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Prophylaxis in bleeding disorders

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ABSTRACT

Primary prophylaxis with coagulation factor concentrates has become the standard of care for children with hemophilia to reduce the risk of bleeding and related morbidity. However, several important questions remain unanswered regarding the optimal use of prophylaxis in patients with bleeding disorders. Limited data are available on the use of primary prophylaxis in adults with hemophilia, although tailoring the dose and schedule of prophylaxis in adults based on the clinical course of the disease may improve convenience and reduce costs without compromising efficacy. Patients with severe forms of von Willebrand disease (VWD) are at risk of serious bleeding episodes and may therefore benefit from prophylaxis; results from ongoing trials, such as the VWD International Prophylaxis (VIP) trial, are expected to provide more insight into the efficacy and safety of prophylaxis in these patients. For patients with other rare bleeding disorders, prophylaxis may be considered, depending on the clinical course of the disease and the availability of factor replacement therapy products; definitive recommendations, however, are not possible given the lack of comprehensive studies evaluating prophylaxis in this setting. Ongoing studies will help further define the role of coagulation factor concentrate prophylaxis in patients with bleeding disorders.

With regard to the treatment of children with hemophilia, there is now global consensus that primary prophylaxis with coagulation factor concentrates is the standard of care and should be initiated at a young age before the onset of overt joint disease in countries where there is reliable access to safe coagulation factor concentrates [1,2]. However, the benefits of secondary prophylaxis, and primary prophylaxis in adults with hemophilia, have not been fully defined. Less is known about the efficacy of prophylaxis in other populations, such as patients with severe von Willebrand disease (VWD) or rare bleeding disorders such as afibrinogenemia. In addition, the optimal dose, schedule, and duration of prophylaxis have not been defined and may vary for different subgroups and individuals. This review highlights some of the current issues clinicians face with regard to the use of prophylaxis in patients with bleeding disorders.

Prophylaxis in hemophilia

Pediatric patients

There is clear evidence that prophylaxis is beneficial in children with hemophilia. In 2007, Manco-Johnson et al. [2] reported the results of a prospective, randomized trial comparing recombinant factor VIII (FVIII) prophylaxis (25 IU/kg every other day) with on-demand therapy (minimum of 80 IU/kg per episode) in 65 boys aged less than 30 months with severe hemophilia A. At the age of 6 years, 93% of patients in the prophylaxis group and 55% of those in the on-demand group had normal index-joint structure on magnetic resonance imaging (MRI) ($p = 0.006$; Fig. 1) [2]. Prophylaxis reduced the risk of joint damage by 83% compared to on-demand therapy. MRI score correlated strongly with the number of bleeding episodes, providing a link between reduced bleeding frequency and joint preservation. Notably, however, some patients with high MRI scores had few or no bleeding episodes, indicating that subclinical joint damage and bleeding may occur and thereby increase the risk of arthropathy.

Other studies have demonstrated that prophylactic therapy can reduce the number of bleeding episodes compared to on-demand therapy (mean 15–31 bleeding episodes annually vs 3–9) [3–5]. A direct relationship between the number of bleeds into a joint and joint damage has been established [3,6]. Aledort et al. [3] initially showed that the radiological Pettersson score of joint damage increased by 1 point for every 30–40 joint bleeding episodes. These findings were confirmed in a later study of 117 cases of severe hemophilia reported by Fischer et al. [6], who also showed that the Pettersson score correlated with the number of bleeds. They noted that the Pettersson score began to increase after the age of 5 years and increased at a rate of 1 point for every 13 bleeding episodes.

Adults

Whether prophylaxis should continue into adulthood remains controversial. Few studies have prospectively evaluated the efficacy,

Abbreviations: FVIII, factor VIII; MRI, magnetic resonance imaging; VIP, VWD, International Prophylaxis; VWD, von Willebrand disease; VWF, von Willebrand factor.

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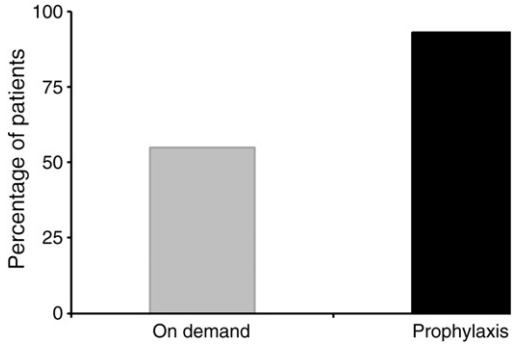

Fig. 1. Presence of normal bone and cartilage by magnetic resonance imaging at age 6 years in patients randomized to on-demand therapy or prophylaxis (25 IU/kg every other day). Data from Manco-Johnson et al. [2].

safety and cost-effectiveness of prophylaxis in young adults with hemophilia [3,7–10], and trials evaluating prophylaxis in older adults are lacking. Because no consensus has been reached with regard to the optimal use of prophylaxis in young adults [11,12], the decision whether to provide prophylactic or on-demand factor replacement therapy is generally left to the treating physician, based on the clinical course of the disease.

Prophylactic use varies by geographic region: in Europe, most children with severe hemophilia A receive prophylaxis [13], whereas rates in Canada (77–84%) and the USA (47%) are considerably lower [14,15]. Among adolescents and adults, prophylaxis use varies even among different European countries [11–13]. The variation in prophylactic use in young adults reflects the limited data available to adequately address this issue.

