Tailoring treatment of haemophilia B: accounting for the distribution and clearance of standard and extended half-life FIX concentrates

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Summary
The prophylactic administration of factor IX (FIX) is considered the most effective treatment for haemophilia B. The inter-individual variability and complexity of the pharmacokinetics (PK) of FIX, and the rarity of the disease have hampered identification of an optimal treatment regimen. The recent introduction of extended half-life recombinant FIX molecules (EHL-rFIX), has prompted a thorough reassessment of the clinical efficacy, PK and pharmacodynamics of plasma-derived and recombinant FIX. First, using longer sampling times and multi-compartmental PK models has led to more precise (and favourable) PK for FIX than was appreciated in the past. Second, investigating the distribution of FIX in the body beyond the vascular space (which is implied by its complex kinetics) has opened a new research field on the role for extravascular FIX. Third, measuring plasma levels of EHL-rFIX has shown that different aPTT reagents have different accuracy in measuring different FIX molecules. How will this new knowledge reflect on clinical practice? Clinical decision making in haemophilia B requires some caution and expertise. First, comparisons between different FIX molecules must be assessed taking into consideration the comparability of the populations studied and the PK models used. Second, individual PK estimates must rely on multi-compartmental models, and would benefit from adopting a population PK approach. Optimal sampling times need to be adapted to the prolonged half-life of the new EHL FIX products. Finally, costs considerations may apply, which is beyond the scope of this manuscript but might be deeply connected with the PK considerations discussed in this communication.

Keywords
Haemophilia B, factor IX, pharmacokinetics, extended half-life, tailored, personalised

Prevention of bleeding in haemophilia B

Although many (1–4) but not all studies (5) have suggested that the phenotype of severe haemophilia B is milder than that of severe haemophilia A, there is no doubt that the prevention of bleeding in persons with haemophilia (PWH) by regular administration of clotting factor concentrates (“prophylaxis”) is worthwhile. Primary prophylaxis has been shown to prevent arthropathy in haemophilia B as it does in haemophilia A patients (6). The major driver of the adoption of prophylaxis in persons with haemophilia B has undoubtedly been the introduction in 1997 of the first (and, until recently, the only) recombinant factor IX (FIX) concentrate [rFIX, BeneFIX, Pfizer, New York, NY, USA] (7–10).

Three new rFIX concentrates with enhanced half-life (EHL FIX) were recently developed. Two concentrates are derived by the fusion of rFIX with the Fc fragment of IgG1 (11) or albumin (12), the other is a PEGylated product (13). All three products offer the potential for less frequent venipunctures which may promote adherence to prophylaxis (14–20). Whereas it has yet to be shown how these new EHL FIX products will impact the treatment of persons with haemophilia B outside of clinical studies, a markedly reduced infusion frequency, a lower weekly FIX consumption (from 80 IU/kg/week to 39 IU/kg/week) and a decrease of ABR from 5.5 pre-study to 2.9 while on-study has been demonstrated (21).

Prevention of bleeding in haemophilia B: a change in the landscape?

Does the availability of EHL concentrates make the management of haemophilia B simpler or more complicated? For sure, the introduction of EHL factor concentrates has prompted an extensive reconsideration of the entire approach to treatment choices in haemophilia B. Mechanistic, genetic and pharmacodynamic considerations have been suggested to explain the paradoxical efficacy of FIX prophylaxis well beyond the predicted post-infusion availabil-
ity of FIX. On theoretical grounds, the value of pharmacokinetic (PK) profiling in addressing the optimal treatment choice for haemophilia B patients is self-explanatory; however, optimal use of PK parameters in daily clinical practice remains to be determined. This review aims to provide a logical framework for evidence based treatment recommendations and informed treatment choices with standard and EHL FIX concentrates.

