

MEETING REPORT

The application of bypassing-agent prophylaxis in haemophilia A patients with inhibitors: a meeting report

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Introduction

In October 2006, an international panel of clinicians experienced in the management of inhibitor patients convened to accomplish two goals: First, examine the current state of knowledge regarding the application of factor eight inhibitor bypassing activity, commercially available as FEIBA VH (Baxter AG, Vienna, Austria), for prophylaxis in haemophilia A patients with inhibitors. Second, formulate consensus recommendations that draw on both investigational data and collective clinical experience.

This meeting focused exclusively on FEIBA prophylaxis and did not consider the utility of prophylactic therapy with recombinant activated factor VII (rFVIIa).

Rationale for prophylactic bypassing therapy

Prophylaxis, the routine scheduled replacement of the deficient clotting factor with the goal of maintaining factor VIII (FVIII) trough levels above 1%, is considered optimal care for patients with severe haemophilia A without inhibitors. Observational

studies [1–3] and the prospective randomized controlled US Joint Outcome Study [4] have established the efficacy of prophylaxis in preventing joint haemorrhage and the subsequent development of arthropathy, target joints and disability. In addition, prophylaxis protects against life-threatening haemorrhage, including recurrent central nervous system bleeding (CNS) following intracranial haemorrhage (ICH) [5], and indirectly improves academic performance [6] and quality of life (QOL) [2,3]. While the pharmacoeconomic value is less certain, prophylaxis has the potential to achieve cost benefits by reducing absenteeism from school and work, increasing productivity, and decreasing the need for emergency room visits, hospitalization, and orthopaedic interventions and other surgeries [1,3].

The benefits of prophylaxis in severe haemophilia A, documented over more than 40 years, have resulted in a paradigm shift towards the broader use of prophylactic regimens, evidenced by the growing use of prophylaxis with bypassing therapy for haemophilia A patients with inhibitors. Up to 30% of patients with severe haemophilia A develop inhibitors [7], and their need for prophylaxis may be even more compelling than that of patients without inhibitors. Bleeding associated with high-titre, high-responding inhibitors [>5 Bethesda units per mL (BU)] is often more difficult to control because of the unpredictable haemostatic effect of the bypassing therapy [8]. Furthermore, no laboratory assays are available that correlate with dosing or efficacy [9]. As

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a result, compared with patients without inhibitors, individuals with inhibitors are at increased risk for severe joint disease [10] and more significant functional limitations [11]. Surgical interventions are less likely to be utilized in inhibitor patients with joint damage, however, because of the greater potential for bleeding complications [12]. Consequently, inhibitor patients often experience significantly impaired mobility and a lower QOL [12,13].

Overview of FEIBA

FEIBA, the only activated prothrombin complex concentrate currently on the market, is a freeze-dried, sterile, human plasma fraction that is used to achieve haemostasis in patients with inhibitors to FVIII or factor IX (FIX) [14]. The primary haemostatic effect of FEIBA is provided by prothrombin (factor II) and activated factor X, both critical components of the prothrombinase complex that converts prothrombin to thrombin downstream from the inhibitor blockade [15]. The half-life of FEIBA activity ranges from 4 to 7 h [16].

FEIBA has been used to bypass the need for FVIII or FIX in haemophilia patients for more than three decades. Thrombosis is the most serious complication of bypassing therapy, but the incidence of thrombotic adverse events with FEIBA is very low [17,18]. Because FEIBA contains residual FVIII antigen, anamnesis may occur with its use [19]. This development does not interfere with the haemostatic efficacy of FEIBA [20], however, and generally is a concern only when immune tolerance induction (ITI) is deferred to allow the inhibitor titre to decline to <10 BU (a predictor of ITI success, according to registry data [21–23]).

Clinical experience with FEIBA prophylaxis

The largest experience with FEIBA prophylaxis involves its use in the perioperative setting, where the efficacy is at least 80% among haemophilia patients with inhibitors undergoing major, minor, or dental surgical procedures [24,25]. Increasingly, FEIBA is also used to prevent bleeding during ITI and in patients who have either failed ITI or are not candidates for or refuse ITI.

Use of FEIBA prophylaxis in the setting of ITI

FEIBA was a component of the original Bonn ITI regimen [26], and it is currently still used in some patients at high risk for bleeding [27].

