A novel population pharmacokinetic model for recombinant factor IX-Fc fusion concentrate including young children with haemophilia B

Sjoerd Koopman¹, Tine Goedhart², Laura Bukkems³, Trevor Mulders³, Frank Leebeek⁴, Karin Fijnvandraat¹, Michiel Coppens⁵, Mary Mathias⁶, Peter Collins⁷, Campbell Tait⁸, Nicola Curry⁹, Jeanette Payne¹⁰, Pratima Crowdy¹¹, Marjon Cnossen², and Ron Mathot¹²

¹Amsterdam UMC Locatie AMC
²Erasmus MC Sophia Children Hospital
³Amsterdam University Medical Centres
⁴Erasmus MC
⁵Amsterdam UMC Location AMC Department of Vascular Medicine
⁶Great Ormond Street Hospital for Children NHS Foundation Trust
⁷Cardiff University School of Medicine
⁸University of Glasgow
⁹Oxford University Hospitals NHS Foundation Trust Nuffield Orthopaedic Centre
¹⁰Sheffield Children’s Hospital NHS Foundation Trust
¹¹Royal Free London NHS Foundation Trust
¹²Amsterdam UMC - Locatie AMC

May 26, 2023

Abstract

Background Recombinant factor IX Fc fusion protein (rFIX-Fc) is an extended half-life (EHL) factor concentrate administered to haemophilia B patients. So far, a population pharmacokinetic (PK) model has only been published for patients ≥12 years of age. Aim Assess the predictive performance of the published rFIX-Fc population PK model for patients of all ages and develop a model that describes rFIX-Fc PK using real world data. Methods We collected prospective and retrospective data from patients with haemophilia B (FIX activity level ≥5 IU/dL) treated with rFIX-Fc and included in the OPTI-CLOT TARGET study (NTR7523) or United Kingdom (UK)-EHL Outcome Registry (NCT02938156). Predictive performance was assessed by comparing predicted with observed FIX activity levels. A novel population PK model was constructed using nonlinear mixed-effects modelling. Results Real world data was obtained from 37 patients (median age: 16 years, range 2-71) of whom 14 were <12 years of age. Observed FIX activity levels were significantly higher than levels predicted using the published model, with a median prediction error (PE) of -48.8%. The novel model showed a lower median PE (3.4%) and better described rFIX-Fc PK, especially for children <12 years of age. In the novel model, an increase in age was correlated with a decrease in clearance (p<0.01). Conclusion The published population PK model significantly underpredicted FIX activity levels. The novel model better describes rFIX-Fc PK, especially for children <12 years of age. This study underlines the necessity to strive for representative population PK models, thereby avoiding extrapolation outside the studied population.

A novel population pharmacokinetic model for recombinant factor IX-Fc fusion concentrate including young children with haemophilia B
ABSTRACT

Background
Recombinant factor IX Fc fusion protein (rFIX-Fc) is an extended half-life (EHL) factor concentrate administered to haemophilia B patients. So far, a population pharmacokinetic (PK) model has only been published for patients [?]12 years of age.

Aim
Assess the predictive performance of the published rFIX-Fc population PK model for patients of all ages and develop a model that describes rFIX-Fc PK using real world data.

Methods
We collected prospective and retrospective data from patients with haemophilia B (FIX activity level \( \geq 5 \) IU/dL) treated with rFIX-Fc and included in the OPTI-CLOT TARGET study (NTR7523) or United Kingdom (UK)-EHL Outcome Registry (NCT02938156). Predictive performance was assessed by comparing predicted with observed FIX activity levels. A novel population PK model was constructed using nonlinear mixed-effects modelling.

**Results**

Real world data was obtained from 37 patients (median age: 16 years, range 2-71) of whom 14 were <12 years of age. Observed FIX activity levels were significantly higher than levels predicted using the published model, with a median prediction error (PE) of -48.8%. The novel model showed a lower median PE (3.4%) and better described rFIX-Fc PK, especially for children <12 years of age. In the novel model, an increase in age was correlated with a decrease in clearance (p<0.01).

**Conclusion**

The published population PK model significantly underpredicted FIX activity levels. The novel model better describes rFIX-Fc PK, especially for children <12 years of age. This study underlines the necessity to strive for representative population PK models, thereby avoiding extrapolation outside the studied population.