Prevention of bleeding in haemophilia B: measurement issues

Any discussion regarding PK must first take into consideration the ability to accurately measure plasma FIX levels. Currently, the most common laboratory test for measuring FIX is the one stage clotting assay, based upon the activated partial thromboplastin time (aPTT). Although clinicians have come to rely upon this assay, there are significant subtleties and some limitations to the accuracy of this test which are being amplified with the use of EHL clotting factor concentrates (22–24). From the limited published data available, it has become clear that accurate laboratory measurement of infused factor for the EHL FIX concentrates is a serious concern, mostly due to the heterogeneity of the many commercially available aPTT reagents. For example, for rFIX Fc, it has been shown that kaolin-based reagents grossly underestimate the level of the infused factor, while ellagic acid reagents can overestimate the level (25). Likewise, the choice of aPTT reagents affects measurements of rFIX FP (Idelvion), (2016 WFH abstract) and glycopegylated rFIX (N9-GP) (2016 EAHAD abstract). These measurement issues need to be addressed to ensure that PK-guided dosing strategies are relying on accurate laboratory measurement of the infused factor.

Prevention of bleeding in haemophilia B: PK considerations

Recent registration studies of diverse FIX concentrates have resulted in a large body of new information on the PK of FIX (Table 1). The large inter-patient variability of the PK profiles of plasma derived (26, 27) or recombinant (28) FIX concentrates was an early finding, immediately associated with the concept of PK driven reduction in FIX consumption (29). On the other hand, the initial PK evidence (30) of lower in vivo recovery (IVR) as well as higher clearance (CL) for r-FIX prompted using almost twice (1.8 times) as much rFIX than pd-FIX, which was not confirmed in a multicentre retrospective observational observation years later (31). The development and availability of new rFIX concentrates changed the landscape. On the one hand, the approval in 2013 of Nonacog gamma (Rixubis®, Baxalta, Vienna, Austria), a new rFIX (32) with very similar PK/pharmacodynamics (PD) characteristics as BeneFIX (Nonacog alfa), along with the obvious proof of the efficacy in prophylaxis (33) introduced, for the first time, an alternative choice for the treatment of haemophilia B and the procurement of rFIX (34). On the other hand, the introduction of EHL-FIX and the clinical observation that many haemophilia B patients were well off with one single weekly dose of rFIX, prompted more research on the PK/ PD of FIX. A randomised cross-over study comparing two different prophylaxis dosages (50 IU/kg twice weekly vs 100 IU/kg once weekly) of BeneFIX (Nonacog alfa) enrolled 50 previously treated patients (PTPs), followed for 56 weeks, over a three-year period (35). Results showed that the ABR decreased from 35.1 during the pre-prophylaxis period to 2.6 in the first group, and 4.6 in the second (p<0.001).

Furthermore, BeneFIX (Nonacog alfa) has been compared to EHL FIX in a mouse model (36) and in the clinical trials validating the new EHL FIX concentrates (11, 12, 14, 15), where it was used as a reference comparator. All these comparisons have resulted in a better understanding of FIX PK. Indeed, a general principle of PK is to obtain biological samples for drug measurement for a length of time equal to or exceeding five times the expected half-life of the molecule one intends to assess, and as a minimum until the plasma concentration has returned to baseline. The ISTH SSC recommendations, FDA and EMA guidance (37–39), have suggested sampling for 48-72 hours (h) post-infusion of FIX or longer as appropriate. When EHL concentrates were introduced, the sampling

| Table 1: Reported PK parameters for standard factor IX concentrate PK assessments. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | Negrier (13)    | Santagostino (12) | Powell (58)     |
| N9-GP            | BeneFIX         | pdfIX            | BeneFIX         | pdfIX           | rFIXFc          | BeneFIX         |
| Dose IU/kg       | 50              | 50               | 50              | 50              | 50              | 50              |
| AUC IU•h/dl      | 7328            | 715              | 913             | 7089            | 976             | 1086            |
| IVR IU/dlIU/kg   | 1.39            | 0.68             | 1.12            | 1.37            | 0.95            | 1.1             |
| Cl ml/h/kg       | 0.74            | 6.99(*)          | 5.48(*)         | 0.75            | 5.24(*)         | 4.76(*)         |
| Vz ml/kg         | 99.5            | 194.98           | 140.58          | 95              | 130.6           | 98.7            |
| Half-life h      | 96.2            | 19.34            | 17.79           | 91.57           | 17.23           | 14.59           |

