Recent Advances in Preventing Bleeding, Reducing Inhibitors, and Managing Acute Bleeding

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Abstract Recent advances in the prevention of bleeding episodes, reduction of inhibitory alloantibodies to factor concentrates (inhibitors), and management of acute bleeding episodes in hemophilia were presented at the 55th Annual Meeting of the American Society of Hematology (ASH). Among the more notable observations were: (1) bleeding tendency is associated with the level of factor VIII (FVIII) activity in patients receiving prophylactic recombinant FVIII crystallizable fragment (Fc) fusion protein; (2) prophylactic treatment with long-lasting recombinant factor IX Fc fusion protein is safe and effective in adolescents with hemophilia B; (3) delayed prophylaxis has long-term deleterious effects in patients with acute hemophilia; (4) magnetic resonance imaging is useful for detecting early hemophilic joint disease; (5) early, low-dose prophylaxis in the absence of immunologic danger signals may reduce inhibitor incidence in patients with hemophilia A; (6) prompt immune tolerance induction at inhibitor diagnosis may increase the success rate in patients with hemophilia A and inhibitors; and (7) four-factor prothrombin complex is superior to plasma administration for achieving hemostasis before urgent surgery. Ongoing studies on prophylaxis, reduction and management of inhibitors, and treatment of acute bleeding are crucial to continuing improvement in the quality of life of patients with hemophilia.

Approval of the first recombinant factor VIII (rFVIII) concentrates in the United States in 1992 improved the product supply, decreased the incidence of viral bloodborne infections to near zero, and advanced the adoption of prophylactic treatment regimens. Prophylactic treatment regimens achieve a less severe clinical phenotype by maintaining hemostatically protective factor levels, accomplished with regularly scheduled infusions. Specific regimens to achieve optimal bleed suppression and prevention vary. Current standard prophylactic regimens commonly use infusion therapy given three times weekly, whereas other regimens require administration every other day. Regimens may be individually modified to achieve optimal bleed suppression and tailored to the patient's individual needs. Often, patients have difficulty in adhering to demanding therapeutic prophylactic regimens that include frequent morning infusion to achieve adequate hemostatic coverage during periods of highest activity. As children progress to adolescence, adherence is often further limited, making these regimens less effective.

Inhibitors, or inhibitory alloantibodies to factor concentrates, develop in approximately 25%–30% of patients with severe hemophilia A and 3%–13% of those with moderate or mild disease. Inhibitors neutralize infused FVIII and greatly affect a patient's ability to achieve hemostasis. A bleeding episode in patients with high inhibitor titers requires the use of a bypassing agent; effective use of prophylaxis is greatly diminished in this subset of patients. Patients with inhibitors require considerable management expertise. The use of bypassing agents and immunotolerance regimens that aim to decrease the inhibitory alloantibodies remain enormously costly. Therefore, much work remains in determining predictors of inhibitor development and in developing regimens to modify the individual's immune response.

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This report will discuss recent advances in prophylaxis and imaging to prevent bleeding episodes, reduction of the incidence of inhibitors, and management of acute bleeding episodes in hemophilia patients.

## PREVENTION OF BLEEDING EPISODES: USE OF PROPHYLAXIS AND IMAGING

### Bleeding Tendency and FVIII Activity Level

Joints can be preserved and bleeding can be minimized when circulating FVIII levels remain ≥ 1 IU/dL.10 Patients receiving prophylaxis with recombinant FVIII who have had prolonged intervals of circulating FVIII levels < 1 IU/dL experience an increase in bleeding episodes and hemarthroses.11 Thus, prophylactic regimens used in patients with hemophilia A have been designed to maintain the FVIII activity ≥ 1 IU/dL.

Pasi et al12 examined bleeding tendency in relation to predicted FVIII activity levels in patients with severe hemophilia A who were treated with recombinant FVIII crystallizable fragment (Fc) fusion protein (rFVIIIFc) in the A-LONG study. A two-compartment population pharmacokinetic model of rFVIIIFc was developed based on activity-time profiles in 180 patients with severe hemophilia A who were 12–65 years of age. Negative binomial regression models were used to correlate the number of bleeding episodes with the annualized time (in days) that the patients’ FVIII activity levels were < 1 IU/dL. Models were adjusted for age, body mass index, baseline human immunodeficiency virus (HIV) and hepatitis C virus status, baseline von Willebrand factor level, number of bleeding episodes, and time on study.

Multivariable negative binomial regression analysis showed that the number of overall bleeding episodes increased the more time that patients experienced a FVIII activity level < 1 IU/dL (P < 0.001). A significant association also was found between the length of time in which patients had a FVIII activity level < 1 IU/dL and different types of bleeding (spontaneous, traumatic, or joint). In addition to their increased bleeding tendency, the chance that these patients would be bleeding-free was lessened. These findings reinforce the importance of a therapeutic threshold of 1 IU/dL of FVIII activity and contribute to building a stronger foundation for designing effective rFVIIIFc prophylactic dose regimens.

