Inhibitor Development

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INTRODUCTION

Individuals with hemophilia are deficient in one of the clotting factor proteins that are vital in the formation of a clot. Classic hemophilia or hemophilia A is a deficiency of factor VIII, while Christmas Disease or Hemophilia B is a deficiency of factor IX. The deficiency of one of these proteins comes about because of a mutation on the X chromosome. Patients with either type of hemophilia are at risk for prolonged bleeding. In order to prevent complications that result from prolonged bleeding, replacement of the deficient protein is currently the recommended treatment. Some patients with hemophilia develop antibodies as a complication of their disease. These antibodies to factor VIII or IX are called "inhibitors." Inhibitors neutralize the administered clotting factor treatment so that bleeding does not stop. Inhibitors arguably represent the most significant risk factor for morbidity and mortality associated with hemophilia, and patients with inhibitors present complex patient management challenges.

The prevalence of inhibitors is defined as the proportion of patients with inhibitors at a specific point in time. The prevalence of inhibitors is thought to be about 5-7%. The incidence of inhibitor development is defined as the number of new cases in a specific period of time. The incidence of inhibitors in individuals with hemophilia A is estimated to be as high as 33%, but only 1-6% in patients with hemophilia B. (1) The reason for the difference between prevalence and incidence has to do with the disappearance of many transient low-titer inhibitors and successful tolerization of others. (2)

While inhibitors are more common in factor VIII deficiency, they are more clinically significant in factor IX deficiency because many patients with Factor IX inhibitors develop anaphylactoid reactions to factor IX during or shortly after an infusion and then go on to have measurable antibody titers to factor IX. (3) Management of inhibitors to factor IX will be discussed separately at the end of this chapter because of their unique challenges.

UNDERSTANDING THE IMMUNE SYSTEM

In order to understand inhibitor development, it is necessary to have a basic understanding of the immune system. The immune system is designed to distinguish between "self" and "non-self" and to make antibodies to "non-self" proteins so that they can be removed from the circulation to prevent further damage or disease. Thus, it stands to reason that individuals who do not make certain proteins would be at risk for developing antibodies to foreign proteins that are infused. Therefore, it is not surprising that most inhibitors occur in patients with severe disease who have

less than 1% factor activity. However, inhibitors can develop in patients with moderate and mild disease. This further highlights the complexity of inhibitor development. Inhibitors in mild disease will be addressed separately towards the end of the chapter.

RISK FACTORS FOR INHIBITORS

Inhibitors tend to occur early in life, often in the first 10-20 infusions, but can occur at any point. Later in life, inhibitors are often associated with significant exposure to factor because of a traumatic injury or surgical challenge. (4)

AGE

There are a number of known risk factors associated with the development of inhibitors. As previously noted, the vast majority (73%) of inhibitors are identified within the first 10-20 exposure days to factor concentrates. (4) While it is known that most inhibitors develop within the first 10-20 exposure days, the association with age is unclear. There has been a suggestion that early exposure to factor concentrates is associated with a higher risk of inhibitor development. However, it is dubious to assume that age is an independent risk factor for inhibitor development. Instead, subsequent studies suggest that the inhibitor development may be related to challenges to the immune system including infection, immunizations, bleeds and other challenges that stimulate the immune system, thus activating and stimulating cytokines which may contribute to inhibitor development. (5)

Investigators performed a retrospective, multicenter, cohort study (CANAL) to delineate the relationship between inhibitor development and risk factors. They noted that exposure to factor at a young age was associated with increased risk of inhibitor development, but when they adjusted for the intensity of treatment, this association disappeared. The investigators found that surgical procedures and intensive treatment were associated with increased risk of inhibitor development. They theorized that this association might be explained by tissue damage and inflammation causing release of danger signals from injured cells. If their theory is correct, the infusion of factor VIII or factor IX early in life in the absence of these danger signals may actually prevent the development of inhibitors. In the CANAL cohort, the theory was supported by their finding that regular prophylaxis was associated with a 60% lower risk of inhibitor development. (6) However, the RODIN cohort failed to replicate this finding. The reduction in the inhibitor rate in this cohort was only seen after the first 20 exposure days and was more notable in low risk mutations. (7)

