**Hemophilia A and B: Disease Differences and the Use of Prophylactic Therapy**

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**Abstract** The treatment algorithm for hemophilia has evolved substantially since the advent of factor replacement. Prophylaxis is now the standard of care for children with hemophilia A and B. However, unresolved treatment decisions, including the age to start treatment, optimal dosing, and continuation of prophylaxis into adulthood, remain. Additionally, exciting new areas of managing hemophilia are on the horizon, including treatment with new recombinant coagulation factors that have prolonged half-lives and potentially curative treatments.

Hemophilia A and B are X-linked, recessive disorders caused by deficiency or absence of coagulation factors VIII (FVIII) and factor IX (FIX), respectively. They are classified into severe (<1%), moderate (1%–5%), or mild (>5% to <40%) categories according to coagulation factor activity.

Hemophilia A is four times more common than is hemophilia B. Because they are clinically indistinguishable, they historically were believed to represent the same disease. It was not until 1952 that hemophilia B was considered to be a separate entity. The two types share many similar components (eg, prolongation of activated partial thromboplastin time, recurrent hemarthrosis), but they have some distinct differences (eg, frequency of inhibitor development, type of genetic mutations). For example, hemophilia B is caused by less severe gene mutations than hemophilia A and is characterized by more missense mutations than null mutations. As a result of these differences, only 35% of patients with hemophilia B have severe disease, compared with 45% of those with hemophilia A.1

The subtypes also differ in coagulation factor pharmacokinetics—the half-life of FIX is 18 hours and of FVIII is 11 hours.2 As a result, post-infusion levels after FIX administration are sustained for longer periods, thereby reducing the risk of recurrent bleeding.2 The reduced incidence of recurrent hemarthrosis may contribute to a threefold difference in the need for total joint arthroplasty in people with hemophilia B as compared with those diagnosed with hemophilia A.1 Nonetheless, the treatment approaches are similar—and most clinical research for treatment bundles the two diseases.

During a Baxter Healthcare-sponsored symposium offered at the 65th Annual Meeting of the National Hemophilia Foundation, experts described the history of hemophilia B therapy and looked toward its future. The panelists included Amy Shapiro, MD, and Natalie Duncan, MPH, of the Indiana Hemophilia and Thrombosis Center in Indianapolis; Erik Berntorp, MD, PhD, of the Malmö Centre for Thrombosis and Haemostasis at Lund University in Lund, Sweden; and Marion Koerper, MD, of the University of California, San Francisco School of Medicine in San Francisco, California.

**EVOlUTION OF CURRENT TREATMENT APPROACHES**

Multiple factor replacements are available in the United States to treat hemophilia B (Table 1).3 At one time, the initial management strategy for hemophilia patients was on-demand treatment to provide factor in response to an acute episode of bleeding or trauma. On-demand factor replacement remains the treatment of choice for all patients with mild disease and most of those with moderate disease. In the 1960s, however, clinicians first thought of “converting” individuals with severe disease to moderate manifestations using scheduled prophylactic treatment.

**Preventative Measures**

Prophylaxis aims to prevent bleeding episodes before they result in arthropathy and life-threatening hemorrhage. Prophylaxis, however, is expensive and inconvenient, because it requires frequent dosing. Therefore, decades of research were necessary before prophylaxis became the standard of care for children with severe hemophilia.

Some initial evidence to support the prophylactic approach arose from large observational studies. One large study of 156 patients with hemophilia compared Swedish and Norwegian individuals di-
TABLE 1
Current Factor IX Replacement Products Available in the United States

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Recombinant or plasma derived</th>
<th>Stable at room temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>AlphaNine SD</td>
<td>Plasma derived</td>
<td>No</td>
</tr>
<tr>
<td>BeneFIX</td>
<td>Recombinant</td>
<td>Yes (up to 6 months)</td>
</tr>
<tr>
<td>Mononine</td>
<td>Plasma derived</td>
<td>No</td>
</tr>
<tr>
<td>Rixubis</td>
<td>Recombinant</td>
<td>Yes (up to 6 months)</td>
</tr>
</tbody>
</table>

Source: Shapiro

TABLE 2
Definitions of Prophylaxis Used by the European Pediatric Network for Hemophilia Management

