Meeting the Challenges of Managing Hemophilia: Prophylactic vs Episodic Therapy and Avoiding Inhibitors

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Abstract Management of hemophilia has changed over the past few decades. However, the most common complication of hemophilia remains the development of joint bleeds leading to hemophilic arthropathy. Coagulation factor replacement for children should be started early and given prophylactically to preserve joint health and prevent complications. For adults started on prophylaxis, limited studies have reported decreased bleeding episodes, but improvement of joint function and quality of life remains unclear. Inhibitor formation as a complication of coagulation factor replacement and its management are reviewed. Future potential therapies for patients with hemophilia are summarized briefly.

Hemophilia is an X-linked recessive bleeding disorder that results from deficiencies in coagulation factors VIII (FVIII) and IX (FIX). Decreased or absent levels of these factors lead to hemophilia A and B, respectively. The severity of hemophilia is classified as mild, moderate, or severe depending on factor activity levels. Mild disease is associated with a factor activity level > 5 IU/dL and < 40 IU/dL; moderate disease with a factor activity level of 1–5 IU/dL; and severe disease with a factor activity level of < 1 IU/dL.

The prevalence of hemophilia A is 1:5,000 male live births and of hemophilia B, 1:30,000 male live births. The most common morbidity noted among patients with severe disease is spontaneous joint bleeding (hemarthrosis), which can affect any joint but which primarily affects the ankles, knees, and elbows. In addition to spontaneous hemarthrosis, patients with severe disease also can develop spontaneous soft-tissue, gastrointestinal, and central nervous system bleeding. Recurrent hemarthroses can lead to debilitating joint disease, also known as hemophilic arthropathy. Patients with moderate disease usually bleed in response to some injury but can have spontaneous bleeding; patients with mild disease typically only bleed in response to major insults such as surgery or significant trauma.

PROPHYLAXIS IN CHILDREN

The cornerstone of hemophilia management is coagulation factor replacement. Over the past two decades, the focus of therapy has shifted from treatment after bleeding has occurred to prevention of bleeding to allow patients to have a more active and fuller lifestyle. Prophylactic factor replacement was first pioneered in Sweden in 1958, when patients with moderate hemophilia were found to be less likely to develop chronic debilitating joint disease than patients with severe hemophilia.

Two recent, randomized, controlled trials that compared prophylaxis with episodic treatment showed definitive benefits with early prophylaxis. Results of these studies—the Joint Outcome Study in the United States and the Evaluation Study on Prophylaxis: a Randomized Italian Trial (ESPRIT)—are summarized in Table 1. Both evaluated the use of prophylactic factor replacement in young boys who had either no or few joint bleeds.

Joint Outcome Study

The Joint Outcome Study enrolled 65 male children with a history of minimal or no joint bleeding (Table 1). The subjects, who were < 2.5 years old at study entry, were randomized to receive either prophylactic or episodic treatment. Children in the prophylactic treatment arm received 25 IU/kg of recombinant FVIII (rFVIII) every other day; those in the episodic treatment arm received 40 IU/kg of rFVIII during each bleed, followed by a single dose of 20 IU/kg 24 and 72 hours later.

As shown in Figure 1, the frequency of bleeding was significantly less in the prophylactic treatment arm than in the episodic treatment arm. As the children grew older and more active, those in the
prophylactic treatment arm continued to have significantly less joint bleeding. Magnetic resonance imaging (MRI) of 56 patients at age 6 years showed that 93% of those in the prophylactic treatment arm did not have joint damage, compared with 55% of those in the episodic treatment arm (Table 2).

**ESPRIT**

The ESPRIT investigators evaluated 40 older male children (median age, 48–50 months) at study entry and who had no physical or radiographic arthropathy (Table 1). These children were randomized to receive either prophylactic or episodic treatment. Boys in the prophylactic treatment arm received 25 IU/kg of rFVIII three times/week, with doses up to 40 IU/kg to obtain trough levels > 1%. Those in the episodic treatment arm received ≥ 25 IU/kg of rFVIII during each bleed, with repeated doses every 12–24 hours until the bleeding resolved. As shown in Table 3, children in the prophylactic treatment arm experienced fewer bleeding episodes and had less radiographic evidence of arthropathy than those in the episodic treatment arm. Quality-of-life (QOL) measures differed significantly between the two groups because the children in the episodic treatment arm had a greater sense of overprotection.

In both studies, significantly more replacement factor was used in the prophylactic treatment arm than in the episodic treatment arm. In addition to greater cost due to more factor consumption, there was also a higher rate of complications related to the placement of indwelling catheters to maintain the prescribed prophylactic treatment regimen.