GENETIC MUTATIONS

Age is not the only factor considered to play a role in the development of inhibitors. Patients with significant gene rearrangements or other mutations have a higher incidence of inhibitor development. Most of these mutations are more common in severe disease. (4) The CANAL cohort confirmed previous reports of increased risk for inhibitor development with intron 22 inversion as well as with nonsense mutations and large deletions. (6) However, there are patients with mild and moderate hemophilia who develop inhibitors, and most mutations are located in the A1-A3 domain where there is a conformational change in the factor VIII protein. (4)

Given the association of inhibitor development with specific mutations, it stands to reason that individuals in a family who share the same mutation would have the same risk of inhibitor development. However, studies of sibling pairs noted concordance in only 73% of the families, which highlights the fact that there are additional factors that play a role in the development of inhibitors. (4)

OTHER GENETIC FACTORS

There seem to be other genetic factors that play a role in inhibitor development. For example, there is a significantly higher rate of inhibitor development in non-Caucasian patients. The rates of inhibitor development are notably higher in African-American, Asian, and Hispanic patients in particular, despite the fact that the mutations are the same across all ethnic groups. There has been increased understanding of the role that polymorphisms in the immune system play in inhibitor development. Investigators are focusing on the role of specific genes in the immune response including major histocompatability complex (class II), tumor necrosis factor, interleukin 10, and cytotoxic T lymphocyte 4. (8)

INTENSITY OF TREATMENT

While the majority of patients who develop inhibitors have severe disease, patients with mild and moderate hemophilia can also develop inhibitors. This inhibitor development often occurs in association with traumatic injury or surgical challenges that result in significant and prolonged exposure to factor concentrates.

As a result of the suggestion that inhibitor development may be linked to the intensity of factor exposure in the face of danger signals, several studies set forth to examine the incidence of inhibitor development in children who were exposed to factor at a younger age. The CANAL cohort showed an association between age and first exposure to factor. However, when they controlled for the reason for factor VIII treatment, the association disappeared. In the CANAL cohort, patients who were treated for surgical procedures were at higher risk for developing inhibitors compared to patients who received their first factor exposure as prophylaxis. (6)

A German group of investigators expanded on this theory. They compared a cohort of consecutive previously untreated patients (PUPs) to a historical cohort. The experimental group started on weekly prophylaxis with 250 units in the absence of any danger signals (surgery, immunizations, etc.). The control cohort received the standard prophylaxis for joint protection, defined as 40-50 IU/kg three times weekly. The experimental group had only one subject develop an inhibitor versus 14 of 30 subjects on standard prophylaxis. (9) The authors felt that their results supported the start of early prophylaxis in the absence of danger signals as a viable method for reducing the risk of inhibitor development.

In contrast, the RODIN study evaluated a prospective cohort of previously untreated patients who were followed for the first 75 exposure days. The results corroborated previous retrospective reviews (CANAL) that suggested that intensive treatment with factor VIII increased inhibitor risk. However, the decreased risk of inhibitors associated with prophylactic

therapy was only evident after the first 20 exposure days, and more notable in patients with low risk inhibitors (7).

CONTINUOUS INFUSION VERSUS BOLUS INFUSION

There have also been retrospective studies that seemed to suggest a link between continuous infusion and increased rates of inhibitor development, but even before the recent studies seemed to suggest alternative explanations, investigators were suspicious about the association. (4) Given the recent studies that suggest an association of inhibitor development with intensive therapy, the method of administration of factor (i.e. continuous infusion versus bolus infusion) may not be the causative factor. To date there have been no definitive studies identifying continuous infusion as an independent risk factor.