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>Primary prophylaxis A</td>
<td>Regular continuous treatment started after the first joint bleed and before the age of 2 years</td>
</tr>
<tr>
<td>Primary prophylaxis B</td>
<td>Regular continuous treatment started before the age of 2 years without previous joint bleed</td>
</tr>
<tr>
<td>Secondary prophylaxis A</td>
<td>Regular continuous (long-term) treatment started after two or more joint bleeds or at an age ≥ 2 years</td>
</tr>
<tr>
<td>Secondary prophylaxis B</td>
<td>Intermittent regular (short-term) treatment, because of frequent bleeds</td>
</tr>
</tbody>
</table>

Source: Donadel-Claeyssens

Clinicians in Sweden have long used prophylaxis as the standard of care, whereas those in Norway had embraced an on-demand treatment approach. Patients given on-demand treatment had five times more episodes of bleeding and used more resources outside of the healthcare setting, but the prophylaxis group had significantly higher annual factor-concentrate consumption.

A similar study compared hemophilic patients in the Netherlands, who were given intermediate-dose prophylaxis, with patients in Sweden, who were given high-dose prophylaxis, and France, who were given on-demand treatment. Higher rates of bleeding and arthropathy were noted among the on-demand treatment group; however, there was minimal reported clinical improvement between intermediate-dose and high-dose prophylaxis. Costs for on-demand and intermediate-dose prophylaxis were similar, whereas high-dose prophylaxis was significantly more expensive.

Despite these and other observational data, authors of a 2006 Cochrane review found insufficient evidence to support prophylaxis and called for randomized, controlled trials. Shortly thereafter, a randomized, controlled trial showed that 25 IU/kg of prophylactic factor replacement given every other day decreased bleeding episodes and hemarthroses in patients with hemophilia A. The prophylaxis group used twice as much factor annually at a higher financial cost.

Subsequent studies have upheld the positive clinical impact of prophylaxis. The latest Cochrane review has recommended prophylaxis to preserve joint function. According to this review, evidence of benefit from prophylaxis in patients with preexisting joint damage is insufficient. Thus, early initiation of factor replacement is needed for children, although the exact age for treatment initiation is uncertain.

Timing and Dosing Are Everything

Multiple methods of prophylaxis have been defined (Table 2), and the best strategy to follow has been hotly debated. An early start is important, since it can lessen future degenerative joint disease. However, starting treatment in toddlers aged 1–2 years is not without its challenges. For example, complication rates associated with central catheter placement brings venous access into question. The model used at the Malmö Hemophilia Center in Sweden (Figure 1) details one approach for primary prophylaxis of hemophilia B. Optimal dosing is another unresolved component of prophylaxis. Internationally, different treatment approaches have been proposed (Table 3). The most expensive scheme, the high-dose Swedish prophylactic regimen, previously was considered the best to prevent joint disease and bleeding. More recently, a retrospective analysis of the Dutch intermediate-dose program compared with the much more costly Swedish high-dose regimen concluded that the latter offered minimal added benefit. The alternative pharmacokinetic approach remains promising, but there is insufficient evidence that factor level peaks and troughs predict bleeding risk. In clinical practice, prophylactic regimens and dosing usually are tailored to patients’ individual needs.

Lower costs have sparked interest in low-dose regimens, especially when they are used in resource-poor settings. Wu et al demonstrated that low-dose prophylaxis used in China reduced the number of bleeding episodes and improved joint function over 12 weeks. Patients with hemophilia A were given 10 IU/kg of FVIII twice weekly, and those with hemophilia B were given 20 IU/kg of FIX once weekly. In the Swedish study, however, the average prophylactic dose was 25–40 IU/kg of FVIII given three times a week for patients

FIGURE 1 Approach to primary prophylaxis of hemophilia B, as practiced at Malmö Hemophilia Center in Sweden. Adapted, with permission, from Berntorp.
TABLE 3