Kreuz *et al.* [28] prospectively evaluated FEIBA prophylaxis in 22 children aged 0.1–6 years with

high-titre inhibitors (>5 BU) undergoing ITI. FEIBA was administered at a dose of 50–100 U kg⁻¹ daily, with the dose increased up to 100 U kg⁻¹ twice daily for breakthrough bleeding. When the inhibitor titre declined to 2 BU or less, FEIBA was discontinued. During FEIBA prophylaxis, the median annual incidence of joint haemorrhage was 1 (range, 0–6), and no patient suffered a life-threatening haemorrhage. No evidence of arthropathy was seen in six of the eight patients evaluated radiographically, and in the remaining two patients, joint pathology was minimal.

Valentino prospectively studied six inhibitor patients, aged 3.7–24.1 years, three of whom received concomitant FEIBA prophylaxis at a dose of 100 U kg⁻¹ daily during ITI [29]. The incidence of joint haemorrhage in these three patients prior to the initiation of prophylactic therapy ranged from 2.5 to 4.08 per 100 days and declined to 0.0–1.42 per 100 days during treatment, a reduction of 43–100%. FEIBA was well-tolerated and did not cause thrombosis.

Use of FEIBA prophylaxis outside the ITI setting

Kreuz *et al.* [30] prospectively evaluated the efficacy of long-term prophylactic therapy with FEIBA in five children with high-titre inhibitors (maximum inhibitor pre-ITI titre of 118–4342 BU) who had previously failed ITI. FEIBA at a dose of 50–100 U kg⁻¹ at least three times weekly and up to twice daily was started during attempts at immune tolerance and continued after ITI failure for a total of 0.7–12.3 years. While patients were on FEIBA prophylaxis, their median annual incidence of joint haemorrhage was 2.5 (range, 0–6), the median annual incidence of muscle bleeds was 0.85 (range, 0.5–1.3) and none experienced life-threatening bleeding or a thrombotic event. Joint evaluation using the orthopaedic and Pettersson scoring systems revealed no or only mild joint damage. Prophylaxis was curtailed or stopped in two patients. One patient died shortly thereafter from thoracic bleeding. The frequency of joint and muscle bleeding increased in the other patient and he quickly developed two target joints.

Hilgartner *et al.* [31] retrospectively evaluated long-term FEIBA prophylaxis in seven patients, aged 5–10 years, with high-responding inhibitors and target joints. Three of the patients had failed ITI, and none was receiving ITI at the time of prophylaxis. FEIBA was administered at a dose of 50–100 U kg⁻¹ every other day or three times weekly for up to 6.5 years. Joint status was clinically assessed at the beginning of the study and again

after 3 years of follow-up (or when therapy was altered). Joints that were judged normal at study onset remained normal at follow-up, while progressive damage occurred in joints that had bled before the study, with some becoming target joints. Overall, progression of target joint arthropathy occurred in five patients, and four patients developed new target joints during prophylactic therapy. The finding of ongoing joint damage is consistent with reports of secondary prophylaxis in patients without inhibitors [1,4]. FEIBA prophylaxis resulted in improved function in two patients who were wheelchair-bound at the start of the study, improved gait in three patients and was associated with a reduction in bleeding episodes in two patients [31]. There were no instances of life-threatening bleeding in any patient, the treatment regimen was well tolerated and no thrombotic events occurred.

Included in the prospective study of six patients with high-titre inhibitors conducted by Valentino were three patients who had failed ITI or who were not considered for immune tolerance [29]. Prior to the initiation of FEIBA prophylaxis, the incidence of joint haemorrhage in these three patients ranged from 2.19 to 7.6 per 100 days. After prophylactic therapy with FEIBA was started at a dose of 100 U kg⁻¹ daily, episodes of joint bleeding decreased to 0.0–1.98 per 100 days, a reduction of 74–100%.

Ewing retrospectively evaluated the efficacy of FEIBA prophylaxis in seven inhibitor patients, aged 4–17 years, six of whom had not responded to ITI [32]. FEIBA, at a dose of 75 U kg⁻¹, was administered daily, every other day, or three times weekly for 6–45 months. All patients who complied with prophylaxis appeared to benefit clinically, experiencing significant reductions in spontaneous haemarthroses and increased physical activity.

Leissingner retrospectively evaluated five patients, aged 3–16 years, with high-titre inhibitors (range, 30.4–1.017 BU) treated with FEIBA prophylaxis for 6 months to 2 years [33]. FEIBA at a dose of 50–100 U kg⁻¹ once daily to three times a week reduced the frequency of bleeding episodes by 33–98% and maintained or improved orthopaedic status in all patients.