RECOMBINANT VERSUS PLASMA-DERIVED FACTOR

Since the introduction of recombinant factor products, there has been concern about an increased incidence of inhibitor development. The reasons for this association are likely multi-factorial. Clearly, monitoring for inhibitor development is performed more often as part of PUP clinical trials than as part of routine hemophilia care. Historical prevalence data with plasma-derived products may underestimate the incidence of inhibitors with these products. Authors point out several flaws with the comparisons between surveillance data and PUP data, including the less frequent inhibitor testing in prevalence studies versus PUP studies, under-reporting of low-titer inhibitors, increased enrollment of African-American participants in PUP studies, and the small enrollment numbers in PUP studies. Studies comparing inhibitor rates between patients on recombinant and plasma- derived products have failed to show a significant difference in the rates of inhibitor development in the past. (4)

There has been particular attention and focus on plasma-derived von Willebrand factor-containing products because of the relationship between factor VIII and von Willebrand factor (VWF). VWF binds to factor VIII at the C2 domain, which is one of the most common sites of inhibitor specificity and binding. By binding to the C2 locus, VWF may block these sites from being recognized and processed by the immune system to produce inhibitors. VWF may also protect against inhibitor development because it prolongs the half-life of factor VIII. In the North American Immune Tolerance Registry (NAITR), there was no difference in ITI success rates in patients using plasma-derived versus recombinant factor. (5)

In an effort to address the role of product choice in the development of inhibitors, investigators conducted an international prospective randomized trial (SIPPET). Patients were treated with either a plasma-derived factor VIII product or a recombinant factor VIII product. The incidence of inhibitors was 26.8% with plasma-derived factor VIII and 44.5% with recombinant factor VIII. When limited to evaluation of high titer inhibitors, the incidence was 18.6% on plasma-derived factor VIII versus 28.4% on recombinant factor VIII. The study was discontinued early because there was some concern about increased inhibitor risk with a second generation recombinant factor VIII product, but even when analysis removed these patients, the hazard ratio remained high (1.98 for all inhibitors and 2.59 for high titer inhibitors). The concern about

increased inhibitor risk with second generation full length recombinant products was not seen in this study cohort. (10)

While the data from this prospective, randomized clinical trial is compelling, it did not include some of the newer products, including extended half-life products and products that use a human embryonic cell line (HEK). There are some who question whether these products may be less immunogenic. (11)

IDENTIFICATION AND MEASUREMENT OF INHIBITORS

Providers may suspect inhibitor development for a number of reasons. If a patient is not responding to factor replacement in the face of an acute bleed, that may lead providers to check for the development of an inhibitor. Similarly, if a patient on prophylactic infusions is suddenly developing frequent break-through bleeds, that may also be cause for concern. Occasionally, inhibitors are identified at the time of an annual visit during routine screening.

In order to understand inhibitors, it is incumbent upon all care providers to understand the identification and measurement of antibodies. Inhibitor titers are measured with the Bethesda assay. Dilutions of the patient's plasma are incubated with normal pooled plasma for 2 hours at 37°C, and the residual factor VIII is measured. One Bethesda unit (BU) is defined as the quantity of inhibitor that neutralizes 50% of the factor VIII in normal plasma after 2 hours' incubation at 37°C.
In 1995 the Bethesda Assay was modified to stabilize the protein and pH during incubation. These adjustments led to fewer false positive low titer results. As a result, the Nijmegen-Bethesda assay was adopted by the International Society on Thrombosis and Hemostasis. In 2012, the CDC adapted the Nijmegen method by using preanalytical heat treatment which allowed testing to be performed without interrupting therapy to have a wash-out period. (12)

CLASSIFICATION OF INHIBITORS

Patients with measurable inhibitors are categorized as low-responder or high-responder based on their Bethesda unit titer. A low-responding inhibitor measures less than 5 Bethesda Units and does not increase with exposure to additional factor.

A high-responding inhibitor is an inhibitor that has historically been above 5 Bethesda units. Some high-responder patients may have a decrease in the inhibitor titer when they have not had recent exposure to factor. However, these inhibitors should always be considered high-responders, because exposure to factor may result in an increase in the inhibitor titer above 5 BU again. This anamnestic response may be delayed for five to seven days, so it may be possible to treat a high-responding patient with factor initially to manage life-threatening bleeding, but the inhibitor titer and factor levels should be monitored frequently, and transition to a bypassing agent may be necessary when the inhibitor titer rises in order to manage long-term treatment. Some high-responding inhibitors do not decrease despite elimination of exposure to factor. Patients with persistently high-responding inhibitors require management with bypassing agents (BPA) to address acute bleeds.