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Principle</th>
<th>Relative cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch regimen (intermediate-dose)</td>
<td>15–25 IU/kg 2–3 times/wk, starting early after the occurrence of joint bleeds</td>
<td>Moderate</td>
</tr>
<tr>
<td>Traditional Swedish dosing regimen (high-dose)</td>
<td>25–40 IU/kg 2–3 times/wk, starting before the occurrence of joint bleeds</td>
<td>Most expensive</td>
</tr>
<tr>
<td>Alternative Swedish dosing regimen (pharmacokinetic dosing)</td>
<td>Individualized to patient needs, starting with a high dose and followed by a reduction in dose and lengthening of the interval between doses</td>
<td>Least expensive</td>
</tr>
<tr>
<td>Canadian regimen (dose escalation)</td>
<td>50 IU/kg weekly, starting early after the occurrence of joint bleeds and intensified stepwise depending upon bleeding frequency</td>
<td>Less expensive</td>
</tr>
</tbody>
</table>

Source: Berntorp and Shapiro

with hemophilia A and 25–40 IU/kg of FIX twice a week for those with hemophilia B. The Chinese low-dose prophylactic approach reduced costs, but whether it prevented long-term arthropathy-related disability remains unclear, since a moderate number of joint bleeds remained.

How Much Is Too Much?

Prophylaxis has dramatically improved quality of life and reduced arthropathy in children with hemophilia. Whether and when to stop prophylaxis remain controversial. Presenting data from the HUGS (Hemophilia Utilization Group Study) VB trial, Koerper18 revealed that two thirds of children and one half of adults with hemophilia B at one US hemophilia treatment center were on prophylaxis. Early retrospective data did not show a significant difference in arthropathy scores when on-demand therapy and prophylactic treatment were compared in adults.19 Definitive recommendations for prophylaxis in adults will require long-term, prospective, randomized trials to adequately assess outcomes.

CHALLENGES IN USING PROPHYLACTIC REGIMENS

One barrier to standard use of the prophylactic regimen is the cost. Prophylaxis has become less expensive, as it has become the standard of care for children with hemophilia in the United States; however, patient adherence to the regimen remains challenging.

With currently available formulations, patients with hemophilia B require prophylaxis two to three times a week. Only 60% of hemophilia patients report infusing at least three fourths of the recommended factor, most commonly missing doses because of their complexity and the time commitment.20 Paradoxically, the ability of prophylactic factor replacement to completely eliminate symptoms decreases adherence.21

This problem, however, is not limited to patients in the United States. A Chinese study examining prophylaxis versus on-demand treatment found that although factor was provided at no cost, adherence rates lagged.22 The primary reason for this phenomenon was that patients and their families did not fully understand the importance of therapy. Recent studies by the same group showed significant barriers to prophylaxis in areas without dedicated hemophilia treatment centers.22

Improving Adherence

Several methods have been developed to improve adherence rates. Two modifiable factors that influence adherence are maintenance of a good relationship between the patient and the healthcare provider and the patient’s positive belief in the necessity of treatment.21–23 With regard to the latter, families reported that expanded health education best facilitated adherence.20 Novel treatment approaches that may help improve adherence rates are being developed.

NOVEL APPROACHES TO HEMOPHILIA TREATMENT

Current hemophilia treatments have improved the quality of life and longevity of patients with hemophilia dramatically, yet limitations such as the inconvenience of frequent dosing and its substantial cost remain. Prolonging the half-life of factor replacement may lower costs and decrease complications and inconvenience related to frequent venous access.

The half-life of therapeutics can be extended by using PEGylation, which involves covalent attachment of polyethylene glycol (PEG) polymer chains to liposomes.24 Another technique involves recombinant fusion proteins, in which FIX is attached to the crystallized fragment region of immunoglobulin G.25 In these trials, bleeding-free intervals or blood clotting times have been prolonged significantly. Currently, at least three phase 3 clinical trials of long-acting FIX, and many more trials in phase 1 or phase 2, are ongoing.26

An alternative approach is gene therapy. Because a small increase in factor level can significantly improve bleeding rates, this method offers a potential cure for hemophilia B. Nathwani et al27 treated six patients with severe hemophilia using a viral vector that expressed FIX. All patients had less need for factor replacement, and four patients stopped using prophylaxis completely. Additional trials of this extremely promising area of research are ongoing.

REFERENCES

5. Shapiro A. Treatment update on hemophilia B. Presented at the 65th Annual Meeting of the National Hemophilia Foundation; October 3–5, 2013; Anaheim, California.

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