**Other Studies in Children**

Other prophylactic approaches also have been used. In the Canadian tailored prophylaxis trial conducted by Feldman et al., 25 boys began primary prophylaxis with 50 IU/kg of rFVIII once weekly, followed by stepwise increases to 30 IU/kg twice weekly and then 25 IU/kg every other day, depending on the frequency of bleeding episodes. After 5 years, 10 of the 25 children were receiving weekly infusions, 8 were being treated twice weekly, and 7 were being treated every other day. At the end of the study, all of the children had normal joints by physical examination and minimal radiographic changes. Only 10 of the 25 children (40%) required indwelling intravenous (IV) catheters, compared with 29 of the 32 children (91%) who were on the prophylactic treatment arm of the Joint Outcome Study. All of the children in the Canadian study had follow-up MRI examinations at age 9 years, and about 50% of them showed evidence of changes in target joints. This approach resulted in a cost reduction of about 20%–25% over the first 5 years, as compared with the cost of a standard high-dose prophylactic regimen over that 5-year period.

In the Netherlands, Fischer and colleagues studied a different approach. Instead of using the standard high-dose prophylactic regimen, they started prophylaxis with lower, intermediate doses (usually 15–25 IU/kg 2–3 times/wk) when joint bleeding began. When compared with a Swedish (high-dose) cohort, the Dutch (intermediate-dose) cohort used less than half as many units of FVIII per patient per year. Outcomes in the Dutch cohort were good but somewhat inferior to those in the Swedish cohort, since some increase in bleeding and more clinical evi-

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**TABLE 1**

Comparison of the Joint Outcome Study and the ESPRIT Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Joint Outcome Study (JOS)</th>
<th>ESPRIT Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean)</td>
<td>&lt; 2.5 (1.6)</td>
<td>1–7 (4.1)</td>
</tr>
<tr>
<td>Prior bleeding</td>
<td>≤ 2 bleeds in index joints (prophylactic therapy arm: 1; episodic treatment arm, 0.6)</td>
<td>≤ 2 bleeds in a single site (unknown)</td>
</tr>
<tr>
<td>Baseline arthropathy</td>
<td>None by physical or x-ray examination</td>
<td>None by physical or x-ray examination</td>
</tr>
<tr>
<td>Treatment regimen (recombinant factor VIII)</td>
<td>Prophylactic therapy arm: 25 IU/kg every other day</td>
<td>Prophylactic therapy arm: 25 IU/kg 3 times/wk, up to 40 IU/kg per dose</td>
</tr>
<tr>
<td></td>
<td>Episodic treatment arm: 40 IU/kg as needed, then 20 IU/kg at 24 and 72 hours</td>
<td>Episodic treatment arm: ≥ 25 IU/kg as needed, then every 12–24 h as needed</td>
</tr>
</tbody>
</table>

ESPRIT = Evaluation Study on Prophylaxis: a Randomized Italian Trial

Source: Manco-Johnson et al (JOS) and Gringeri et al (ESPRIT)

Mean number of hemorrhages per month

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**FIGURE 1** Frequency of bleeding events in the Joint Outcome Study among boys receiving prophylactic or episodic factor replacement therapy. Adapted, with permission, from Manco-Johnson et al.

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dence of arthropathy were noted among the Dutch children (Table 4).

Other Considerations

Patients with hemophilia historically have been encouraged to be sedentary because of the risk of bleeding. Now, however, with the major societal problem of obesity, treatment centers are encouraging patients with hemophilia to be more active. When compared with inactive patients, active individuals with hemophilia do not develop worse joint disease, although their activity should be coordinated with prophylactic dosing.

No single approach for primary prophylaxis is optimal for every child. However, early primary prophylaxis (ie, starting before age 2.5–3.0 years) decreases hemophilic arthropathy and improves joint outcomes. Costs and complications resulting from indwelling IV catheters must also be taken into consideration. Prophylactic dosing using high-dose protocols has the best outcomes, and intermediate-dose protocols have good outcomes.

All of the previously mentioned studies evaluated children with hemophilia A. Because comparative data on patients with hemophilia B receiving prophylactic versus episodic treatment are limited, most treatment centers extrapolate the results from patients with hemophilia A and apply similar principles to maintain FIX activity levels ≥ 1% in children with hemophilia B.

PROPHYLAXIS IN ADULTS

About one third of young adults who received primary prophylaxis as children choose to switch to episodic treatment. One analysis of a self-reported cohort of Danish and Dutch men with severe hemophilia A (median follow-up, 3.6 years) compared outcomes of those who continued on prophylaxis with those of individuals who switched to episodic treatment. Although men who chose to switch to episodic treatment experienced more joint bleeding, the incidence (3.2 joint bleeds per year) was still considerably lower than the incidence of joint bleeds previously reported in other cohorts of adults with severe hemophilia who were managed with episodic treatment for their entire lives.