MANAGEMENT OF ACUTE BLEEDS

Patients who have a low-responding inhibitor may continue to receive factor VIII or factor IX but will require higher dosing to achieve adequate recovery of factor activity to treat a bleeding episode. One suggested method of calculating a treatment dose in a patient with a low-responding inhibitor is to use 25-40 units/kg/BU. This dosing regimen should neutralize the inhibitor in addition to providing enough additional factor activity to treat an acute bleed. (13)

Management of acute bleeds continues to be an issue in patients with high-responding inhibitors. There are several BPA that have an FDA indication for use in patients with inhibitors. Bypassing agents are factor products that are able to bypass the inhibitor and allow clotting to take place. Recombinant activated factor VII (rFVIIa) and plasma-derived activated prothrombin complex concentrates (aPCCs) have both been shown to demonstrate efficacy in managing acute bleeds in patients with inhibitors.

Recombinant activated factor VII (rFVIIa) is thought to act on activated platelets in addition to its better understood role as tissue factor. This interaction increases thrombin generation, which speeds up clot formation and prevents breakdown of the clot by activation of a fibrinolytic inhibitor. (12) rFVIIa may be considered preferable in patients with inhibitors to factor VIII and IX because plasma-derived aPCC contains factor IX and small amounts of factor VIII which could induce an anamnestic response in patients with high-responding inhibitors. Since rFVIIa is a recombinant product, it may be preferred for pediatric patients who have been using exclusively recombinant products. (12)

However, rFVIIa has a very short half-life (2.3-2.7 hours); therefore, repeat dosing is generally indicated every two to 3 hours. The recommended dose of rFVIIa is 90 mcg/kg every 2-3 hours. However, there are numerous reports in the literature that compare this standard dose to a dose of 270 mcg/kg given less frequently with similarly efficacious results. (14)

Currently, there are no methods to monitor the efficacy of rFVIIa. Clinicians are reliant on subjective reports by the patient and few, if any, objective measures. However, use of rFVIIa does not result in an anamnestic response in inhibitor patients with either factor VIII or factor IX deficiency.

It is important to remember that patients with hemophilia who develop inhibitors are not deficient in factor VII. There are concerns that infusion of rFVIIa could lead to thrombotic complications. While rFVIIa has a good safety record, there have been reported cases of adverse events, and caution should be used to dose appropriately and observe for signs or symptoms that might suggest thrombosis.

Activated prothrombin complex concentrates (aPCCs) have been used for many years to treat inhibitor patients. aPCC is a plasma-derived factor concentrate that has been virally inactivated. This may make it less appealing for use in pediatric patients who have only been treated with recombinant products. aPCC contains activated factor VIIa, activated factor Xa, and thrombin (factor IIa), but it also has some factor IX and small amounts of factor VIII activity. As a result

of the presence of factor VIII and factor IX, it is often not used for first-line management of bleeds in patients with inhibitors.

The half-life of aPCC is thought to be about 4-7 hours, but this is based on fibrin clot generation, as there is no specific method to measure efficacy of aPCC. (13) Patients are usually given 50-100 units/kg/day to manage bleeding symptoms. This dose is repeated every 6-12 hours. Response is based on subjective report by the patient and limited objective measures. Exceeding 100 units/kg/dose or 200 units/kg/day-(maximum dose) is associated with increased risk of thrombosis. Use of concomitant anti-fibrinolytic therapy is contraindicated.

