achieved with bolus dosing is important for hemostasis. Similarly to treatment of severe bleeding, 90 to 120 mcg/kg rfVIIa is given every 2 hours for the first 48 hours. Treatment is then tapered by increasing the interval between doses to complete a course of treatment. As with management of HA patients without an inhibitor, longer durations are needed for major surgery, whereas short durations (1-3 days) are adequate for invasive procedures and minor surgery. If FEIBA VH is used, major surgery requires higher doses (200 U/kg per day) for the first 2 to 4 days which are then tapered over the subsequent days to complete a course of treatment. For minor surgical procedures,

such as placement of central venous access device, less intensive therapy (150 U/kg per day) can be used and treatment limited to 3 days.[50] Disseminated intravascular coagulation (DIC) has been reported to occur at doses greater than 200 U/kg per day and with more extended treatment courses. In these instances, fibrinogen, and d-dimer should be monitored to detect the onset of DIC.

Prevention of bleeding in hemophiliacs with inhibitors

The benefit of prophylactic therapy in hemophiliacs without an inhibitor has led many to consider prophylactic infusions of bypassing agents in hemophiliacs with an inhibitor.[51] A clinical trial compared the frequency of joint bleeds during a pretreatment observation period and treatment period of 3 months during which patients were randomized to rfVIIa 90 mcg/kg per day or 270 mcg/kg per day.[52] Both regimens led to a reduction in bleeding frequency and improvements in health-related quality of life.[52,53] The ongoing ProFEIBA study is a randomized crossover evaluation of the use of FEIBA VH, 85 U/kg 3 times per week, over a 6-month period. Although bypassing agents may reduce bleeding frequency leading to fewer missed days from work and improved quality of life, whether prophylaxis can improve joint health or reduce the rate of joint deterioration in inhibitor patients is unknown and will likely require additional clinical trials. Factors to consider when deciding whether to use rfVIIa or FEIBA VH prophylaxis includes: frequency of infusions, volume of infusion, cost, and anamnestic response. We prefer to use rfVIIa for prophylaxis in those that are planning to undergo immune tolerance induction (ITI) to avoid the small risk of anamnesis and FEIBA prophylaxis in those that are currently on ITI, are not planning on starting ITI, or have failed ITI to limit the number of infusions. Regardless of the product used, the frequency and dose should be adjusted to find a regimen that is practical, financially feasible, and effective. When to start prophylaxis is subjective since what is considered frequent bleeding will vary significantly among patients. In general, when bleeding is perceived to be interfering with the patient's activities and quality of life, prophylaxis should be considered.

Radionucleotide synovectomy (RNS) is an alternative or adjunctive approach to prophylaxis in the setting of recurrent joint hemorrhage. RNS should be considered in patients with recurrent hemorrhage in a target joint that has evidence of synovial hypertrophy, ideally before significant bone or cartilage damage has been done.

Long-term eradication of inhibitory antibodies

Immune tolerance can be achieved in approximately 70% of patients who receive regular and prolonged infusions of fVIII with or without immune modulation.[54,55] Despite the development of multiple ITI protocols since its inception in the 1970s (Table 5), the mechanism of tolerance induction and the best means to achieve tolerance remains unknown. Proposed mechanisms of tolerance development include clonal deletion, anergy or ignorance, induction of suppressor T cells and synthesis of anti-idiotype antibodies.[56,57]

Data on parameters influencing the success of ITI has been gained from single institutions using a standard approach or from registries. In both the North American Immune Tolerance Registry (NAITR) and the International Immune Tolerance Registry (IITR), the pretreatment inhibitor titer (< 10 BU/mL) and the maximum historical titer (< 200 BU/mL) predicted successful ITI.[54,55] In contrast to inhibitor titer, the 2 registries have found conflicting importance of daily dose. In the IITR, patients receiving more than 200 IU/kg per day had the most favorable outcome whereas the

Table 5. Immune-tolerance induction protocols

Bonn protocol[72]	Malmo protocol[63]	Van Creveld[73]
fVIII 100 U/kg BID	Immunoadsorption using	Factor VIII 25-50 IU/kg
FEIBA 100 U/kg BID	protein A column if inhibitor titer >10 BU/mL	BID for 1-2 weeks, then 25 IU/kg every other day
	Cyclophosphamide 12-15 mg/kg IV daily × 2 days then 2-3 mg/kg PO daily × 8-10 days	
	FVIII is given to achieve a 40%-100% fVIII level followed by fVIII infusion every 8-12 hours to achieve 30%-80% level	
	IVIG 2.5-5 g IV immediately after the first fVIII infusion followed by 0.4 g/kg daily days 4-8	

