

Prophylaxis for Severe Hemophilia: Clinical Challenges in the Absence as Well as in the Presence of Inhibitors

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Current Status of Factor Prophylaxis in the Hemophilia Population

Victor Blanchette, Canada

Prophylaxis is known to prevent joint bleeds and the development of arthropathy in patients with severe hemophilia. However, questions and challenges remain concerning when it should be started, how often it should be administered and what is the optimal dosage, said Dr. Victor Blanchette.

Patients with severe hemophilia and low factor levels are prone to recurrent bleeds, most commonly in the elbows, knees, and ankles. Left untreated, patients suffer pain, swelling, limitation of movement, and eventually joint damage. Prophylaxis, defined as “treatment by intravenous injection of factor concentrate in anticipation of, and in order to prevent, bleeding” offers a reliable strategy to significantly limit, and in many cases, prevent hemophilic arthropathy.

Prophylactic treatment has advanced over the decades as researchers have gained understanding of joint pathophysiology – the complex interactions of toxins released into the bleeding joint that lead to a vicious cycle of synovial inflammation, synovial hypertrophy, recurrent joint bleeds and hemophilic arthropathy.

The European Paediatric Network for Haemophilia Management (PEDNET) proposed the following definitions for primary and secondary prophylaxis in the context of musculoskeletal bleeding:

- primary prophylaxis consists of regular, continuous treatment started after the first joint bleed and before the age of two years, or regular, continuous treatment started before the age of two years without a previous joint bleed.
- secondary prophylaxis consists of regular, continuous (long-term) treatment started either after two or more joint bleeds or after the age of two years, or intermittent, regular (short-term) treatment because of frequent bleeds.

Intermittent, short-term prophylactic treatment is sometimes used in countries with limited availability of clotting factor concentrates.

Thirty years ago the WFH endorsed an orthopedic joint scoring system, the WFH Orthopedic Joint Score, introduced by Gilbert in 1985 that is based on a careful physical examination of the six index joints (elbows, knees, ankles) to assess the following:

- Swelling
- Muscle atrophy
- Axial deformity (knees and ankles)
- Range of motion

- Flexion contracture
- Crepitus on motion
- Instability
- Pain (additional separate measure)

The WFH Radiological Joint Score, introduced by Pettersson et al. in 1980, measures types of change in the six index joints using a 0 to 2 scoring system for each item (a perfect score is 0), with a total score per joint of 0 to 13. The items (joint changes) measured by diagnostic imaging are:

- Osteoporosis
- Enlarged epiphysis
- Irregularity of the subchondral surface
- Narrowing of joint space
- Subchondral cyst formation
- Erosion at joint margins
- Incongruence between joint surfaces
- Joint deformity

A 2002 Dutch study by Fischer et al. showed that Pettersson scores do not identify the effects of joint bleeds until quite late – in some cases after more than 100 bleeds.

In Sweden, the Malmö study of a high-dose prophylaxis regimen in 60 patients with severe hemophilia demonstrated that prophylaxis started at an early age results in fewer joint bleeds than secondary prophylaxis in older patients. A further study pooling data from 121 patients with severe hemophilia A or B found that primary prophylaxis in individuals with severe hemophilia should be started at an early age, but can be individualized. However, the proportion of children with a perfect joint score of 0 declines significantly if prophylaxis is not started until after two years of age, with notable negative impact if prophylaxis is not begun until later childhood years.

For maximum benefit, prophylaxis must be started at a very young age (one to two years of age) before the onset of clinically significant joint bleeding, Dr. Blanchette said. The Malmö centre, the National Hemophilia Foundation in the U.S., and other groups have endorsed early initiation of primary prophylaxis (prior to the onset of frequent bleeding), with a target of monitoring trough factor levels above 1% between doses. Dose and frequency vary from the original Swedish regimen of 20–40 IU/kg three times per week, to lower-dose and step-up regimes starting with 15–25 IU/kg once weekly, and increased dose and frequency in the case of bleeds. Subclinical joint bleeding can lead to hemophilic arthropathy; therefore, compliance with the prophylaxis protocol is essential for an excellent musculoskeletal outcome, Dr. Blanchette said.