PREVENTION OF BLEEDING

While patients with inhibitors are no more likely to bleed than those without inhibitors, management of acute bleeding episodes is often more challenging because it requires the use of bypassing agents. It is not uncommon for patients with inhibitors to develop target joints because of recurrent bleeding. With the availability of bypassing agents, there has been increasing discussion of the role of prophylaxis for the prevention of bleeding in inhibitor patients. In these individuals, prophylaxis is done using a bypassing agent. Studies have demonstrated that there is some reduction in joint bleeding in patients who infuse aPCC three times weekly. (15) Some case reports suggest that rFVIIa can be used prophylactically to reduce bleeding episodes. (16) Additionally, a prospective study described a decrease in bleeding episodes during three months of prophylaxis with rFVIIa, but the authors were surprised to note persistent benefit for three months after prophylaxis with rFVIIa was discontinued. (17)

In 2017 the FDA licensed the first of a number of non-factor therapies that are indicated for prevention of bleeding in inhibitor patients. Hemlibra (Emicizumab) is a bispecific antibody that replaces the role that factor VIII plays in bridging activated factor IX to activate factor X. This product is administered subcutaneously. Patients enrolled on the clinical trials showed significantly reduced rates of bleeding. However, there were some thrombotic complications. Several patients, all of whom were being treated for bleeding with activated prothrombin complex concentrates (aPCC) at doses higher than 100iu/kg or for more than one day, developed thrombosis or thrombotic microangiopathy (TMA). As a result, the US Food and Drug Administration (FDA) included a warning on the package insert regarding caution in use of aPCCs with Hemlibra.

Laboratory monitoring is also a unique challenge with Hemlibra, as it interferes with coagulation studies including the aPTT, factor VIII activity and inhibitor titers. As a result, clot-based laboratory tests should not be used.

There are other non-factor therapies currently in clinical trials including an RNA interference therapy that is designed to reduce antithrombin levels in an attempt to reduce bleeding. (19) Several other new therapies are designed to inhibit Tissue Factor Pathway Inhibitor (TFPI). (20,21)

While these non-factor therapies open up new possibilities for preventing bleeding in patients with hemophilia, they also pose new challenges with thrombotic risk and issues with lab monitoring.

IMMUNE TOLERANCE INDUCTION

Ultimately, the goal of management for patients with inhibitors is eradication of the inhibitor itself. This may be achieved with immune tolerance induction (ITI). Immune tolerance induction is defined as the administration of frequent doses of factor to induce the immune system to accept the infused clotting factor. Once the inhibitor is eradicated, patients can manage bleeding episodes with the factor that they are missing, response to therapy can be measured, and the cost of care is significantly reduced.

A group in Germany was the first to use ITI to eliminate inhibitors successfully. The Bonn group used high-dose factor VIII every 12 hours. Patients also received aPCCs. The success rate was reported to be 92-100% initially, but about 70% overall because some patients relapsed when ITI was discontinued. (22) However, countless others have shown success using various dosing regimens and infusion schedules. The Malmö group incorporated immune suppression into their intensive ITI treatment regimen. The regimen included high dose factor plus immune modulation with IVIG and cyclophosphamide as well as immuno-absorption. The success rates with this regimen ranged from 59-82%. (23) Despite the variation of dosing and frequency and the use of additional modifying agents, the success rates of ITI continue to be less than optimal in some patients.

In the 1990s a number of groups began to collect data in retrospective chart reviews to determine if there were prognostic factors that were influencing the response to ITI. The International Immune Tolerance Registry (IITR) reviewed the data available in their cohort of patients and determined that younger patients with an inhibitor titer < 10 Bethesda units (BU) at the time ITI was started and a historical inhibitor titer < 200 Bethesda Units tended to have a better success rate using doses of > 100 units/kg/day. (24) The North American Immune Tolerance Registry (NAITR) reviewed their data and agreed that a lower maximum inhibitor titer and a lower inhibitor titer at the start of ITI were associated with improved outcomes. However, they showed an inverse relationship between dosing and time to response, with higher doses for ITI showing faster response to ITI. (5) Historically, ITI was started at the time that an inhibitor was identified. However, the registry data seem to support waiting to initiate immune tolerance induction until the inhibitor titer has decreased to <10 BU. Most providers recognize the poor prognosis associated with inhibitors in excess of 200 BU, which is consistent amongst the various registries.

