Issues surrounding therapeutic choices for hemophilia patients

Of the several clinical issues surrounding therapeutic choices for hemophilia patients, prophylactic therapy stands out as the most positive. The first study comparing prophylactic and on-demand treatment, which involved 22 years of follow-up, found that the primarily prophylactic treatment strategy led to better outcome at equal treatment costs in young adults with severe hemophilia.[1]

In contrast, one of the most challenging issues in hemophilia treatment is development of inhibitors to factor VIII (FVIII). Previous reports of inhibitor development risk have varied widely, ranging from approximately <5% to 40%.[2-5] This variability may stem from patient-related, therapy-related, and assay-related influences on inhibitor development and detection, as reported by Wight and Paisley in a current review.[2] Their systematic review concluded that, based on large-scale prevalence studies and hemophilia registry data, 5% to 7% of all hemophilia patients have antibodies to FVIII, with a substantially higher prevalence of approximately 13% among those with severe disease (with prevalence referring to the proportion of the patient population with inhibitors at a given time).[2] On the other hand, the cumulative risk of inhibitor development (number of new cases over a prolonged period adjusted for different patient follow-up durations) varied from 0%[6] to 39%.[7] In any case, inhibitor development complicates patient management and may require immune tolerance induction. Other important issues attendant on FVIII therapy, whether preventive or acute, include cost, venous access, FVIII dosage and dosing intervals, and joint scoring systems.

Prophylaxis or on-demand therapy?

The rationale for prophylactic treatment of hemophilia is based on observations that patients with moderate hemophilia (FVIII/FIX >0.01-0.05 IU/mL) rarely develop chronic arthropathy.[8] Moreover, many studies have shown that, even at high doses, on-demand therapy is not effective in preventing arthropathy.[9,10]

The possibility of changing the clinical phenotype of patients with severe hemophilia to a moderate phenotype has been a challenge. Without adequate therapy, patients with severe hemophilia (FVIII/FIX < 0.01 IU/mL) have a life expectancy of about 20 years, during which they suffer from severe bleeds, spontaneous or from minor trauma, and early, crippling arthropathy.[11] Those with moderate disease experience only traumatic bleeds and, in turn, develop far less arthropathy. It follows, therefore, that increasing the level of clotting factor activity to at least 1% with prophylactic therapy should prevent bleeding in patients with severe hemophilia.

As defined by the European Paediatric Network for Haemophilia Management, primary prophylaxis is started before the age of 2 years, either before or after the first joint bleed.[12] Classic treatment consists of thrice-weekly doses for hemophilia A, to achieve permanent minimum factor VIII levels of >1%. Another option is one dose every 2 days. Dosage varies between 20 and 50 IU/kg of weight, depending on the pharmacokinetic properties of a particular product in each patient and dosing intervals. The program is continued until the end of the growth period, when the patient has the option of suspending continuous prophylaxis and changing to on-demand treatment interspersed with periods of prophylaxis if appropriate.

Prophylaxis has been practiced for many years in Sweden and The Netherlands, as well as other European countries.[1,8,13-18] A number of early studies demonstrated that long-term prophylaxis can prevent arthropathy. The first study to compare on-demand with primary prophylactic treatment involved 49 Dutch (prophylaxis) and 106 French (on-demand) patients.[1] All were born between January 1970 and January 1981; none had a history of antibodies to FVIII or FIX. On-demand therapy was given per bleeding episode; prophylaxis was started at an early age according to each patient's bleeding pattern, in most, after several joint bleeds. For prophylaxis, intermediate doses of 15 to 25 IU/kg were administered twice or three times a week, with doses adjusted in cases of breakthrough bleeds. Patients with very mild bleeding patterns received only episodic prophylactic treatment, and some discontinued prophylaxis in adulthood.[19] Compared with those primarily treated with prophylaxis, on-demand patients had more joint bleeds, higher clinical scores, and higher Pettersson scores.[1]

In the United States, the Orthopedic Outcome Study, a 6-year prospective, cross-national follow-up study of clinical outcomes associated with different patterns of factor VIII utilization, confirmed the beneficial effects of prophylaxis compared with on-demand therapy.[10] On the basis of these positive data, the Medical and Scientific Advisory Council of the National Hemophilia Foundation recommended prophylaxis as optimal therapy for individuals with severe hemophilia A and B.[20]

Among the concerns raised about prophylactic therapy is the potential increased exposure to blood-borne infectious agents with large donor pooled plasma

Table 1. Rate of infection in hemophilia patients using central venous lines.