*blood sampling limited to 48 h; $ blood sampling limited to 72 h. Values reported are average values reported in individual studies. IU = International Units; AUC = Area Under the Curve; IVR = In Vivo Recovery; Cl = Clearance; Vz = Apparent volume of distribution during the terminal phase. (*) 4 FIX studies reporting on 95 additional patients did not report on the laboratory tests used; studies on EHL FIX concentrates were not included.
timelapse was extended to longer times, appropriately. Coupled with modern information technology, the availability of these research datasets have allowed confirmation of what was already proposed by Bjorkman (40), i.e. that the PK of FIX is not linear and most likely best represented by three compartmental modelling (Figure 1) (41, 42). This finding has important consequences: first, depending on the modelling choices, data obtained for different FIX products may or may not be directly comparable (41); second, for a classical estimation of the drug kinetics, at least two sampling points per compartment are recommended, making studies in young children very difficult (Figure 2); third, the time concentration curve of a drug following a multi-compartment model cannot be “guessed” based on peak and trough measurement; fourth, assuming a multi-compartmental model implies that the drug in question, here specifically FIX, follows a complex disposition, with receptor binding or compartmentalisation in some extra-vascular space, which may have PD and perhaps clinical relevance.

**Prevention of bleeding in haemophilia B: Role of rFIX in the extravascular space**

Since the first studies of FIX concentrates, it became apparent that the volume distribution area (VdArea) for FIX is very large. Considering the theoretical normal plasma volume of 40–41 ml/kg, a four factor, PCC (Bebulin) showed a VdArea of approximately double than that of the theoretical plasma volume of the patient. Values for purer FIX concentrates are four or five times higher than the estimated patient plasma volume (26, 43–46). Plasma volume decreases with increasing weight, an observation used to explain why the clearance and volume of distribution of FIX in haemophilia B children are larger than in adults (28).

### Figure 1: Comparison of one, two and three compartment models.

- **A)** Linear decay of a drug following a single compartment structural model. The concentration decreases by half over a constant period of time, the half-life.
- **B)** Observations in plasma for a drug with an initial distribution phase (phase 1 for example, rapid binding to another plasma protein, for example VWF for factor VIII), and an elimination phase (phase 2, usually renal clearance); the kinetic is not linear anymore but is the combination (overlap) of two linear phenomena, e.g. (a), the rapid distribution, and (b) the actual elimination from plasma. The terminal half-life is the halving time calculated on (b). C) Observations in plasma for a drug with an initial rapid distribution phase (phase 1 for example, rapid distribution to the extravascular space), a slower distribution phase (phase 2, for example, binding to a matrix protein) and an elimination phase (phase 3, usually renal clearance); the apparent kinetic is now the combination (overlap) of three linear phenomena, and the terminal half-life is the halving time calculated on (c). It should be obvious that modelling the same PK with one, two or three compartment models will lead to the estimate of three very different terminal half-lives, while other PK parameters, like AUC, Vd, or clearance might be much less affected.

- **Figure 2)** (41, 42). This finding has important consequences: first, depending on the modelling choices, data obtained for different FIX products may or may not be directly comparable (41); second, for a classical estimation of the drug kinetics, at least two sampling points per compartment are recommended, making studies in young children very difficult (Figure 2); third, the time concentration curve of a drug following a multi-compartment model cannot be “guessed” based on peak and trough measurement; fourth, assuming a multi-compartmental model implies that the drug in question, here specifically FIX, follows a complex disposition, with receptor binding or compartmentalisation in some extra-vascular space, which may have PD and perhaps clinical relevance.

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Figure 2: Estimating a three-compartment model kinetic with and without a population approach. A) Having one single sample in each of the three phases of a three-compartment model does not allow to “fit” the best fitting line. Indeed, many curves can be fitted through the three points. B) Population approach (Bayesian forecasting) fits the most likely curve joining those three points by using previous knowledge from the population regarding at what point most patients would be at those specific concentrations. This is represented by the narrow confidence intervals around the estimated line (panel B has been generated with the WAPPS-Hemo application for the same points depicted in panel A, for a patient treated with rFIX-Fc).

As a result, the observed terminal half-life and trough of FIX are influenced by the inter-compartment exchanges and do not directly correlate with clearance, which represents the fraction of plasma cleared as a balance between the amount removed from central compartment and that received back from extravascular one. In other words, this explains why the terminal half-life of FIX is longer than that of FVIII, even though FIX clearance is higher. With regard to EHL rFIX, the volume of distribution of rFIX-FP (24) and N9-GP (25) are similar or lower than that of the pd-FIX high purity concentrates. The outcomes of PK cross-over Phase I/II studies of EHL rFIX concentrates are reported in ▶Table 1.