Prophylaxis in Patients with Inhibitors

Manuel Carcao, Division of Haematology/Oncology, The Hospital for Sick Children, Associate Professor of Pediatrics, University of Toronto, Toronto, ON, Canada.

Patients with severe hemophilia A have the potential to maintain a nearly normal life with virtually no joint damage provided they are placed on prophylaxis at a young age, are compliant, and continue on prophylaxis. The development of a high-titer FVIII inhibitor, which occurs in approximately 15% of patients with severe hemophilia A, can change this excellent outcome. These patients experience an increased risk of recurrent joint bleeding primarily because they cannot be treated with conventional prophylaxis.

Fortunately about two-thirds of patients with inhibitors can be successfully tolerized (rendered responsive to FVIII), generally within 1-2 years of starting immune tolerance induction (ITI) therapy. However, some patients continue to have persistent inhibitors and consequently experience recurrent bleeds that are difficult to treat, worse joint disease, and overall poorer quality of life. Dr. Carcao reviewed two studies (Leissingner et al, *Blood*, 2001; Gringeri et al, *Blood*, 2003) both of which showed significantly worse joint disease in patients with inhibitors than in those without inhibitors.

Dr. Carcao raised the issue - is prophylaxis an option for patients with hemophilia and inhibitors?

Dr. Carcao described some of the emerging evidence describing the use of bypassing agents (FEIBA and rFVIIa) for prophylaxis in patients with inhibitors. These encouraging studies suggest that prophylaxis is a viable option for patients with inhibitors, that it substantially reduces the number of bleeds that these patients experience, and improves their quality of life.

The use of FEIBA for prophylaxis dates back to the early 1970s when Dr. Brackmann incorporated FEIBA into the Bonn ITI regimen. On the original Bonn protocol patients received between 50 U/kg/day to 150 U/kg twice/day of FEIBA. Since then several investigators have reported on the use of FEIBA in patients on ITI. In general these reports all suggest that the addition of FEIBA to ITI reduces the number of bleeds. FEIBA has also been used in the setting of patients not on ITI. Reports in 2000 by Kreutz et.al and in 2003 by Hilgartner et.al documented that FEIBA is well tolerated and safe with no thrombotic events being reported when used for prophylaxis. These studies suggest that prophylaxis with FEIBA should be started relatively early, and not after patients have developed target joints, Dr. Carcao said. In a recent meta-analysis, which was presented in poster format at the WFH 2008 meeting, Valentino and colleagues reviewed 6 studies of using FEIBA for prophylaxis. These 6 studies showed that 31 / 33 patients on prophylaxis with FEIBA experienced a significant reduction in the frequency of joint bleeds after starting FEIBA prophylaxis (overall a 74% decrease in the number of bleeds).

Dr. Carcao then presented the more limited experience with using rFVIIa for prophylaxis in patients with inhibitors. Four case reports of patients (n=7) with inhibitors and high bleeding tendencies demonstrated a "significant reduction in number and severity of bleeds and overall improvement in joint status" following the initiation of prophylaxis with rFVIIa (different regimens were used). In 2007 Morfini and colleagues summarized the experience of using rFVIIa for prophylaxis in patients with inhibitors (n=13) in various European centers. Overall these was a mean reduction in the number of bleeds from 2.5/month to 0.6/month.

Finally Konkle et.al in 2007 recently completed a multicenter, randomized, double-blind parallel group trial investigating the efficacy and safety of rFVIIa prophylaxis in patients with inhibitors and very frequent bleeding. There was a substantial decrease in bleeding frequency (joint bleeds as well as all bleeds) in patients after commencing prophylaxis with either 90 IU/kg/day or 270 IU/kg/day of rFVIIa. Other benefits of prophylaxis included fewer hospital admissions and less days absent from school or work. Follow-up analysis by Hoots et al. in 2008 showed improved quality of life of patients after starting prophylaxis with rFVIIa.