DiMichele and Négrier conducted a retrospective postlicensure survey of FEIBA that included data on 14 patients with haemophilia A and inhibitors who received FEIBA for 15 prophylactic treatment periods [34]. The mean duration of prophylaxis (data available for 12 patients) was 19.5 months (range, 0.25–26 months), with six of the patients receiving treatment for <6 months. Before starting prophylaxis, 12 of the 14 patients exhibited evidence of

arthropathy, primarily affecting the knees or elbows, and six patients had developed at least one target joint. The mean FEIBA dose per infusion was 69 U kg⁻¹ (range, 15–100 U kg⁻¹) administered once daily to once weekly, with every-other-day prophylaxis the most common regimen. The frequency of bleeding episodes decreased during 10 of the prophylactic treatment periods and was unchanged in three; information was missing for two periods. Quantitative data, available for eight of the treatment periods, showed a mean decrease in bleed frequency of 53% (range, 10–85%). During the 13 treatment periods for which data were available, clinical joint status was maintained in eight, improved in three, and deteriorated in two.

General consensus recommendations for FEIBA prophylaxis

Primary prophylaxis, defined by a European consensus panel as long-term, continuous treatment initiated at a very young age (1–<3 years) and/or before the onset of multiple haemorrhages into a given joint [35], is possible in inhibitor patients who have no arthropathy. In these patients, FEIBA prophylaxis should be initiated before the third joint haemorrhage, irrespective of whether they are receiving ITI therapy. Because of the difficulty in controlling bleeding episodes [8] and the heightened risk for severe joint disease [10], many inhibitor patients begin to exhibit some degree of arthropathy very soon after the development of the inhibitor and before primary prophylaxis can be initiated. These patients may benefit from secondary prophylaxis, defined as long-term continuous treatment initiated after the onset of joint damage or other significant bleeding [35]. Secondary prophylaxis should not be expected to halt the progression of existing joint disease [31]. Nonetheless, data from haemophilia patients with and without inhibitors indicate that secondary prophylaxis may reduce bleeding frequency [1,3,4,32–34], prevent joint disease in previously unaffected joints [1,31], slow the progression of pre-existing joint disease [1,31] and improve QOL by permitting an increase in the activities of daily life [2,3,31].

Short-term FEIBA prophylaxis of at least 3–6 months, depending on the response, may be considered for older patients with target joints. Episodic, event-related prophylaxis may be another option for patients who do not receive ongoing, continuous prophylaxis [29,36]. The administration of FEIBA prior to episodes of strenuous or high-risk activities may reduce the likelihood of subsequent bleeding.

Intracranial haemorrhage has the highest mortality of any type of bleeding event in patients with haemophilia. ICH survivors often experience serious long-term sequelae, including seizures and neurologic impairment [37], and recurrent CNS haemorrhage is common [5]. In patients without inhibitors, prophylaxis has been shown to significantly reduce recurrent CNS bleeding [3]. Because of the potential consequences of such recurrence, FEIBA prophylaxis is recommended for any inhibitor patient who has experienced an ICH.

In haemophilia patients without inhibitors, prophylaxis has traditionally been reserved for children because they have a higher frequency of bleeding episodes than adults [36] and, thus, are at increased risk for joint damage. Long-term FEIBA prophylaxis in older patients should be carefully considered after weighing the potential for thrombosis [17]. While thrombotic risk likely increases with atherosclerotic changes [17], this risk remains very low when FEIBA is used in doses $<200 \text{ U kg}^{-1}\text{day}^{-1}$ [10].

FEIBA prophylaxis should be considered a failure and discontinued if there is no clinically significant reduction in the number of haemorrhages, QOL fails to improve, or the patient experiences a clinically evident thrombotic event.

Dosing

Depending on the particular clinical circumstances, various FEIBA prophylactic regimens may be appropriate. Ideal body weight, as determined by lean body mass, should be used when calculating doses for obese patients.

Prophylaxis before ITI

When ITI is postponed to allow the inhibitor titre to decline to $<10 \text{ BU}$, FEIBA is not recommended for first-line prophylaxis because of the potential for anamnesis [19,38]. If FEIBA is deemed appropriate, the recommended dose is $50\text{--}100 \text{ U kg}^{-1}$ daily, every other day, or three times weekly [30–34].

Prophylaxis during ITI

Because ITI may protect against bleeding, consideration can be given to stopping prophylaxis during ITI [28]. However, if clinically significant haemorrhage occurs while patients are on ITI, prophylaxis should be initiated or reinstated. The recommended dosing for FEIBA prophylaxis during ITI, based on extensive experience with the Bonn regimen, is $50\text{--}100 \text{ U kg}^{-1}$ daily, with dosing tailored to bleed frequency. FEIBA

administration should coincide with ITI dosing, if possible, to avoid additional infusions for prophylactic doses, and the central venous access device (CVAD) line should be flushed thoroughly after every use. Consider tapering FEIBA prophylaxis when the inhibitor titre falls below 5 BU . Discontinue prophylaxis when the inhibitor titre is $<2 \text{ BU}$ and FVIII levels are measurable [27,28], as that situation may predispose to thrombosis [39].