While the costs associated with prolonged prophylaxis in adulthood are not negligible, some evidence suggests that prophylaxis may not be much more expensive in adults than in children [16–18]. The pharmacokinetics of FVIII differs in children and adults, and children require relatively higher doses per kg/body weight of replacement therapy [16,17]. When assessing specific pharmacokinetic parameters in children (aged<6 years) and young adults (median age 18 years), FVIII *in vivo* recovery was lower in children (1.9 IU/dL/kg vs 2.4 IU/dL/kg) and the half-life shorter (9.7 hours vs 12 hours). As a result, lower doses of FVIII replacement therapy may provide adequate prophylaxis in adults [18]. This may allow for tailoring of the dose and dosage interval to the individual patient's needs, thereby reducing the cost of therapy without negatively influencing outcomes or quality of life. Further studies are needed to confirm the cost-effectiveness of FVIII replacement prophylaxis in adults with hemophilia.

Determining which patients may benefit from continued prophylaxis remains a priority. Fischer et al. [8] generated a score that helps identify which patients are most likely to benefit from continuing prophylaxis with individualized dosing. Scores are based on several factors, including the patient's age at the start of prophylaxis, the weekly dose of prophylaxis, and the frequency of joint bleeds on prophylaxis. A high score indicates that the patient can successfully discontinue prophylaxis and switch to on-demand FVIII replacement therapy. A low score suggests that continued prophylaxis at a dose tailored to the clinical course of the disease may be beneficial in terms of maintaining a low bleeding frequency.

Prophylaxis in VWD

VWD is characterized by a qualitative deficiency in von Willebrand factor (VWF; types 1 or 3 VWD) or defective VWF (type 2 VWD). Severe bleeding symptoms are common in patients with type 3 disease, but may also occur in patients with types 1 or 2 VWD, especially upon trauma or surgery. Up to 40% of type 3 VWD patients may have joint bleeding with joint damage increasing with age [19,20]. Other patients will develop recurrent gastrointestinal bleeding [21], and women with VWD are at risk of developing menorrhagia. Some children with VWD will experience epistaxis of sufficient frequency, duration, or severity to cause anemia [21]. Prophylaxis with VWF-containing FVIII concentrates may therefore help reduce the frequency of bleeding events in patients with severe VWD.

Few studies have evaluated prophylaxis in VWD [22], and most of the reported experience has involved secondary prophylaxis for patients who have already developed recurrent joint bleeding, gastrointestinal bleeding, epistaxis, or menorrhagia. In a study of 35 VWD patients with ages ranging from 3 to 65 years, secondary prophylaxis was shown to reduce the number of bleeding events substantially [23]. Most patients had type 3 VWD (n = 28), and four patients had type 2B, two had type 2A, and one had type 1 VWD. Among the adults, 63% had received prophylaxis for more than 10 years. In older patients who started prophylaxis for joint bleeding, the number of joint bleeding episodes was markedly reduced (0–4 annually). Notably, the indication for prophylaxis varied according to age: younger patients were more likely to receive prophylaxis for epistaxis, while older patients started prophylaxis for joint or gastrointestinal bleeding. Based on this experience, it appears that long-term prophylaxis is warranted in most patients with type 3 VWD and certain patients with type 1 or 2 disease.

At the Hemophilia Center Bonn, we analyzed prophylactic use with Haemate® P in 24 patients with severe type 3 VWD [Oldenburg et al., Prophylaxis in patients with type 3 von Willebrand disease. Manuscript in preparation]. The median age was 34 years (range 10–66 years) and patients were well distributed across the entire age range. Most patients had epistaxis and joint bleeding (approximately 80% for both) and one-half of the patients had gastrointestinal bleeding; of the 13 women, 11 (85%) had menorrhagia. The median duration of treatment was over 200 months (range 53–420 months). Some patients received prophylaxis continuously and others received prophylaxis intermittently with periods of on-demand therapy (Fig. 2). The median dose used in a single prophylactic dose was 26 IU/kg, but the dose ranged widely (8–50 IU/kg), suggesting that therapy was tailored to the individual patient's needs. Similarly, the median weekly dose of prophylaxis was 71 IU/kg, ranging from 12 IU/kg to 350 IU/kg. The most common sites of joint bleeding were the ankle (43%) and knee (25%), and arthropathy was also more common at these sites. Approximately one-half of patients had arthropathy of at least one joint, and one-third of patients had arthropathy at two or more joints, indicating that significant arthropathy is common in patients with type 3 VWD. Notably, the mean number of bleeding episodes per year was lower during periods in which prophylaxis was given.

Ongoing international trial

An international trial evaluating the role of prophylaxis in patients with clinically severe VWD is ongoing. The trial, known as the VWD International Prophylaxis (VIP) trial, is an investigator-initiated study sponsored through an unrestricted grant by CSL Behring (NCT00557908). The primary objectives are to identify patients with VWD who may benefit from long-term prophylaxis, to study the effect of prophylaxis on bleeding frequency, and to establish optimal treatment regimens for specific patient groups characterized by joint bleeding, gastrointestinal bleeding, epistaxis, or menorrhagia. Secondary objectives include changes in quality of life, the development of inhibitory antibodies to VWF, safety, and rates of hospitalization.

A total of 160–200 patients will be enrolled in this nonrandomized, dose-escalation trial. Inclusion criteria are listed in Table 1. Patients will receive prophylaxis with VWF/FVIII concentrate (the type of product is left to the discretion of the treating physician), and the dose will be escalated in three steps until sufficient control of bleeding is achieved. Initial dose and dose-escalation schemes are tailored to the