**Keywords:** pharmacokinetics, haemophilia B, factor IX, extended half-life

**INTRODUCTION**

Haemophilia B is an inherited bleeding disorder caused by mutations in the \( F9 \)-gene on the X-chromosome\(^1\). These mutations result in a coagulation factor IX (FIX) deficiency, leading to impaired haemostasis. Severely and moderately affected haemophilia B patients suffer from spontaneous bleeding or bleeding after minor trauma, especially into joints and muscles. When left untreated, these bleeds may be life-threatening or lead to arthropathy with ultimately long-term disability\(^2\). FIX replacement therapy - both prophylactically and on demand - is mainstay of treatment, leading to a normal life expectancy with good quality of life\(^3\). Extended half-life (EHL) FIX concentrates have further ameliorated the burden of disease by substantially decreasing the frequency of intravenous FIX concentrate administration to on average once every week\(^4\).

Recombinant factor IX Fc fusion protein (rFIX-Fc) is an EHL-FIX concentrate which consists of a single recombinant FIX molecule fused to the dimeric Fc domain of human immunoglobulin G1 (IgG1)\(^5\). This fusion delays the lysosomal degradation by recycling rFIX-Fc back into circulation. As a result, half-life is prolonged from 17h for rFIX to 82h for rFIX-Fc in patients \( \geq 12 \) years of age\(^4\). The pharmacokinetics (PK) of FIX concentrates are complex and demonstrate a high level of interindividual variability (IIV)\(^6-9\). As a result, FIX activity levels vary substantially between patients\(^10-12\). The variability in PK parameters of individual subjects entails individual adjustments for administration of FIX replacement therapy by application of Bayesian forecasting. This application using population PK models has been shown to be successful to individualize factor concentrate dosing in haemophilia treatment\(^13,14\). Furthermore, Bayesian forecasting methodology allows for limited sampling in contrast to traditional modelling methods\(^15\).

To establish the PK characteristics of rFIX-Fc and identify covariates, Diao et al. developed a rFIX-Fc three-compartment population PK model\(^16\) using data from several clinical trials. To our knowledge, this is the only population PK model currently published for this EHL factor concentrate. Importantly, this model has not been externally validated. Moreover, this model was constructed using data of only a limited number (\( n = 11 \)) of children, all \( \geq 12 \) and <18 years of age. Therefore, the accuracy of this model in children <12 years of age may be limited. The aim of this study is to validate and assess the predictive performance of the published rFIX-Fc model using new independent real world patient data. The secondary aim is to develop a novel population PK model describing the PK in a more extended age range, including children <12 years of age.

**METHODS**

Data collection
We collected data from haemophilia B patients (endogenous FIX activity level \( \geq 5 \) IU/dL) treated with rFIX-Fc (eftrenonacog alfa, Alprolix(r)) included in the OPTI-CLOT TARGET study (NTR7523\(^{17}\)) or United Kingdom (UK)-EHL Outcome Registry (NCT02938156). Briefly, haemophilia patients in the OPTI-CLOT TARGET study received nine months of PK-guided dosing to investigate the reliability and feasibility of the Bayesian forecasting procedure. FIX samples for PK profiling were obtained pre-infusion and approximately 15-30 minutes, 4, 24, 72-120 and 168h after infusion. During PK-guidance, a minimum of four FIX activity (at nonspecific time points after infusion) levels per patient was collected in a minimum of two visits to validate predicted FIX. The UK-EHL Outcome Registry contains patient characteristics and treatment information, including FIX infusions (timing and doses) and FIX activity level measurements. During PK profiling, FIX activity levels were measured at pre-infusion and approximately 15 minutes, 24, 72, 120 and 168h after infusion. Additional FIX activity levels were sampled during visits at 10 days, 3, 6, 12 and 18 months after initiation of rFIX-Fc treatment. In both studies, no wash-out was required during PK profiling if three prior infusions were documented. Informed consent was obtained from all patients and/or caregivers.

**Patient data handling**

In both cohorts FIX activity was measured using the one-stage assay (OSA) according to local protocol. Laboratory specifications of all participating sites are shown in Supplementary Table 1. All FIX activity levels measured during bleeding episodes or surgeries\(^{18}\) were excluded from this analysis.