### Long-Lasting Recombinant Factor IX Fc Fusion Protein (rFIXFc)

Prophylactic replacement of FIX, which is used to treat people with hemophilia B, requires up to three weekly intravenous injections. To reduce the frequency of injections, a long-acting recombinant protein (rFIXFc) consisting of one rFIX molecule covalently bonded to the Fc domain of immunoglobulin G1 (IgG1) was developed. Fc fusion uses an endogenous IgG recycling pathway to prolong the half-life of therapeutic proteins. The phase 3 B-LONG study (ClinicalTrials.gov ID No. NCT01027364) examined the pharmacokinetics, safety, and efficacy of rFIXFc given to previously treated subjects with hemophilia B.13 Age may affect the half-life of recombinant coagulation factors.14

A planned subgroup analysis by Shapiro et al15 examined whether age influenced the pharmacokinetics, safety, and efficacy of rFIXFc use. Male subjects with severe hemophilia B (≤ 2 IU/dL) who were at least 12 years of age, who were without inhibitors to FIX, and who had ≥ 100 exposure days to FIX were assigned to one of four treatment arms. Arm 1 included those who had weekly prophylaxis, arm 2 included those who had individualized interval prophylaxis, arm 3 included those who had episodic treatment of bleeding episodes, and arm 4 included those who had perioperative management. The study was stopped when prespecified exposure was achieved and the specified number of major surgical procedures were completed. The pharmacokinetic parameters of rFIXFc were estimated in all study participants by a noncompartmental analysis based on a one-stage clotting assay. A sequential subgroup analysis compared the pharmacokinetic profile of rFIXFc with that of rFIX in arm 1. The primary endpoints were annualized bleeding rate (ABR), the incidence of adverse events, and inhibitor development. This subgroup analysis compared the outcomes in adolescents (12–17 years of age) with those of adults (18–65 years of age). Efficacy of rFIXFc was assessed by comparing the ABR in arms 1 and 2 with that in arm 3 separately for adolescents and adults.

A total of 123 patients were enrolled at 50 study centers in 17 countries. The median treatment duration was 51.4 weeks across all arms. Eleven adolescents were enrolled in arms 1–3 and none in the perioperative management arm (arm 4). All adolescent patients had evaluable rFIXFc pharmacokinetic profiles. The terminal half-life, clearance, incremental recovery, and volume of distribution at steady state were similar between adolescents and adults. The ABRs of adolescents also were comparable to those of adults. Both adolescent and adult subgroups in the prophylactic arms (arms 1 and 2) had lower ABRs than did those in the episodic treatment arm (arm 3). No distinctive safety issues were observed in adolescents; their safety profile was similar to that of the adult population.

Pharmacokinetic parameters, safety profiles, and ABRS with rFIXFc prophylaxis were similar in adults and adolescents. This analysis supported the primary result of the B-LONG study, showing that rFIXFc is well tolerated and effective for preventing bleeding episodes in both adults and adolescents with hemophilia B.

### Delayed Prophylaxis Has Long-Term Effects in Patients with Severe Hemophilia

The Joint Outcome Study (JOS) was a randomized, controlled clinical trial in boys with severe FVIII deficiency comparing prophylaxis (ie, 25 IU/kg of FVIII given every other day, beginning before age 30 months) with an enhanced episodic regimen used only in response to bleeding.16 At age 6, patients were discontinued from the study, and joint outcome by sensitive magnetic resonance imaging (MRI) and physical examination of six index joints (including both ankles, knees, and elbows) were evaluated. The JOS data...
demonstrated the superiority of prophylaxis over episodic therapy (P < 0.05). At the end of the study, all parents were informed of the study results, and patients were switched to prophylaxis.

The JOS Continuation Study (JOSc) currently is being performed to determine the results of early prophylaxis on joint development until age 18 years and the impact of delaying initiation of prophylaxis until age 6 years. All boys in the original JOS trial were eligible to enroll in the continuation study. Data being collected include the cumulative number of index, joint, and total hemorrhages; joint physical examination score of six index joints, using the Colorado Pediatric Joint Assessment Scale; MRI, soft-tissue, osteochondral, and total scores; and total scores of six index joints using the expanded MRI 45 Scale. Additional data are being collected on prophylaxis adherence, activities, surgeries, quality of life, and replacement factor use.

To date, results from 26 (40%) of the original 65 boys, including 16 on early and 10 on delayed prophylaxis, comprising a total of 156 index joints are available for analysis. Following delayed initiation of prophylaxis, adolescents manifested increased numbers of hemarthroses and increased MRI damage affecting particularly their bones and cartilage. MRI was more sensitive than was joint physical examination in determining joint outcome.