Two prospective randomized clinical trials were developed to examine the impact of dosing and product choice on outcomes. Participants were randomized to a regimen using 200 units/kg/day or 50 units/kg three times weekly. This clinical trial began enrollment in 2002 and was closed early in 2009. While investigators saw similar success rates of 75-90 % between the two arms, the time to success was significantly shorter (50%) in patients on the high dose arm. More importantly, there were a significantly higher number of bleeding episodes on the low-dose arm which led to the early closure of the study. (25,26) The second trial (RESIST) compared

recombinant factor VIII versus a von Willebrand factor-containing plasma-derived factor VIII product in patients with poor prognostic risk factors. This study is not currently enrolling, but no results have been published to date. (Accessed 9/4/2018 at https://clinicaltrials.gov/ct2/show/study/NCT01051544?term=RESIST&cond=Hemophilia+A&rank=1).

In 2015 another review led to updated US ITI guidelines. (27) Regarding the start of ITI, the consensus guidelines suggest that ITI should be started as soon as possible if the titer is >5 BU and <10 BU. If greater than 10 BU, they recommend delaying the start of ITI unless there is life-threatening or frequent bleeding requiring prophylaxis with bypassing agents. However, ITI should be started if the inhibitor titer has failed to drop below 10 Bethesda Units after one to two years of observation.
The review did not find sufficient data to support one factor VIII product over another. Nor did it support the use of von Willebrand factor-containing factor VIII products for ITI. However, the guidelines do suggest VWF-containing products as a possible salvage for patients who do not respond to initial ITI therapy. (27)
Lastly, with respect to prophylaxis in patients with inhibitors, the guidelines suggest that prophylaxis should be considered if patients continue to bleed before or during ITI. However, they recommend rFVIIa prior to the start of ITI to minimize the potential for anamnestic increase in the inhibitor titer. The guidelines recommend monitoring the factor VIII recovery as the inhibitor titer decreases, because recovery of factor VIII activity could result in thrombotic complications in patients who are also receiving a bypassing agent either for prophylaxis or for treatment of bleeds. (27)

Another retrospective review of 58 subjects evaluated successful tolerization based on the inhibitor titer at the start of ITI. 96% of the subjects who started ITI within one month of inhibitor detection were tolerized. This is in comparison to 64% of subjects who delayed the start of ITI more than 6 months to allow the inhibitor titer to drop below 10 BU. The investigators recommended prompt initiation of ITI, suggesting that time from inhibitor detection to ITI start may play a role in ultimate success. (28)

Taking these findings into consideration, the United Kingdom Haemophilia Centre Doctors' Organisation developed a protocol for immune tolerance induction. One of the considerations was inhibitor titer at the start of ITI. The investigators acknowledge that it is not known whether an inhibitor <10BU is associated with increased rates of success, but they were concerned that delaying the start of ITI increased the risk of bleeding. This recommendation in the protocol contradicts the current (2017) UK guidelines (29,30)

SPECIAL CONSIDERATIONS: MILD HEMOPHILIA

Most inhibitors occur in patients with severe disease. However, inhibitors have been known to develop in patients with mild and moderate disease. In general, inhibitors develop later in life in patients with mild or moderate disease. Often, these patients suddenly develop recurrent bleeding and may have a factor level that measures below their historical baseline level. When patients with mild or moderate hemophilia develop inhibitors, it is usually in association with intensive factor exposure such as a surgical or traumatic challenge. (31) The UK National Hemophilia

Database showed that 28% of inhibitors occurred in patients with mild and moderate hemophilia. (32) Patients with mild and moderate hemophilia who develop inhibitors often have mutations that are located in the A2 domain, where there is a conformational change in the factor VIII protein. (4)

A case-controlled study of over 2700 patients with non-severe hemophilia A noted that surgical intervention increased the odds-ratio by 4.2, and higher mean dose factor (>45 IU/kg) was associated with a 7.5 increase in the odds ratio. The authors recommend consideration of inhibitor risk when determining the need to move forward with surgery and/or high dose factor. (33)

SPECIAL CONSIDERATIONS: INHIBITORS IN HEMOPHILIA B

Inhibitors in hemophilia B are less common. There is a significantly increased risk of inhibitor development in patients with large deletions and non-sense mutations. (3) A recent retrospective review noted that 70 percent of inhibitors were associated with high-risk mutations, prompting the investigators to concur with previous recommendations that mutation testing should be performed early in severe hemophilia B patients. (34) These inhibitors are often associated with anaphylactoid reactions at the time of factor infusion and concomitant inhibitor development. This risk has prompted providers to recommend that the first 10-20 infusions of factor IX be administered in the clinical setting. (3)