NAITR found an inverse correlation between fVIII dose and success rate. However, lower doses required a longer duration to achieve tolerance. Accordingly, the optimal dosing scheme of fVIII for ITI is unclear. Currently, there is an ongoing International Immune Tolerance Trial comparing 200 IU/kg per day with 50 IU/kg 3 times per week in children with HA and high titer inhibitor (> 5 BU/mL).[58] Outside of a clinical trial, we favor using higher doses of fVIII (100 IU/kg per day) to achieve tolerance in the shortest possible time. However, in patients who are reluctant to do daily venipuncture and wish to avoid placement of a central venous access device, 3 times per week treatment can be considered and may be successful.

The type of fVIII product to use during ITI is also debatable. Some have observed a higher success rate when fVIII products containing VWF are used.[59,60] Some patients who did not respond to ITI with high-purity or recombinant fVIII products have subsequently responded to intermediate purity fVIII products containing VWF.[61] However, this observation has not been studied in a prospective, controlled fashion. Given the lack of compelling evidence for one product type over another, we use the product that the patient was using at the time of inhibitor development.

It is our practice to consider ITI in all patients with a newly diagnosed inhibitor and in adults with a long-standing inhibitor that have not previously received ITI. The latter is particularly important in the adult patient if a surgical procedure is necessary, has developed a serious bleed necessitating the use of fVIII, or has frequent bleeding with a marginal response to bypass therapy. Although tolerance is less likely to be achieved in patients with a longstanding inhibitor or with a historical inhibitor titer more than 200 BU/mL, we do not consider these exclusion criteria. In patients with a newly diagnosed inhibitor in which the inhibitor titer is greater than 10 BU/mL before starting ITI, we use bypassing agents (preferably rfVIIa) until the inhibitor is less than 10 BU/mL.[44] Ideally, once the inhibitor titer is less than 10 BU/mL, ITI is initiated without delay. However, because of the high degree of commitment required, not all patients and families are suitable to begin ITI at the time a nontransient inhibitor is diagnosed. In these cases, education accompanied by planned initiation for a later date, preferably within 5 years, is an appropriate alternative approach. Successful tolerance is defined as a titer of less than 0.6 BU/mL, a recovery greater than 66% of normal, and a half-life of fVIII of more than 6 hours.[62] When to consider someone an ITI failure is difficult and needs to be assessed individually. Some physicians suggest that the likelihood of success is not clinically meaningful if tolerance has not been achieved after 2 years of ITI. In the Immune Tolerance Trial, failure is defined as a lack of a 20% decrease in the inhibitor titer over a 6-month period or a lack of tolerance by 33 months. Although both of these definitions can be helpful in understanding when failure may occur on a population basis, individual patient failure should be determined within the context of that patient's clinical course. We favor continuing ITI if a patient is continuing to make progress and tolerating therapy, even if there is less than a 20% decrease over

a 6-month period. In addition, we favor continuing ITI in patients who achieve a detectable fVIII level and/or a favorable clinical response (decreased bleeding frequency) despite a persistently positive inhibitor titer or abnormal recovery.

Since the development of alloantibodies depends on the immune system, it has been postulated that modulation of the immune system can improve response rates to ITI. Immune modulation, although part of the Malmo protocol,[63] is not routinely used in other ITI protocols. Early approaches include intravenous immunoglobulin, cyclophosphamide, corticosteroids, and immunoadsorption. In the NAITR, 40% of patients received at least one of these methods of immune modulation without impact on outcome.[54] More recently, the combination of rituximab (Rituxan) and ITI has been reported to be successful in several patients who had previously failed ITI alone.[64-68] A prospective investigation of rituximab in HA inhibitor patients is ongoing. We do not use immune modulation in ITI.

Conclusions

The development of inhibitory antibodies in patients with HA remains a major complication of therapy. Important areas for ongoing research include (1) improving our understanding of why some develop inhibitors to facilitate better risk assessment; (2) developing alternative factor products with reduced immunogenicity or other therapeutic modalities to prevent inhibitor formation that can be used in patients at high risk for inhibitor development; and (3) improving our understanding of factors necessary for successful immune tolerance therapy, specifically which patients will and will not benefit from ITI and which treatment regimen will provide the highest success rate. With better understanding of the factors involved in the immune response to fVIII, inhibitor development in HA will become predictable and avoidable and more targeted approaches to inhibitor treatment will be feasible.

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Authorship

Contribution: C.L.K. and G.C.W. wrote the paper and are responsible for its content, style, and composition.

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