The multinational longitudinal Orthopaedic Outcome Study first supported initiation of prophylaxis in adults because of benefits to joints. Patients given full-time prophylactic therapy who were followed for 6 years had less progressive hemophilic arthropathy, as measured by physical and radiographic examinations.

Three recent studies in adults evaluated the efficacy of prophylaxis versus episodic treatment and compared the outcomes of both treatment regimens. Collins et al treated 20 adult patients (age, 30–45 years) sequentially with episodic treatment for 6 months and then crossed them over to 6 months of high-dose prophylaxis (20–40 IU/kg of rFVIII three times weekly). A comparison of the two interventions showed that patients with significant joint bleeding histories who were maintained on episodic treatment had no bleeding episodes once switched to prophylaxis. However, because this study was brief, it did not show improvement in joint function or QOL measures.

Valentino et al first treated 66 adult patients with 6 months of on-demand

### TABLE 4
Outcomes of Intermediate- vs High-Dose Prophylaxis for Patients with Severe Hemophilia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intermediate dose (n = 44)</th>
<th>High dose (n = 24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at evaluation, years (range)</td>
<td>22.7 (20.4–25.3)</td>
<td>17.2 (15.2–20.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Joint bleeds/year (range)</td>
<td>2.5 (1–5.7)</td>
<td>0.5 (0.2–1.8)</td>
<td>0.050</td>
</tr>
<tr>
<td>Patients without joint bleeds</td>
<td>5%</td>
<td>25%</td>
<td>0.042</td>
</tr>
<tr>
<td>Clinical score (maximum = 90)</td>
<td>2 (0–5)</td>
<td>0 (0–4)</td>
<td>0.449</td>
</tr>
<tr>
<td>Pettersson score (maximum = 78)</td>
<td>10 (3.5–17.5)</td>
<td>4 (0–15)</td>
<td>0.750</td>
</tr>
<tr>
<td>Pettersson score = 0</td>
<td>11%</td>
<td>46%</td>
<td>0.560</td>
</tr>
</tbody>
</table>

Source: Fischer et al

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### TABLE 2
Magnetic Resonance Imaging Findings in the Joint Outcome Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prophylactic therapy (n = 32)</th>
<th>Enhanced episodic treatment (n = 33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with primary outcome data</td>
<td>27</td>
<td>29</td>
<td>0.73</td>
</tr>
<tr>
<td>Number (%) with joint damage</td>
<td>2 (7%)</td>
<td>13 (45%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Number (%) with no joint damage</td>
<td>25 (93%)</td>
<td>16 (55%)</td>
<td></td>
</tr>
</tbody>
</table>

Source: Manco-Johnson et al
treatment and then randomized these individuals to either 12 months of high-dose prophylaxis (20–40 IU/kg of rFVIII every other day) or a pharmacokinetically tailored arm in which patients were infused with 20–80 IU/kg of rFVIII every third day to maintain trough levels of > 1%. The annualized bleeding rates for both prophylactic groups were reduced by 99%, but there was no evidence of improvement in joint function. QOL measures for pain and physical function were improved at the end of the prophylactic treatment period.

The third study, the multinational Trial to Evaluate the Effect of Secondary Prophylaxis with rFVIII Therapy in Severe Hemophilia A Adult and/or Adolescent Subjects Compared to That of Episodic Treatment (SPINART), was recently completed. In all, 84 patients were randomly assigned to treatment with a high-dose prophylactic regimen or episodic treatment. All patients underwent MRI examination of index joints on study entry and had yearly joint examinations and QOL assessments thereafter. At the end of the 3-year treatment period, the patients underwent another MRI examination. Patients in the prophylaxis arm were treated with 25 IU/kg of rFVIII three times per week (escalation by 5 IU/kg to a maximum of 30 or 35 IU/kg was allowed in patients with bleeding episodes after 1 and 2 years, respectively). For the episodic treatment arm, rFVIII replacement was left to the discretion of the treating physician.

An interim report (median follow-up, 1.4 years) showed a 93% decrease in bleeding rate among patients in the prophylaxis arm. There was also an implication that bleeding episodes in the prophylaxis arm were less severe. Data from target joint examinations and MRI and QOL assessments have not yet been reported.