Study	*Number of patients*	*Rate of infection per 1000 patient days*	*Comment*
Blanchette *et al*., 1996[25]	19	0.7	3 patients with inhibitors, 3 HIV+
Perkins *et al*., 1997[22]	35	1.2 (central) 0.7 (peripheral device)	7/32 inhibitors, 2/32 vWD
Ljung *et al*., 1998[24]	53	0.19	11 patients with inhibitors
Santagostino *et al*., 1998[26]	15	0.3	2 inhibitor patients, 13 on prophylaxis
Miller *et al*., 1998[27]	41	0.14	Includes external
McMahon *et al*., 2000[28]	58	1.6 (without inhibitor) 4.3 (with inhibitor)	77/86 devices Port-A-Cath; 37/58 patients hemophilia
Tusell [*personal communication, 2002*]	35	0.28 (prophylaxis) 0.68 (ITI)	Port-A-Caths used for prophylaxis/on demand or ITI

ITI, immune tolerance induction; vWD, von Willebrand disease. Adapted from Ljung,[23] with permission.

products. This concern has been obviated by modern donor screening, plasma-derived FVIII concentrate purification and virucidal procedures, and the introduction of recombinant products.[21]

Venous access

Regimens of primary prophylaxis beginning in the first year of life can prevent hemophilic arthropathy. However, reliable venous access is needed for these treatments and repeated peripheral venipuncture can be difficult or impossible in very young children. Thus, central venous catheters (CVCs) are commonly used in these patients, with the attendant risks of infection and deep venous thrombosis (DVT).

Most studies with implantable venous access devices (IVADs) have been conducted using the Port-A-Cath system. However, peripheral ports have been associated with a higher frequency of thrombophlebitis and thrombosis. In a study of central and peripheral ports in 35 children, the rates of local infection and bacteremia with central devices were 3% and 33%, respectively, compared with rates of local infection of 25% and bacteremia of 25% with peripheral ports.[22] One patient required removal of a central port due to thrombosis. The majority of infections were cleared with antibiotics, and ports remained intact. Both types of IVADs were associated with high patient and parent satisfaction.

Infection is the most frequent complication when using an IVAD. Several recent, large studies are listed in Table 1.[23-28] A 1998 review reported that 50% to 83% of patients with inhibitors can be expected to get an infection.[29] One possible reason for this is that the patients have small hemorrhages around the port post-injection, which can stimulate bacterial growth in subcutaneous tissue. For patients without inhibitors, the need for a port has to be considered together with risk of complications. Whether the infection frequency in these children is acceptable depends on individual patient factors and treatment regimens.[24] A recent case of catheter-associated *Staphylococcus aureus* septicemia in a hemophilic child (eradicated with antibiotics injected via the catheter) prompted a warning to clinicians.[30] In another study of CVCs in 23 children with severe congenital coagulopathy, despite 13 documented catheter infections (five children had inhibitors), both clinicians and parents believed the potential hazards of the devices to be acceptable given the considerable benefits.[31]

Thrombosis in patients with bleeding disorders is seemingly paradoxical. Nevertheless, thrombi do occur, albeit more slowly, perhaps because hemostasis is only intermittently normalized by factor infusions. Figure 1 depicts the probability of a patient remaining free of DVT after insertion of a CVC.[32] Among 15 boys with severe hemophilia, eight had evidence of DVT on contrast venograms. However, these children had had CVCs in place for at least 4 years. The investigators concluded that removal of catheters within 4 years might prevent thrombosis, and screening venography may be warranted for patients who require the devices for longer periods.

