The principles of PK-tailored prophylaxis

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Summary
While prophylaxis with factor VIII (FVIII) is considered the first choice therapy for patients with severe haemophilia A the optimal prophylaxis regimen is still under scientific debate. A recent study demonstrated efficacy and safety of a PK-tailored prophylaxis regimen with rFVIII (ADVATE) aimed to maintain FVIII trough levels of ≥1% (19). The annual bleed rate (ABR) could be significantly reduced compared to the previous on-demand treatment period (p < 0.0001) and bodily pain, a health-related quality of life dimension of the SF-36v1 questionnaire also significantly improved (p = 0.0007). Thus PK-tailored prophylaxis with ADVATE might offer a valid alternative to standard prophylaxis. Open issues to be considered for implementation of PK-tailored prophylaxis are: What FVIII trough level is needed to prevent any bleed? Do patients with target joints need higher FVIII trough levels to stay bleed-free? Are there user-friendly tools available to calculate individualized PK-driven prophylaxis doses and frequency without the need for a full 9-sample PK curve? Current knowledge on these aspects as well as some considerations about the future of PK-tailored prophylaxis is discussed.

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Zusammenfassung
Prophylaxe mit Faktor VIII gilt als Therapie der Wahl für Patienten mit schwerer Hämostaseologie 4a/2013
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While prophylaxis with factor VIII (FVIII) is considered the first choice strategy for managing severe haemophilia A patients the optimal prophylaxis regimen is still under scientific discussion. Haemophilia treatment is evolving to become more personalized, adapted to each person’s period of life, bleeding frequency and lifestyle.

Personalized medicine is an approach based on tailored treatment to the needs of each patient, rather than the traditional „one size fits all“ medical model.

A recent study (19) compared the efficacy of standard prophylaxis using 20–40 IU/kg body weight rFVIII (ADVATE) every other day with a pharmacokinetic (PK)-tailored prophylaxis regimen using 20–80 IU/kg ADVATE every third day, both regimens intended to maintain FVIII trough levels at or above 1%. Comparable safety and effectiveness for the two prophylaxis regimens was demonstrated.

• Both regimens significantly reduced bleeding compared to the previous on-demand treatment period, from a median annualized bleeding rate (ABR) of 44 to 1 (p < 0.0001), with 42% of per protocol patients showing no bleeding at all.
• Patients on both prophylaxis regimens as compared to the on demand treatment period showed a statistically significant improvement (p = 0.0007) in „bodily pain“, a health-related quality of life dimension of the well established SF-36v1 questionnaire.

Of note, 94–97% of the 66 PTPs with severe to moderately severe haemophilia A (FVIII ≤ 2%) had one or more target joints.

In this study PK-tailored prophylaxis with ADVATE offered an alternative to standard prophylaxis for the prevention of bleeding with comparable costs of both regimens.
The rationale for keeping FVIII trough levels $\geq 1\%$ was based on the finding that the risk to experience a bleed was shown to correlate with the time spent with FVIII plasma levels below 1\% (4). The purpose of this study called ADAPT (Analysis of Data from ADVATE Prospective Trials) was to improve the knowledge about factors that have an effect on the occurrence of break through bleeds during prophylaxis, in order to help improving cost-effectiveness of prophylaxis whilst optimizing clinical outcomes. With its 143 subjects (44 children 1–6 years old and 99 adolescents and adults 10–65 years) with severe haemophilia A (FVIII $< 1\%$) included in the study, this represents the biggest PK analysis ever carried out in haemophilia patients. Several recent studies indicated the need for trough levels substantially higher than 1\% in order to prevent most if not all spontaneous bleeding events.

**FVIII trough level**

**What FVIII trough level is needed to prevent any bleed?**

A recent analysis of 122 patients with mild haemophilia from a Dutch haemophilia treatment center (7) showed that with a FVIII baseline level of $> 12\%$ joint bleeds no longer occurred. In another study also performed in the Netherlands in patients with moderate haemophilia (FVIII 1–5\%) a median number of joint bleeds of 0 (IQR: 0–1.2) was found in patients with $> 3\%$ residual plasma FVIII activity (6).

This suggests that current prophylaxis regimens with the goal to keep plasma trough levels of patients with severe haemophilia above 1\% by regular injection of FVIII concentrates might be suboptimal in preventing every spontaneous joint bleed and much higher doses would be needed.