Since the OSA does not distinguish FIX activity from the respective FIX concentrates (e.g. residual FIX activity levels from the previous FIX dose or currently present FIX concentrate), it is required to correct for previously administered factor concentrates. To do so, we performed the following corrections in line with Diao et al.\(^{16}\) and previously reported PK analyses with FIX concentrates\(^{9,12,19,20}\):

1. **Residual decay correction** = \((\text{Predose activity} - \text{baseline}) \times e^{-kt}\)
2. **Corrected FIX activity** = \(\text{Measured FIX activity} - \text{baseline} - \text{residual decay correction}\)
3. \(k = \frac{\ln(2)}{t_{1/2}}\),

in which \(k\) represents the elimination rate constant of the previously used concentrate for rFIX-Fc (Alprolix(r)), rFIX (Benefix(r)) or rIX-FP (Idelvion(r)) calculated for each age group (<6, \[\geq\]6-12, \[\geq\]12-18 and \[\geq\]18 years). For these calculations, we used typical half-lives \(t_{1/2}\) of each age group as reported by the respective European Public Assessment Report (EPAR)\(^{21–23}\). Other patient characteristics collected were age, height, body weight, lean body weight (LBW) and fat free mass (FFM). Occasions were defined as a visit with PK assessment, as described in literature\(^{24}\).

**Validation of published population pharmacokinetic model**

The predictive performance of the published rFIX-Fc population PK model by Diao et al.\(^{16}\) was assessed with our data using NONMEM software (v7.4.1, Icon Development Solutions, Gaithersburg, Maryland, United States)\(^{25}\). Data visualization and evaluation were performed in R (version 4.1.1), Pirana (version 2.9.8) and PsN (version 4.8.1). Predictive performance was visualized in goodness-of-fit (GOF) plots showing predicted versus observed FIX activity levels. A priori population predicted (PRED) activity was obtained using typical PK parameters which can be calculated on basis of patient characteristics (e.g. body weight). Individual PK parameters were obtained after Bayesian estimation providing a posteriori individual predicted activity (IPRED). Next, predictive performance was evaluated by comparing predicted versus observed FIX activity levels. The prediction error (PE, Eq. 4) was determined to assess bias. The root mean squared error (RMSE, Eq. 5) was determined to elaborate on differences between individual predictions of the published and novel model.

\[
\text{(4) PE} = \left(\frac{C_{\text{pred}} - C_{\text{obs}}}{C_{\text{obs}}}\right) \times 100\%
\]
\[ \text{RMSE} = \sqrt{\frac{\sum_{j=1}^{n} (C_{\text{ipred}} - C_{\text{obs}})^2}{n}} \]

\( C_{\text{pred}} \) represents the population predicted and \( C_{\text{ipred}} \) the individually predicted FIX activity level of measurement \( j \). \( C_{\text{obs}} \) represents the observed FIX activity level. The total number of measurements is denoted by \( n \). A negative or positive PE indicates a systematic under- or overestimation of population predicted FIX activity levels. A median PE between -5% and 5% is deemed as not biased. RMSE was determined for peak (time after dose 0-2 h), mid (time after dose 2-120 h) and trough (time after dose 120-300 h) FIX activity levels separately.

Furthermore, for patients <12 years of age, we investigated potential bias due to possible relationships between covariates and population PK parameters volume of central compartment (V1), volume of peripheral compartment (V2), clearance (CL) and intercompartmental clearance (Q). Therefore, we plotted interindividual variability (ETA; \( \eta \)) in these PK parameters against the patient characteristics age and body weight. Plots of an unbiased model should not show trends, indicating that \( \eta \) in these PK parameters are divided randomly over patient characteristics.

Finally, terminal elimination half-lives (\( t_{1/2} \)) were determined by post hoc calculation for patients <12 years of age, patients \( \geq \)12 and <18 years of age and adults. Results were compared with results from the novel model (see below). As the \( t_{1/2} \) estimates are influenced by the number of compartments, the respective compartments of both models were taken into account.

**Development of a novel population pharmacokinetic model**

When the predictive performance of the published model was inadequate, an alternative population PK model was constructed. During construction, the number of compartments was evaluated. In this study, the initial visit with PK profiling was considered as the first occasion. Subsequent occasions were defined as a visit with a PK assessment. PK parameters were expressed by CL, Q, and V; inter-individual (IIV) and inter-occasional variability (IOV) of these parameters was estimated. Residual error is described with a combined additive and proportional model. We evaluated candidate models by examination of PK parameter estimates, their respective residual standard errors (RSE), objective function value (OFV), GOF plots and visual predictive checks (VPC).