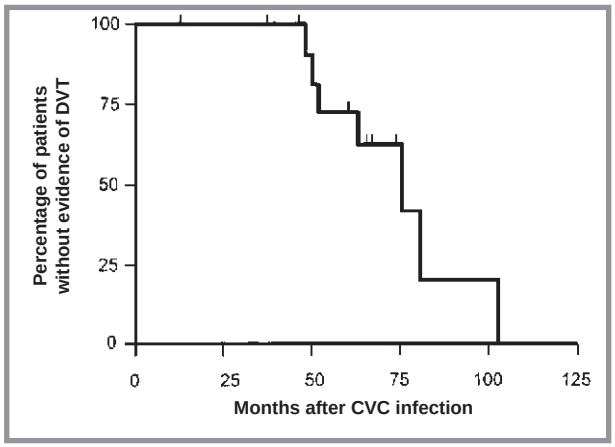

Figure 1. The probability of hemophilia patients remaining free of deep venous thrombosis (DVT) at various intervals after insertion of a central venous catheter (CVC). No patient whose catheter was in place for < 48 months had an abnormal venogram, whereas all those with catheters in place for >73 months had venographic evidence of DVT. Adapted from Journeycake *et al.*,[32] with permission.

Others have reported little or no infection and no DVT associated with implantable catheters; rather, their use has permitted optimal prophylactic home treatment by parents,[33] low risk of infection and other complications,[27] and overwhelming enthusiasm by parents and children with no major complications.[34]

Cost

Cost is the main reason why prophylaxis is not implemented on a larger scale. Several studies have attempted to measure the cost-effectiveness of this approach.[35–37] One major cost analysis was conducted using data from the Orthopedic Outcomes Study.[35] A total of 831 patients with severe hemophilia aged 1 to 31 years from 19 centers were included. Patients were categorized into three groups according to the number of weeks in which they received prophylactic regimens, and costs of hospitalization, surgery, days lost from school or work, and factor VIII utilization were estimated. Patients who received factor VIII on demand incurred substantially greater disability-related costs (most accounted for by hospitalization for hemophilia-related conditions) than those who received prophylaxis for some or all of the study period. Reductions in non-factor healthcare costs and disability associated with prophylactic therapy helped to offset the much higher costs of the prophylactic regimen. Although frequent on-demand treatment may be more expensive than full-time prophylaxis for certain patient subgroups, total healthcare expenditures were highest among patients receiving prophylaxis, given the high cost of year-round factor VIII use.

Several groups have tried to reduce cost by modifying strict prophylactic regimens, including using early but progressive, escalating-dose, or individualized regimens.[38,39] Treatment is started equally early, before 2 years of age, but the interval between doses is adjusted according to each patient's clinical behavior. These and other studies suggest it is possible to select patients for prophylaxis based on clinical factors. Using the date of the first joint bleed as a parameter of clinical severity, one group found the age to range from 0.4 to 7.7 years (mean 2.4 years).[40] Whereas prophylaxis would have been routinely started at 1 year of age, in this study population, 50% of the patients would have been treated a minimum of 1.5 years before experiencing their first joint bleed. These investigators have also shown that waiting for the first joint bleed before starting prophylaxis does not increase the risk of arthropathy.[41]

Dosing and dose interval are important issues in efforts to optimize hemophilia care (primarily orthopedic outcomes)[10] and treatment costs. Low doses at frequent intervals and ideally, as continuous infusion, will probably give the best cost efficacy of prophylaxis.[18] Prophylaxis can be targeted at preventing spontaneous joint bleeds (intermediate-dose regimen), or at maintaining minimum clotting factor activity levels (high-dose regimen).[42] In young adults, clotting factor consumption for intermediate dose prophylaxis is similar to consumption for on-demand treatment, whereas outcome is more favorable. Clotting factor consumption for high-dose prophylaxis is two-fold higher, but outcome is only slightly better than that achieved with intermediate-dose prophylaxis.[42]

One group suggested prophylaxis as a standard treatment until the age of 18 years,[43] and recently a cohort study in 49 patients suggested that 22% of patients with severe hemophilia could safely stop taking prophylaxis in adulthood.[19] Apparently, these patients were all treated with early prophylaxis, but were characterized by a milder bleeding pattern than the patients who continued prophylaxis. However, the long-term effects of discontinuing prophylaxis in patients with milder bleeding patterns should be assessed, preferably in a prospective study, before becoming standard treatment.