We should always keep in mind that normal FVIII plasma levels in non-haemophiliacs are constantly above 40\%. On the other hand replacement therapy with the goal to keep patients at $>12\%$ or even $>40\%$ FVIII activity would by no means be affordable even in today’s developed countries.

Although there are no established criteria for determining how many joint bleeds can be tolerated before irreversible damage occurs (16), some studies reported that less than 2–5 joint bleeds in total did not lead to impaired joint scores (8, 9, 11) whereas other studies proposed that annual bleed rates between 0.1 and 2.7 did not lead to joint damage (1, 13, 20).

How many joint bleeds actually lead to arthropathy may be subject to inter-individual variation (14). Although the pathogenesis of haemophilic arthropathy is not completely understood, in vivo experiments have shown that a single bleed may already be deleterious (15). It was also proposed that chronic microhaemorrhage into joints or subchondral bone in young boys with haemophilia cause deterioration of joints without clinical evidence of haemarthrosis and that this subclinical process could be prevented by prophylaxis (12).

**Do patients with target joints need higher FVIII trough levels to stay bleed-free?**

The tendency to have frequent spontaneous joint bleeds depends on many factors that may be unrelated to factor replacement therapy and plasma trough levels such as

- patient’s age,
- life style (activity level),
- joint status (presence of arthropathy),
- regular exercise,
- muscle strength etc.

Thus, people with haemophilia may need very different FVIII trough levels according to their life and health condition. A recent survey on bleeding frequency and location including 100 haemophilia subjects from the UK showed that the traditional pattern of joint bleeding in haemophilia has changed over the last years.

The ankle and the elbows have replaced the knee as the most common joints affected (17).

This may indicate a shift towards a more active life style where ankles and elbows are more exposed to a bleeding risk than the knee and thus may require higher FVIII plasma levels to stay bleed free.

If only factor trough levels were important to prevent bleeds the most effective therapy would be daily low dose prophylaxis thus minimizing the level fluctuation. Although a daily injection is a demanding approach for patients, revealing results from a randomized cross-over study including eight patients with severe haemophilia A and two with haemophilia B were recently published (10). Patients were randomized to 12 months standard prophylaxis (20–50 IU/kg three times per week to every other day) or 12 months daily prophylaxis (individual daily doses to keep FVIII trough level $\geq 1\%$) in a cross-over fashion. Plasma FVIII or IX trough levels were 1–3.2\% in the standard prophylaxis period and 2.5–16\% in the daily prophylaxis period. Despite the higher trough levels under daily prophylaxis, no difference was found in the total number of spontaneous bleeds of subjects with healthy joints (Haemophilia Joint Health scores, HJHS: 0–3) between standard and daily prophylaxis: mean 0.5 bleeds (range: 0–2) and 1 bleed (range: 0–3), respectively.

However, when the group of subjects with target joints ($n = 4$ with HJHS scores 6–38) was included, the total number of spontaneous bleeding events was significantly ($p = 0.034$) higher in the daily dosing arm despite higher plasma trough levels:

- mean 2 bleeds (range 0–4) on standard prophylaxis versus
- mean 6.8 bleeds (range 5–11) on daily prophylaxis.

Another finding from this study was a 30\% reduction in cost of daily prophylaxis as compared to standard prophylaxis. But, on the other hand, daily treatment had a greater impact on daily life and the patients found it more stressful. In that respect it is interesting to note that of 53 suitable patients, 32 showed interest, 13 patients agreed to participate and only 10 finally completed the study. The primary reason for refusal was that adherence to the protocol was perceived as too cumbersome. The authors of the study concluded that prophylaxis with daily dosing may be feasible and efficacious in some patients and it could be hypothesized that additional factors other than trough levels may play a
role in bleed prevention. A high joint score seems to be a risk factor for break through bleeds.

Thus, patients with joint damage may need higher trough (or longer peak?) levels to stay bleed free.

A similar lesson can be learned from the recent report on successful gene therapy (18) where six subjects with haemophilia B reached FIX plasma levels between 2 and 5% after a single dose of an AAV-related vector carrying the human FIX gene. Two subjects without joint disease could stop prophylaxis completely whereas two other patients with joint disease despite constant FIX plasma levels of 2% still needed prophylaxis treatments (although less frequent than before). The other two patients – one reached 3%, the other 5% FIX plasma levels – could also stop prophylaxis entirely. Again this seems to indicate that subjects with target joints may need higher factor trough levels than patients with healthy joints to stay bleed free.