Dr. Carcao concluded by pointing out the advantages and disadvantages of FEIBA and rFVIIa in the context of prophylaxis in patients with inhibitors. The main advantage of FEIBA is its longer half-life, which may allow it to be given less frequently than rFVIIa and yet still be effective in preventing bleeds; however, disadvantages of FEIBA include a much larger diluent volume for reconstitution, necessitating a longer time for administration, and the fact that it is plasma-derived. The advantages of rFVIIa are that it is a recombinant product, in a small infusion volume, allowing it to be given as a bolus injection, and the fact that it has been used with tranexamic acid (a useful antifibrinolytic agent for treatment of mucosal bleeds). The biggest disadvantage of rFVIIa is its very short half-life and the consequent need for very frequent infusions.

Challenges remain in using these bypassing agents for prophylaxis, including determining which patients should be started on prophylaxis and when. The efficacy and safety of these agents when used for prophylaxis must be evaluated, and optimal dosing and frequency of administration determined. Furthermore, while prophylaxis with bypassing agents is feasible, it is expensive and difficult for patients due to the need for frequent administration of the bypassing agent. Consequently it is as yet only practiced in a small number of patients. There is an urgent need for large prospective studies to determine the benefits of prophylaxis for inhibitor patients using FEIBA and rFVIIa, Dr. Carcao said.

Prophylaxis for Severe Hemophilia: Challenges for the First, Second, and Third Decade of Life
Kathelijn Fischer, The Van Creveldkliniek Hemophilia Center - UMC Utrecht, The Netherlands

Hemophilia requires lifelong treatment, and although the benefits of prophylaxis over on-demand therapy are clear, many challenges remain regarding lifetime management of prophylactic treatment for individuals with hemophilia, said Dr. Kathelijn Fischer.

“As our patients grow older, they have different needs in life, and we face different challenges in taking care of them,” she said. “In progression from childhood to adulthood, patients experience different physical aspects of growth, susceptibility to cartilage damage, changes in bleeding patterns, and mental changes. Intensive treatment is important, and must address physical, mental, and social arenas.”

Dr. Fischer outlined the main challenges regarding optimal prophylaxis and treatment management:

- First decade of life: when to start primary prophylaxis in young boys with severe hemophilia, and how to deal with the challenges presented by frequent venous access. Children are at greater susceptibility for joint damage than adults.
- Second decade of life: how to maintain prophylaxis during the patients' transition to independence, self-infusion, and self-treatment. Adherence to treatment can be an issue for teenagers, whereas the majority of adults maintain their regimen.
- Third decade of life: when, if ever, and in which patients prophylaxis could be discontinued.

Data from the Swedish study by Astermark et al. in 1999 and the Dutch study by Fischer et al. in 2002 provide support for starting primary prophylaxis early in life (generally by age two or three years) and after no more than one or two joint bleeds. Primary prophylaxis preserves joint function into adulthood and prevents the onset of arthropathy. Generally, the principles of optimal treatment in the first decade of life have been well established: start prophylaxis early, preferably no later than after the second joint bleed, and increase dose and frequency to prevent hemarthrosis and allow full activity.

At the median age of 21, about 35% of patients are able to stop prophylaxis and taper to on-demand treatment. Dr. Fischer noted that the 2007 Dutch multicentre cohort study led by Gouw et al. suggests that early prophylaxis may be protective against inhibitor formation in boys with severe hemophilia.

The data also indicate a striking difference in the timing of bleeds; across the age spectrum, more bleeds occur during the summer. Physical limitations and bleeding patterns also change with age: predominantly, joint bleeds are associated with an individual's sports and other physical activities. These are important considerations in prophylaxis management, since frequent bleeds and arthropathy have a substantial impact on the patient's ability to participate in school, work, sports, and social activities, Dr. Fischer said.