The widespread distribution in the body of cells bearing the FcR could explain this huge volume of distribution of rFIXFc. It has been shown that about 40% of infused FIX distributes in the lymph or binds to collagen type IV in the sub-endothelial space (50, 51). Binding to endothelial cells and collagen type IV happens mostly at residue K5 of the FIX Gla domain. rFIX with different mutations of the K5 domains have been used to explore the extravascular fate of rFIX. rFIX with the K5R mutation binds extravascular sites as well as standard rFIX, while rFIX with K5A mutation does not. Infused in the FIX deficient mice, 79% of K5R or standard rFIX have been found in the liver after 2 minutes from the end of infusion and 17% in the circulation, compared to 59% in the liver and 31% in the circulation after infusion of rFIX with mutation K5A (52). A direct evaluation of volume of biodistribution of FIX for the EHL concentrates was investigated in rats by means of \(^{3}\text{H}-\text{labelled rIX-FP, Albumin and BeneFIX (Nonacog alfa). Whole body autoradiography and PK was performed.}^{3}\text{H}-\text{rIX-FP and}^{3}\text{H}-\text{albumin radioactivity was detected during the first 10 days, while that of}^{3}\text{H-rIX rapidly declined. The tissue distribution of}^{3}\text{H-rIX-FP and}^{3}\text{H-rIX were similar while the}^{3}\text{H-albumin clearance from plasma was lower (53). These observations suggest that the rIX moiety determines the tissue distribution and the albumin moiety determines the long plasma half-life of rIX-FP concentrate. The saturation of the extravascular pool by dysfunctional native FIX, incapable of clotting through inability to bind collagen, may play a role in the IVR of rIX. IVR was, on average, lower in haemophilia B patients with low or immeasurable FIX antigen (the so called CRM negative patients) (8). The lower total consumption of N9-GP by haemophilia B patients on long-term

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The diagram describes a three-compartment PK model. The concentrate is infused in the central compartment (plasma), but it rapidly redistributes to both compartment 2 and 3. We do not necessarily know what these compartments physically are, but we assume they are, for the sake of the example, a protein binding site (comp 2) and the extravascular space (comp 3). The distribution to compartment 2 and 3 is rapid and intense. This determines the rapid drop of the plasma level of the concentrated (steep phase 1 in the time concentration curve, segment A of the top right diagram). After saturation of binding sites (comp 2) or reaching equilibrium (comp 3), the concentrate begins to flow back (re-distribution) toward the central compartment, with different velocity and for a different duration. The net effect of redistribution is a relative increase in the plasma concentration, which appears on the concentration time-curve as a slower (segment B of the top left diagram), and finally slowest (segment C of the top left diagram) decrease in the concentration.

Prophylaxis in the 10 IU/kg once weekly arm, might suggest a similar saturation of the extravascular space (19). During the multinational randomised phase 3 trial (80), 74 patients on prophylaxis for one year with nonacog alfa pegol showed an approximate 50% decrease of clearance, 0.36–0.43 ml/h/kg, with respect to 0.74 ml/h/kg as observed during the single dose PK phase I/II study (Table 1). Two interesting and still only partially answered questions stem from the evidence of the extravascular distribution of FIX. The first question is whether FIX is playing any physiological role in the extravascular space. It is interesting to consider that a similar extra-vascular biodistribution has been documented for another Gla-domain rich clotting factor, rFVIIa. Of interest, the efficacy of FVIIa has been related to its large extravascular pool (54, 55). What role can FIX play in the extracellular space without factor VIII, an essential co-factor to generate tenase activity? The extravascular distribution of rFVIII is smaller (± 16%) than that of FIX due to its very fast association with circulating von Willebrand factor (vWF). However, the binding of vWF to collagen type IV can also localise FVIII in the sub endothelial space (56, 57) as well as FIX. The second question is about the relevance of prolonged sampling in FIX PK studies. The assessment of PK parameters in multiphasic kinetics is very sensitive to the number of samples analysed. An interesting example of this comes from the results obtained when studying BeneFIX® as a comparator to the EHL molecules. The duration of blood sampling from patients treated with comparators was very short (48 h) in N9-GP and rIX-FP Phase I/II studies. The blood sampling was prolonged for up to 96 h in the rFIX-Fc study, similar to previous PK studies. Consequently, in the N9-GP and rIX-FP phase I/II PK studies, the area under the curve of comparators was smaller and the clearance was ten times higher. The terminal half-life was longer, up to 33.8 h, and the clearance was slower in the rFIXFc study when the samples of rFIX were collected for up to 96 h (58). Similar findings were reported from an Italian multicentre study on BeneFIX (Nonacog alfa) PK (41).
mounting but not unanimous evidence that a three compartment model is superior to less complex models (40–42), the comparison has sometimes been performed on a statistical ground, more often by “visual inspection”, but it has never been tested whether its adoption makes any difference at the clinical level. PK comparisons are not sufficient to identify the optimal treatment, for costs and affordability of treatment is an important issue in many countries; how cost may affect patient’s choices is beyond the scope of this paper.