MRI to Detect Hemophilic Joint Disease

Arthropathy can be prevented by routine replacement of FVIII in patients with hemophilia A.16 However, whether prophylaxis retains efficacy if it is initiated after the onset of recurrent hemarthroses or in individuals with established arthropathy (secondary or tertiary prophylaxis) is unknown.

At the ASH meeting, Glorioso et al19 presented the results of a meta-analysis that examined the natural history of hemophilic arthropathy in patients with hemophilia A who were treated only in response to acute bleeding (on-demand therapy) as a baseline for future work. The researchers sought to estimate the amelioration of arthropathy attributable to secondary or tertiary prophylaxis.

Data were aggregated from participants given on-demand therapy during three studies—the JOS10 (and JOSc17), baseline results from the SPINART study,10 and the Cross-Sectional MRI study21—into a single database. To be eligible, patients had to have a FVIII level ≤ 2%; a negative history for inhibitors; a bleeding history of ≥ 12 months before study data acquisition; and assessments of both ankles, knees, and elbows. Joints were assessed using physical examination and T2 gradient echo MRI scored using the World Federation of Hemophilia Gilbert score and the 45-point extended MRI Scales.8,18 MRI data were divided into soft-tissue and osteochondral changes. Bleeding episodes and Gilbert scores for all six joints and MRI data for knees and ankles were analyzed using standard descriptive statistics; regression methods were used to quantify the rate of change in scores of joint damage with age.

Results from the three studies provided data on 275 patients between 1 and 50 years of age. Clinical findings, Gilbert scores, and MRI data were extracted and analyzed from multiple joints in each of 157 individuals given on-demand treatment only. The number of bleeding episodes was approximately constant at 20 per year, regardless of age. Gilbert scores showed a steeper rise in young patients but did not increase as patients passed the late-teenage years. However, when compared with bleeding rates and Gilbert scores, MRI scores showed continued age-related deterioration. Age-related total and osteochondral deterioration on MRI increased steadily with age (on average, 2 MRI points per year of age; P > 0.0001). Soft-tissue scores increased rapidly to approximately 9 by age 20 years and then plateaued at approximately 10 for ages 20–50 years (0.08 MRI points per year; P = 0.28).

The authors of this study concluded that individual patient meta-analysis of bleeding frequency, joint physical examination, and MRI joint structure are useful for determining the natural history of hemophilic arthropathy in patients receiving on-demand therapy. Joint bone and cartilage abnormalities increased continuously across the age span despite an early leveling in bleeding rate and joint physical function. These data will be critical for determining the quantitative effects of prophylaxis begun at various ages on mitigation of joint deterioration following the onset of joint bleeding.

REducing the Incidence of inhibitors

Early Low-dose Prophylaxis in the Absence of Immunologic Danger Signals

The development of inhibitors is regulated by patient-specific and treatment-related factors associated with the immune response. Of the known risk factors, intensive treatment at an early age has been shown to be significant. Early prophylaxis, defined as first exposure to FVIII in the absence of a bleed in the first year of age, may induce FVIII tolerance, thereby protecting patients from inhibitor development.

The Early Low-Dose Prophylaxis in the Absence of Immunological Danger Signs (EPIC) Study22 prospectively assessed the ability of a once-weekly, low-dose prophylactic regimen started before 1 year of age and before the onset of a severe bleeding phenotype (ie, joint bleed) combined with the minimization of immunologic danger signals to reduce the incidence of inhibitor formation in previously untreated patients with severe and moderately severe hemophilia A.

This study enrolled 22 patients, 19 of whom received treatment with FVIII. All patients had severe hemophilia A. Eleven (58%) of these patients were never exposed to factor VIII before, whereas the remaining 42% previously were treated with FVIII concentrates. Eight subjects developed a confirmed inhibitor, and two of these individuals had only borderline positivity at inhibitor testing. Thus, the incidence of an inhibitor titer > 0.6 Bethesda units (BU) was previously untreated patients was 27%. However, 67 major protocol deviations were reported in 15 patients; 44 deviations were reported in 10 patients and were related to the treatment
regimen. These deviations contrasted with the protocol intention, which was to minimize immunologic danger signals and low-dose prophylactic regimens. As a result of the observed inhibitor incidence, the study was terminated based on a futility analysis (the probability to achieve the primary endpoint of inhibitor rate reduction to ≤ 15%).

A significant number of violations in the setting of a demanding study protocol made it difficult to determine whether treatment decisions in the presence of immunologic danger signals correlate with inhibitor formation. Thus, the investigators could not verify or disprove the hypothesis that early low-dose prophylaxis given in the absence of immunologic danger signals might reduce inhibitor incidence in previously untreated patients with hemophilia A.