Breakthrough haemorrhage should be managed in the same manner as any bleeding event in an inhibitor patient who is not receiving ITI or prophylaxis. However, if FEIBA is used for the management of acute haemorrhage as well as prophylaxis, the total daily dose should not exceed 200 U kg^{-1} [14]. If rFVIIa is used to treat acute bleeding in a patient receiving FEIBA prophylaxis, FEIBA and rFVIIa doses should be given at least 6 h apart [40] unless the bleeding event is life-threatening.

Prophylaxis after failed ITI or in patients who are not candidates for ITI

For patients who fail ITI because the inhibitor is not eradicated and for those who are not candidates for or refuse ITI, the recommended dose of FEIBA is $50\text{--}100 \text{ U kg}^{-1}$ daily, every other day, or three times per week [29–32]. Adjust dose and frequency on the basis of the frequency and severity of haemorrhage, and intensify the dosing regimen if the patient continues to have breakthrough bleeding. Prophylaxis should be continued through adolescence.

Short-term prophylaxis in adults with target joints

Long-term prophylactic therapy is generally limited to children and adolescents, but a short course of FEIBA prophylaxis may reduce bleeding in adults with target joints. The recommended dose is $50\text{--}100 \text{ U kg}^{-1}$ every other day or three times weekly. If the patient begins to bleed frequently following 3–6 months of prophylaxis, treatment may be extended or escalated in intensity to control bleeding after weighing the risks and benefits.

Episodic prophylaxis

The administration of prophylaxis prior to strenuous activity may prevent bleeding in patients with inhibitors. If FEIBA is used for this purpose, the group recommended a dose of $50\text{--}100 \text{ U kg}^{-1}$ administered 30–60 min prior to the activity.

Prophylaxis after ICH

Prophylaxis is recommended for a minimum of 6–12 months after ICH to prevent recurrent CNS bleeding. The recommended minimum dose of FEIBA is 50–100 U kg⁻¹ three times per week.

Outcome measures

Clinical assessment at least every 3 months, and more often if complications develop, is key to monitoring the efficacy and safety of FEIBA prophylaxis. Other strategies for assessing prophylactic efficacy include reviewing the number and type of haemorrhages, the number of hospital admissions or ER visits, joint evaluation, orthopaedic joint score, periodic radiographs or magnetic resonance imaging, functional score, activity level and QOL [1,3,4,31,35].

Measuring the FVIII inhibitor titre every 3 months for patients on ITI ensures that prophylaxis is discontinued before the haemostatic system normalizes. Brackmann recommends stopping FEIBA prophylaxis once the antibody level falls below 1 BU [27]; discontinuing prophylaxis at 2–5 BU is a more conservative approach. When clinical signs are suggestive of disseminated intravascular coagulation or thrombosis, or when circumstances (e.g. dose escalation, sequential therapy) increase the likelihood of such complications, laboratory assessment of the platelet count, fibrinogen, D-dimers and fibrin degradation byproducts is recommended [40]. The development of CVAD-related complications or thromboembolic events may require CVAD removal and/or the discontinuation of prophylaxis.

Areas of future research

Whether the advantages of FEIBA prophylaxis extend beyond the prevention of haemorrhage and the protection of joints remains unclear and provides areas for future research. It is speculated that by averting major bleeding, FEIBA prophylaxis may shorten the duration of ITI and improve the likelihood of successful immune tolerance. It also is theorized that FEIBA prophylaxis may reduce infections associated with CVADs used to administer ITI. By preventing localized bleeding around CVADs and subsequent haematoma formation, which are linked to an increased risk of infection [41], FEIBA prophylaxis has the potential to reduce interruptions in ITI and improve the odds that tolerance will be achieved. Moreover, FEIBA prophylaxis may prevent the development of synovitis and the impairments in QOL that follow arthropathy.

The efficacy, safety and cost-effectiveness of each of these possibilities should be tested in prospective, randomized trials.

Conclusion

The established benefits of prophylaxis observed in patients with severe haemophilia A can be extended to patients with high-titre inhibitors through the use of prophylactic therapy with the bypassing agent FEIBA. FEIBA prophylaxis can be utilized in a variety of clinical settings and, depending on the particular circumstances, is appropriate for long-term, short-term and episodic administration.

While rFVIIa prophylaxis was not discussed at this meeting, this bypassing agent may also be useful for preventing bleeding episodes. Additional clinical data are needed to determine the optimal application of bypassing-agent prophylaxis in haemophilia patients with inhibitors.

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