**Individualized PK-driven prophylaxis**

PK parameters such as FVIII recovery, half-life and clearance widely differ in the haemophilia population.

The ADAPT study clearly demonstrated that individual FVIII half-life is important to set prophylaxis dosing frequency.

In fact, in this study the time for FVIII to fall to 1% differed by 32.9 hours between patients with a FVIII half-life of 7.4 hours (= 5th percentile) and those with a half-life of 13.1 hours (= 95th percentile). Thus, only for patients with longer half-life every 3rd day FVIII prophylaxis would be appropriate (3). Although the need for less frequent injections may increase convenience for the patient and thereby also his compliance with the prescribed regimen it is important to mention that the low annual bleed rate that can already be achieved with current products, should not be traded off for an increase in convenience.

Currently, FVIII dosing is mostly based on kg body weight and prophylaxis is started with standard doses and frequencies that can vary for regions, countries or even centers. After that, the prophylaxis regimen is adapted to the individual clinical outcome. For patients with a higher bleeding tendency prophylaxis dose and/or frequency is/are increased until their annual bleed rates are deemed acceptable. In contrast a prerequisite for PK-tailored prophylaxis would be to know the individual PK parameters, the assessment of which is not current practice.

Current clinical guidelines request that for a full PK analysis blood samples should be taken before injection of 25–50 IU/kg body weight of the FVIII product and at 30 minutes, 1–3, 4–6, 7–9, 10–14, 20–26, 28–30 and 32–48 hours after the infusion (5).

A full 9-point PK analysis is demanding as the patient has to stay in or close to the center for all blood samples over a course of 48 h. On the other hand, PK cannot be predicted from age, weight, body mass index etc., thus the current practice of dosing based on body weight and bleeding phenotype is not very accurate and may not be suitable for optimal treatment. To facilitate this procedure Björkman et al. recently proposed a limited sample PK analysis that can predict half-life and trough levels by the comparison with a population model using the Bayesian approach (2). Validation of the model showed that sparse sampling at 4, 24 and 48 h was found to give practically the same PK information as a full, conventional (7–10-sample) study. Even the 1-point method (using a single blood sample 24 h after FVIII injection) provided adequate data for initial dose tailoring with an absolute prediction error of 17–26% whereas dose tailoring based on body weight failed completely.

Considerations about the future of PK tailored prophylaxis

User-friendly tools for easy PK estimation are needed and are under development. These tools should allow estimates of individual half-lives based on a maximum of three blood samples followed by a fast identification of the optimal prophylaxis dose and frequency with the goal to maintain FVIII plasma levels above the desired trough levels. However, each PK-tailored prophylaxis regimen should always still be adapted to the clinical outcome by regular assessment of the bleeding rate: a new PK estimation should probably be considered at least every six months after each change in prophylaxis regimen.

The possible implications that longer-acting FVIII and IX concentrates currently under development may have for patients on prophylaxis is unclear. Although it will take longer for the plasma FVIII or FIX level to fall below 1% with these products the length of time spent at low levels will be substantially increased and these low levels would occur during both day and night as opposed to night alone. If prevention of bleeds is dependent on time spent above trough levels, an increased bleeding risk would be the result. Knowledge of individual patient FVIII half-life with these products could be even more important than with conventional products when designing prophylactic regimens.

On the other hand longer-acting products used at similar frequencies as current products could bear the opportunity to maintain higher trough levels which might be beneficial especially for patients with very active life-styles. It was proposed by Peter Collins at WFH 2012 that the FVIII trough level might be important for the prevention of break through bleeds whereas the FVIII peak level might be important to prevent activity-related bleeds and the area under the curve (AUC; factor VIII level versus time after infusion) to prevent subclinical bleeds.

**Conclusions**

Given the serious issues associated with bleeds, efficacy should be the primary consideration when selecting a haemophilia treatment and zero joint bleeds should be the ultimate goal even in patients with joint disease.

Convenience is an important aspect for people with chronic diseases that require life-long regular treatment. However, less frequent dosing even with longer acting products should only be considered as long as clinical outcome is not impaired.
In addition, it would be important to further assess the influence of FVIII peak and trough levels on clinical outcome. A 3-point PK analysis to predict individual half-life and more user-friendly tools under development will probably help with optimizing prophylaxis regimens and ultimately offer a better life to haemophilia patients.

Conflict of interest

The authors are full time employees of Baxter Innovations GmbH.

References