Stepwise covariate modelling (SCM) was used to perform covariate analysis applying the generalized additive models (GAM) approach. This approach allows to test if potential patient characteristics are able to explain IIV and IOV in PK parameters. We applied a forward inclusion and backward elimination process. Age, height, body weight, LBW, FFM, BMI and centre of inclusion were available and explored as covariates. Allometric scaling was applied with fixed exponents of 0.75 for CL and 1.00 for V. As height was not available in two patients, their height was fitted by a linear regression model based on available height and age of other patients, and used to calculate LBW and BMI. We explored the impact of the centre on FIX predictions as haemophilia treatment centres used different laboratory specifications according to local protocol. This was tested by incorporating a residual error per centre.

In the SCM, covariates were screened for relevance by univariate analysis. Improvement of the model was deemed significant if addition of a covariate to the model decreased the OFV (\( \Delta \text{OFV} \)) with 3.84 (p<0.05, Chi-square distribution, 1 df). When two parameters were added simultaneously, e.g. during expansion of a two-compartment model to a three-compartment model, a \( \Delta \text{OFV} \) of -5.99 (p<0.05, Chi-square distribution, 2 df) was warranted. Subsequently, all significant covariates were simultaneously added to the model, followed by backward elimination. Elimination of a covariate that resulted in an OFV increase of >6.64 (p<0.01, Chi-square distribution, 1 df) was regarded as a significant improvement to the model.

The novel population PK model was internally validated with a visual predictive check (VPC) to compare the distribution of the observations with the distribution of the predictions. The robustness of the param-
eter estimates was assessed by bootstrap analysis. Bias of the novel population PK model were assessed throughout the PE (Eq. 4).

**Individual dosing advice**

To evaluate the clinical impact of the choice of model on dosing regimens, we compared the dose (IU) for each individual with a PK profile assessment of rFIX-Fc (n=36) as calculated by application of Bayesian forecasting using both the published and the developed novel model. Individual PK parameters were calculated for the clinical situation in which a peak, trough and random mid FIX activity level were available. Doses were targeted at maintaining a FIX level >3 IU/dL at 168h after infusion of rFIX-Fc during steady-state (Dose3%). We wanted to perform Bayesian forecasting on data that was not included in the development of the model. Hence, five separate datasets including 29-30 patients were created on which population PK parameters were estimated. These estimates were used for Bayesian forecasting using three individual samples of the remaining 6-7 patients not included in the dataset. Differences in calculated doses between the two models were explored by the permutation test, as the doses were not normally distributed and contained too many ties to perform a Wilcoxon signed rank test. This analysis was also performed separately for children <12 years of age, since the previously published model did not include children <12 years of age, whereas the newly developed model did.

**RESULTS**

**Patient characteristics and pharmacokinetic profiling**

Real world data from 35 severe and 2 moderately-severe haemophilia B patients was available for assessment of the predictive performance of the published rFIX-Fc population PK model (Table 1). Median age was 15.8 years (range 2.3-71.0), and 14 patients were below the age of 12 years. Patients received a median dose of 36 IU/kg rFIX-Fc concentrate (range 10 – 132 IU/kg). In total, 287 FIX activity levels measured by OSA were available for analysis. Three FIX activity levels (1% of the data) were below LLOQ and therefore excluded in the analysis29,31. During PK profiling, a median of five FIX activity levels (range 3-7) in adolescent and adult patients (≥12 years of age) and four FIX activity levels (range 3-7, mean 4.5) in children (<12 years of age) were sampled. PK data was obtained during a median of 2 occasions per individual (range 1-9).

**Predictive performance of the published model**

The predictive performance of the published population PK model for rFIX-Fc was evaluated by comparing the model-predicted and observed FIX activity levels. Figure 1A and Figure 1B present the population predictions goodness-of-fit (GOF) plots for all patients and children <12 years of age separately. Observed FIX activity levels are higher than their respective predictions (Fig. 1A and 1B) and a clear deviation of trend lines from identity lines can be seen in all patients (Figure 1A), but especially in children <12 years of age (Figure 1B). These observations indicate structural bias (underprediction) of the published model. This is also illustrated by the median PE of -48.8% (IQR: -29.9 – -63.9) for all patients and -54.1% (IQR: -43.3 – -65.8) for children <12 years of age (Supplementary Table 2A). The RMSE is shown in Supplementary Table 2B.