Evaluation of joints

A main goal of prophylaxis is to prevent not only joint bleeds but also the development of arthropathy, which is independently associated with the age of prophylaxis initiation.[44] However, neither the orthopedic nor the radiologic (Pettersson) joints score, both of which are approved by the World Foundation of Hemophilia (WFH),[45,46] detects very early joint changes

in young children. The advent of magnetic resonance imaging (MRI) has opened up new possibilities of precise evaluation of small joints,[18] resulting in more consistent assessment of changes and more targeted treatment.[47] Comparison of findings from clinical examination (including bleeding scores, pain scores, and physical examination scores) and MRI assessments of blood, synovia, and cartilage in 21 joints of 16 hemophilia patients showed little correlation.[48] Clinical examination revealed evidence of a bleeding episode in 12 joints, whereas MRI identified blood or blood products in 15 joints. Given the MRI findings, therapeutic management was changed from on-demand to prophylactic therapy in six study patients. MRI is difficult to perform in young children, however, who require general anesthesia for the procedure. It is also time-consuming and costly.

FVIII inhibitors

Development of inhibitors is a primary concern of physicians with current use of highly purified blood products and recombinant FVIII preparations. The immune systems of patients with severe hemophilia A recognize administered FVIII as foreign, and in some patients, mount an immune response. The resulting antibodies rapidly inactivate FVIII, dramatically decreasing treatment efficacy.

Inhibitor development appears to relate to defects in the factor VIII gene rather than to concentrate infusion.[3] Mutations leading to the absence of endogenous factor VIII protein (for example, large multidomain deletions, nonsense mutations, or intron 22 inversions) are associated with the highest risk of inhibitor development.[49,50] It has been confirmed that other factors also influence inhibitor development. For example, severity of disease seems to be an important risk factor, whereas few patients with mild disease acquire the antibodies.[5] Some families seem more likely to develop inhibitors,[5] as do children of African and Hispanic descent.[48] Recently, study results demonstrated that age at first exposure was associated with inhibitor development.[5,51] Patients who received their first exposure very early had a higher probability of developing an inhibitor. Other studies are necessary to confirm these results.

Patients with FVIII antibodies are generally categorized into two groups: low responders (inhibitor titer ≤ 5 BU) and high responders (>5 BU), based on the Bethesda assay.[52] Development of a high titer inhibitor is the strongest challenge in the field of hemophilia therapy.

Previously treated patients (PTPs) seem to be at lower risk for inhibitor formation than those previously untreated (PUPs), although this has not been definitively established. For example, the Cooperative Inhibitor Study sponsored by the National Heart, Lung, and Blood Institute reported an incidence of new inhibitor formation of 8 cases per 1,000 patient years of observation, but based these findings on a patient population of PTPs.[53] In prospective trials with rFVIII preparations (both full length and B-domain deleted), the percentage of PUPs with severe hemophilia A who developed FVIII inhibitors has varied between 28.3% and 30.6%.[54] Many of the inhibitors were transient, however, disappearing while the patient was receiving on-demand treatment, others responded to immune tolerance induction regimens with rFVIII alone, while other inhibitors persisted. Moreover, in trials with rFVIII preparations in PTPs, no or only one subject per trial developed an inhibitor.

Although immune tolerance induction is generally seen as the therapeutic goal for patients with inhibitors, opinions differ regarding how to perform induction, and cost remains a deterring factor. Several regimens of FVIII products have been described, involving low, moderate, and high doses. Another, termed the Malmö regimen, combines factor VIII infusions with immunomodulating treatment with cyclophosphamide and high-dose intravenous gamma globulin followed by a regular prophylactic program of factor VIII therapy.[55] For patients who are resistant to immune tolerance induction, or for whom it is impossible for economic or availability reasons, treatment of acute bleeding has been possible with so-called bypassing agents. Recombinant activated factor VII is reported to induce hemostasis in many patients,[56] and prophylaxis with activated prothrombin complex concentrate has successfully controlled bleeding episodes in patients with high-titer inhibitors.[57]

Induction of early immune tolerance (already tested in animal models)[58] or use of recombinant factors that lack immunogenic regions of factors VIII or IX to prevent inhibitors from developing in the first place,[59] are both potential solutions to a problem that continues to jeopardize outcome of hemophilia patients.

Conclusions

The hemophilia community generally agrees that factor prophylaxis is the 21st-century method-of-choice for treating severe hemophilia A or B. A number of prophylactic regimens are currently in use, all of which markedly reduce/prevent bleeding episodes and prevent arthropathy. Some concerns remain, however, including the high cost of such therapy and its requirement for long-term venous access in young patients.

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