Optimal sampling time for reduced sampling individual PK studies

For the classical approach, two data points per “compartment” are needed and three are more than sufficient (when using Bayesian forecasting in population PK framework) to properly define an individual’s PK. Given the rapid clearance of rFIX from the central compartment, at least two data points in the first hour might be needed to reasonably estimate peak and recovery; two samples in the subsequent 6–24 h should be drawn to estimate the drug elimination during the apparent dominance of the second compartment; and two samples between 72 and 124 h should be used to estimate the terminal half-life. For a population PK approach, however, one point in each compartment will suffice (Figure 2), i.e. 2 points, taken any time on day 2 or 3 after the infusion should be enough to obtain robust estimates in patients treated with standard FIX (42). Also, post-infusion samples showing that factor activity is not measurable anymore, also known as Below Level of Quantitation (BLQ) samples, are informative and should be used in the estimation. Optimal sampling points for extended half-life FIX are yet to be defined.

Considerations on fitting a non-linear kinetic PK profile

The likelihood of a classical interpolation method providing inaccurate estimates increases with the complexity of the PK disposition and the lower amount information provided by drawing less samples (40). From this viewpoint, a population PK approach can compensate the paucity of individual information by interpreting that information in light of the information provided by the underlying population (59–61). Worthy of note, the population PK approach works better when relevant covariates are taken into account (62–64). However, due to the need of having available a population PK model and performing an iterative Bayesian estimation, the adoption of a population PK approach to individual estimation cannot happen without a collaborative approach among several partners. A flexible, web-available solution has been implemented and is currently available to estimate standard and EHL FIX concentrates (WAPPS, www.wapps-hemo.org) (60, 65, 66). Due to the large inter-patient variability in PK estimates (Table 1), in doses and regimens used in clinical practice and in the associated ABR (10, 67–70), as well as the complex multi-compartmental PK of FIX, there is a reasonable expectation that knowledge of individual PK profiles might be of value in optimising individual prophylactic regimens for haemophilia B patients. A specific example is provided and commented on in the Suppl. Material (available online at www.thrombosis-online.com) to help understand the complexity of using PK information to tailor treatment and the need of using the entire PK profile and not partial information such as peak, trough or terminal half-life.

Recommendations for research and clinical practice

We suggest that guidance for the assessment of FIX PK is modified to account for the use of multi-compartment models and the expected longer half-life for both standard and extended half-life concentrates. We recommend to sample patients for at least five expected half-lives, or return to baseline, accounting for below level of quantitation samples in the estimation process. Cross-over studies should be the only design adopted for comparative purposes and the same structural assumptions should be used for both (all) concentrates being compared.

We suggest that PK and PD aspects of treatment be discussed with each individual patient. We further suggest that for each individual patient the trough level required to prevent bleeding is identified, and that time-concentration curves are used to fine tune the treatment regimen best suited to the life style and bleeding phenotype of each patient. We recommend that each patient undergo a (simplified) individual PK study with the FIX product he is using and the one he plans to switch to. Time-concentration curves for the old FIX product are useful to interpret PK results with the new FIX product, particularly for patients with short half-lives or those who experience clinically significant breakthrough bleeding.

We suggest that information about peak, trough, dose regimen (type, dose and number of infusions), bleeding events (including time from the last dose, dose used/required to treat, time to bleed resolution) are collected prospectively on haemophilia B patients on tailored prophylaxis regimens to enrich our understanding of the PK and PD of infused FIX.

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