Prophylaxis in adults decreases bleeding frequency by > 90% and the severity of bleeding episodes. There is early evidence that prophylaxis in adults improves arthropathy and QOL, but this still must be confirmed. Also, if evidence from the pediatric and pharmacokinetic studies is considered, many adults with hemophilia A probably can achieve bleeding control with less than the standard dose of 20–40 IU/kg of rFVIII three times per week, since the 48-hour trough levels with this dosing regimen have been 3–6 IU/dL in recent studies. Taking this approach also would help to decrease the discrepancy between the amounts of replacement factor used by the prophylaxis treatment groups and the episodic treatment groups. Given that each adult has a different bleeding history, hemophilic arthropathy, and factor activity level, dosing strategies should be individualized to optimize the costs of factor replacement and attain the best outcomes.

**INHIBITORS AND CURRENT MANAGEMENT OPTIONS**

Alloimmune inhibitory antibodies to FVIII (inhibitors) are serious complications of treatment with factor concentrates and develop in about 25%–30% of patients with severe hemophilia A. Inhibitors normally are detected fairly early in treatment after a median of 14–16 treatment days. The most significant risk factor that predisposes patients to developing inhibitors is the F8 gene mutation. Patients with large multixenon gene deletions have a much higher rate of inhibitor formation than do those with missense mutations, and those with inversions have an intermediate risk of inhibitor formation. Race is another risk factor—black males have a higher rate of inhibitor development than do white males, although the etiology is unclear.

Treatment-related factors also have been associated with inhibitor development. For example, early intensive factor exposure has been associated with increased inhibitor formation, and there may be some protection from inhibitor formation with the use of prophylaxis.

**Immunogenicity of Therapeutic Products**

Another potential risk factor involves plasma-derived products that are rich in von Willebrand factor (vWF) and less immunogenic than are recombinant factor products. Previous data were based on retrospective studies. The Research of Determinants of Inhibitor Development among Previously Untreated Patients with Haemophilia (RODIN) trial is the first study to prospectively observe whether some products are more immunogenic than others. Investigators collected prospective data on 574 previously untreated patients with hemophilia and followed them for 75 exposure days. There was no immunogenic difference between patients treated with plasma-derived products and those treated with recombinant factor. An analysis of individual factor products suggested that a second-generation, full-length recombinant factor might be related to a slightly higher relative risk for inhibitor formation, but the observational nature of this study cannot lead to definitive conclusions.

The ongoing Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) is randomizing previously untreated patients to receive either rFVIII or plasma-derived FVIII product with vWF to determine whether some products are more immunogenic than others. Other risk factors for inhibitor formation reported in the literature include polymorphisms in immune regulatory genes and associations with specific human leukocyte antigen (HLA) class II alleles, but the evidence has been inconsistent, and any association with inhibitor formation remains unknown.

**Immune Tolerance Induction (ITI)**

Eradication of inhibitors uses ITI with frequent regular infusions of FVIII and works in about 60%–80% of cases (median time to tolerance, approximately 9–12 months). However, the optimal dose of
factor and optimal product (recombinant or plasma-derived) remain unknown.

The International Immune Tolerance Study looked at the issue of dose and randomized good-risk patients (defined as having a peak historical inhibitor titer of ≤ 200 BU/mL, starting titer level of ≤ 10 BU/mL before randomization, and age < 8 years at the time of randomization) to either a high-dose arm of 200 IU/kg daily of rFVIII or to a low-dose arm of 50 IU/kg three times a week. Inhibitor titers and half-life recovery studies were collected throughout the study. There was no difference in the time to tolerance induction and the rate of tolerance induction, although the time to negative inhibitor titer and time to normal recovery were slower in the low-dose arm. The trial was stopped early due to significantly more bleeds in the low-dose arm and to futility, since enrollment was not robust enough to determine equivalence between the arms.

Patients who cannot have their inhibitor eradicated and have a high inhibitor titer (> 5 BU/mL) are treated with bypassing agents, such as activated prothrombin complex concentrate (FEIBA), FVIII inhibitor bypass activity, or recombinant factor VIIa. Prophylactic treatment with either bypassing agent resulted in improved bleeding control when compared with episodic treatment.22,23

### POTENTIAL FUTURE TREATMENT OPTIONS

New advances on the horizon include long-lasting factor concentrates soon to be available for both patients with hemophilia A and those with hemophilia B. Also, three active studies are examining gene therapy for patients with hemophilia B. These studies are employing adeno-associated virus (AAV) serotype 8 vector, which expresses FIX. Only the trial from the University College London/St Jude Children’s Research Hospital has reported data thus far, noting stable FIX levels of 1%–6% among 10 patients 8–40 months after treatment.24 In this study, higher doses of AAV-8 vector genomes yielded higher plasma FIX levels but were associated with abnormalities in liver function tests and immune responses to the AAV-8 capsids. These patients were managed with short courses of corticosteroids.

### REFERENCES