Furthermore, deviations were observed in plots of conditional weighted residuals (CWRES) versus population predictions (PRED, Sup. Fig. 1A) and time after dose (TAD, Sup. Fig. 1B).

Bayesian analysis was performed to obtain individual PK parameter estimates. For children <12 years of age, Figure 2A and 2B show the deviation from the individual PK estimate from the typical population value over the weight range. For the evaluation of these graphs, it is important to realize that an adequate population model would have random inter-patient variability with an average of zero and no trend with weight. Figure 2A and 2B clearly demonstrate that children’s CL and V1 are lower than would typically be expected over the studied weight range and advocate the development of a new model.

**Development of the novel model**

*Structural model*
A novel rFIX-Fc population PK model using clinical data including children <12 years of age was developed (Table 2). A two-compartment model with a central and a peripheral compartment adequately described our data. Addition of a second peripheral compartment did not improve the fit of the model to the data. All PK parameters were allometrically scaled. With allometric scaling, body weight is included in the structural model. IIV could be estimated for CL, V1 and V2, with a correlation between CL and V1. The clinical data supported the estimation of IOV on CL.

**Covariate analysis**

Age, height, LBW, FFM, BMI and centre of inclusion were explored as covariates. In univariate analysis - using the structural model without application of allometric scaling – the separately weight-related covariates body weight, FFM and LBW were significantly related to CL and V1. We chose however to allometrically scale these parameters with body weight as it is easy and routinely measured, as opposed to LBW and FFM. Incorporation of a separate residual error for one haemophilia treatment centre improved the model (p<0.05), but was not significant after the backward selection reprocess (p<0.01). Therefore, all centres were described by the same residual error model. CL decreased with age; the latter was the only covariate that improved the fit of the model to the data. On basis of this relationship typical clearance of a 73 kg patient would decrease from 1.89 dL/h at an age of 20 years to 1.36 dL/h at an age of 70 years.

**Diagnostics of the novel model**

The internal validity throughout the visual predictive check (Figure 3) shows observed FIX activity levels being adequately predicted by the novel model. Bootstrap results are presented in Table 2. The trend lines in the GOF plots are close to the line of identity for both all patients (Fig. 1C) and children <12 years of age (Fig. 1D). The trend line in children <12 years of age (Fig. 1D) shows a slight deviation at high FIX activity levels, but this may be caused by the sparse number of samples in this range. A slight bias was detected for the novel model, as the median PE was 3.4% (IQR -22.2 – 25.8) for all patients and 6.5% (IQR -20.8 – 27.5) for children <12 years of age (Supplementary Table 2A).

CWRES plots (Sup. Fig. 2C and Fig. 2D) show an improved fit compared to the published model (Sup. Fig. 2A and 2B). In addition, the vast majority of values in the new model is within the warranted -2 and 2 range, in contrast to the values of the published model.

Typical parameter values (Table 2) differed between the published and novel model. For a typical 16 year old 73 kg patient, CL was 1.41 dL/h and lower than the value of the published model (2.39 dL/h). In addition, distribution volume at steady-state (Vss) was lower as well with respective values of 153 dL and 198 dL. Likewise, terminal t\(\frac{1}{2}\) was lower in the novel model compared to the published model for children <12 years of age (70 h vs 88 h), adolescents [?]12 and <18 years of age (76 h vs 99 h) and adults (88 h vs 101 h) (Supplementary Table 3).

Lastly, the validity of the model for children <12 years of age is illustrated in Figure 2C and 2D. The figure demonstrates random variability of CL and V with an average not different from zero. Of note, an adequate covariate model shows no trend and deviations from zero in the IIV.

**Individual dosing advice**

To maintain a FIX level >3 IU/dL 168h after rFIX-Fc infusion, individual doses were calculated by application of Bayesian forecasting using the published and the novel model by taking three clinically relevant samples into account (Figure 4). The individually predicted Dose\(\text{3%}\) was significantly higher (p<0.01) when predicted by the published model (median 1750 IU (range 250-3500)) than with the novel model (median 1500 IU (range 250-2000)) when all patients were considered. Surprisingly, however, when focusing on children <12 years no significant differences in Dose\(\text{3%}\) were found. Median dose was 750 IU (range 250-2500) and 1000 IU (range 250-1750) (p=0.63).