As opposed to the prospective randomized clinical trial that suggested that plasma-derived products may have a reduced rate of inhibitor development, one retrospective review of hemophilia B patients with inhibitors seemed to suggest that recombinant products had a reduced rate of inhibitor development. The authors suggested that the increased rate of clearance with recombinant products may be an explanation for the finding, but they acknowledge that additional investigation is necessary to confirm the conclusion. (34)

Patients who develop inhibitors to factor IX may have anamnestic responses to management with aPCC as a bypassing agent because it contains factor IX. Therefore, the choice of bypassing agent may be limited to rFVIIa.

Response to ITI has not been as successful in patients with hemophilia B. In addition to the risk of anaphylactoid reactions, patients may also develop nephrotic syndrome during ITI. Patients who develop nephrotic syndrome may not respond to steroid therapy, and symptoms may persist if exposure to factor IX is not discontinued. (35) For patients who are able to tolerate immune tolerance regimens, the dosing and frequency of factor replacement is very similar to the ITT regimens in hemophilia A. (33) Patients with anaphylactoid reactions to factor IX may require desensitization prior to starting an ITI regimen (36) For those who cannot or chose not to pursue immune tolerance for inhibitors to factor IX, there may be treatment options with non-factor therapies in the future.

COST OF TREATMENT

Hemophilia is an expensive disease to manage. The development of inhibitors can significantly increase the cost of care. Factor concentrates account for most of the costs associated with hemophilia. Not surprisingly, when patients develop inhibitors to factor concentrates, the cost of care rises exponentially. Fortunately, patients with inhibitors do not bleed more often, at least initially. However, when they do bleed, frequent factor replacement with bypassing agents has been the only option. This type of acute management may take longer to get control of bleeding. Recurrent bleeding can result in arthropathy and other long-term co-morbidities. However, the advent of prophylaxis with bypassing agents and, more recently with non-factor therapies, may significantly decrease bleeding in patients with active inhibitors. However, the question of cost versus benefit may be a consideration for payers.

Some studies have evaluated the cost of care between inhibitor and non-inhibitor patients. For many patients with inhibitors, the cost of care is not significantly different than for patients without inhibitors. However, some inhibitor patients have much higher costs of care. In general, the differences in the cost of care have to do with inpatient admissions and the cost of bypassing agents. (37) A retrospective multicenter study examined the relationship between ITI outcome and the cost of treatment. Of the 71 patients enrolled, 84% were successfully tolerized. While the cost of ITI is considerable, the investigators concluded that the investment in ITI was less expensive in the long run when compared with ongoing inhibitor treatment. Moreover, they site improved life expectancy and health-related quality of life as additional benefits. (38)

THE FUTURE OF INHIBITOR MANAGEMENT

While continued investigation has led to a better understanding of risk factors that may lead to inhibitor development, there is still much that has yet to be fully explained. The management of acute bleeds in patients with inhibitors and the ultimate eradication of inhibitors continue to be challenging treatment issues. Inhibitor patients continue to have significantly more issues with morbidity and mortality, and the cost of their care can be considerable, even amongst other patients with hemophilia whose care is already expensive. Investigators continue to ponder the questions related to identification of patients at risk for inhibitor development, prevention of inhibitors, management of acute bleeding in patients with inhibitors, and eradication of inhibitors. The success of these investigations will hinge on collaboration within the bleeding disorders community.

With the advent of new and innovative treatment approaches, prevention of bleeding and eradication of inhibitors may change for some. At some point, non-factor therapies may change the treatment landscape for hemophilia patients who develop inhibitors, preventing bleeds despite persistently high inhibitor titers, in combination with immune tolerance and perhaps even preventing inhibitor development in previously untreated patients, but this has yet to be studied. This is an exciting time in the hemophilia community, but it requires cautious optimism and careful ongoing evaluation to insure that patients and families have access to information to make informed choices about therapeutic options, including consideration of risk and benefits.

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