**Prompt Immune Tolerance Induction at Inhibitor Diagnosis**

Immune tolerance induction (ITI) for patients with hemophilia A with inhibitors has an overall reported success rate of 60%–80%, yet it is the only modality known to effectively eradicate inhibitors. One debate concerns the optimal time to start ITI. Recent guidelines recommend delaying ITI until the inhibitor titer is < 10 BU.23

Nakar et al24 performed an analysis to determine the success of ITI relative to time from inhibitor detection to ITI initiation. Data were collected retrospectively from two hemophilia centers in the United States. Patients with severe or moderate (≤ 5%) FVIII deficiency underwent ITI; investigators gathered information on the time interval from inhibitor detection to ITI start, inhibitor titer, and outcome. High-dose ITI was practiced by both centers at ≥ 100 IU/kg per day. Success, partial success, and failure were defined practically, with success involving a negative inhibitor titer and the ability to use FVIII concentrate routinely to treat and prevent bleeding. Partial success involved an inhibitor titer < 5 BU with the ability to use FVIII concentrate to treat bleeding episodes. Failure was defined as ongoing ITI > 3 years without achieving success or partial success or as discontinuation of ITI.

Patients were first divided into a low-responding inhibitor (LRI) subgroup and a high-responding inhibitor (HRI) subgroup based on peak inhibitor titer. The HRI subgroup was further subdivided based on the time to ITI initiation; the first subgroup initiated therapy within 1 month, the second from 1 to 6 months, and the third > 6 months from diagnosis of the inhibitor. The HRI subgroup starting ITI within 1 month was analyzed based on pre-ITI inhibitor titers.

This analysis included male patients with adequate ITI history documentation. Almost all (95%) had severe FVIII deficiency. Overall, 49 of 58 patients (84%) underwent successful ITI. Among those with LRIs (19 patients [33%]), ITI success was 100%. Among 39 patients (67%) harboring HRIs, tolerance was achieved in 30 (77%), and partial success and continued ITI was achieved in 1 individual (3%); therapy failed in 7 (18%).

Of 23 patients who started ITI within 1 month of detection, 91% achieved success. All 13 patients (100%) starting ITI with a pre-ITI inhibitor titer ≥ 10 BU achieved success. Of the 11 patients who started ITI 6 months after detection of inhibitor, only 7 (64%) achieved success; therapy failed in 4 (36%).

These results suggest that the time interval from inhibitor detection to the start of ITI may play a critical role in eventual outcome. An inhibitor titer ≥ 10 BU did not influence outcome when ITI was used within 1 month of detection, supporting this approach in contrast to the commonly accepted practice of delaying the start of ITI until an inhibitor titer < 10 BU is achieved. Patients with hemophilia A may benefit from prompt ITI regardless of the current inhibitor titer and are not subjected to wait periods when bleeding is more likely to occur. Prompt ITI should be considered a worthwhile therapeutic option in newly identified inhibitor patients irrespective of inhibitor titer.

**Management of Acute Bleeding**

Four-Factor Prothrombin Complex in Achieving Hemostasis

When rapid correction of coagulopathy is required, as in cases of intracranial hemorrhage, administration of prothrombin complex concentrate (PCC) may offer some advantages over infusion of fresh frozen plasma. Historically, the major drawback of PCCs has been the risk of thrombotic complications.25 However, PCCs have many benefits. For example, they are subjected to at least one viral inactivation step, which reduces the risk of pathogen transmission. Further, they are nanofiltrated, so they are unlikely to provoke transfusion-related acute lung injury.

A four-factor prothrombin complex concentrate (4F-PCC) recently was approved by the US Food and Drug Administration for urgent vitamin K antagonist (VKA) reversal in patients with major bleeding. Rapid reversal of VKA-induced anticoagulation is often needed for patients requiring urgent surgical procedures. Plasma currently is the standard of care in the United States for VKA reversal prior to emergency surgery.

A prospective phase 2b, open-label, noninferiority trial compared the efficacy and safety of 4F-PCC with those of plasma in patients requiring VKA reversal before undergoing an urgent surgical procedure.26 Patients were randomized to receive a single dose of either 4F-PCC or plasma. Dose was based on baseline international normalized ratio (INR) and weight. There were two primary endpoints: effective hemostasis (prevention of excessive perioperative bleeding from the start of study product infusion...
CONCLUSION

Over the past 50 years, the lifespan of an individual affected with severe hemophilia has increased from a mere 20 years to near that of the general unaffected population. This improvement is a result of parallel advances in the development and manufacturing of safe and effective coagulation factor replacement therapies and prophylactic regimens. Furthermore, these strides are products of technologic leaps that allow for rapid control of acute, life-threatening bleeds. Ongoing studies will be crucial in continually improving the quality of life of people with hemophilia and decreasing the cost of their care.

REFERENCES