**DISCUSSION**
In this study, the predictive performance of a published rFIX-Fc population PK model was evaluated using independent real world data\textsuperscript{16}. The published model was based on patients \textgreater12 years whereas in this study children with age <12 years were included as well. The published model significantly underpredicted the observed FIX activity levels in all patients, especially for children <12 years of age. Consequently, a new population PK model was developed which should preferably be used to perform PK guided dosing in young children.

Compared to the previously published model, our newly developed model better describes the PK profiles of children <12 years of age that were included. These improvements are not surprising as weight normalized CL and V1 are generally larger in children compared to adults\textsuperscript{12}. This phenomenon has also been reported for recombinant factor VIII-Fc fusion protein (rFVIII-Fc)\textsuperscript{33}. For children <12 years specifically, the novel model shows adequate characterization of CL and V1 (Fig. 2C and 2D).

Observed inter-patient variability of CL and V1, and within-patient variability of CL were somewhat increased in comparison to reported values (Table 2). As real word data is obtained from a highly heterogenic population, a larger variability is imminent compared to selected clinical study populations. This also explains why the residual proportional error in the novel model (16.3%) was slightly higher compared to the published model (10.6%) (Table 2). Real world clinical data may contain more noise due to variability in assay precision, variability in administration and sample times.

Surprisingly, this study found a near two-fold lower typical clearance than reported by Diao et al.\textsuperscript{16} (Table 2). A possible explanation for this may be related to the neonatal Fc receptor (FcRn), to which the Fc domain of the IgG1 molecule in rFIX-Fc binds. FcRn concentrations are negatively correlated with body weight\textsuperscript{34}. Consequently, children have higher concentrations of weight-adjusted FcRn, possibly resulting in lower CL. This is in contrast to the expected higher FIX CL in children, as is found in factor VIII (FVIII)\textsuperscript{35,36}. As half of our population was paediatric (<18 years) and 38% was <12 years of age, the age related effect on FcRn may have influenced CL estimation.

Our real world clinical data was best described by a two-compartment model and not by a three-compartment model as previously constructed by Diao et al.\textsuperscript{16} This is due to differences in sampling times during PK profiling between both study populations. More specifically, the published model was constructed based on a rich sampling schedule during a 10-day period, whereas the current study used a maximum of six FIX activity levels sampled during a 7-day period. In the present study, less FIX activity levels were sampled at early time points. This could explain why we were not able to describe a third compartment that characterizes the rapid distribution phase of rFIX-Fc occurring within 2-3 hours after the end of administration\textsuperscript{37}. Notwithstanding these limitations, our model adequately described the terminal elimination phase which determines the trough concentration on which doses are generally adjusted for in clinical practice.

The observed difference in terminal $t_{1/2}$ between the models is due to the difference in the estimated PK parameters. Nevertheless, the $t_{1/2}$ of the novel model (70, 76 and 88 h for <12 years, [?]12 and <18 years and adults, respectively) are closer to the reported $t_{1/2}$ in the Alprolix® SmPC\textsuperscript{21} (70, 82 and 82 h) than those calculated for the published model (88, 99 and 101 h).

In this study, we have illustrated the clinical impact of underlying population PK models on dosing advice when personalizing treatment. In general, a population PK model should be applied that is representative for the patients for which individual PK are characterized. In our study, however, we did not observe a difference in dose for patients <12 years of age which could be due to the limited number of patients. When considering data from all patients, a significant dose difference was observed, probably caused by the difference in population PK parameters.

In this context, it is important to realize that individual PK parameters are calculated by combining information from both the population and the individual. When more samples are available (5 or more) per individual, individual PK parameters are mainly determined by information from this individual. In the present study, an intermediate clinically representative (3) number of samples was available, hence individual PK parameters were mostly determined by the individual observations. It should however be realized that
large differences in dose predictions may occur when less samples are available for an individual patient.

The strength of the present study is that it contains real world data reflecting clinical variability. A study limitation is the relatively sparse sampling method with aforementioned consequences at early time points. The impact of FIX extravascular distribution is recognized by a growing body of literature and should be incorporated in future models. Investigation of extravascular binding of FIX could be of clinical importance, as studies in mice suggest a haemostatic function of extravascular FIX. We, carefully, advocate the use of other techniques, like physiology-based pharmacokinetic (PBPK) models, to investigate an estimation of this extravascular compartment.

CONCLUSION

Population PK parameters derived from our novel model differ considerably from those reported previously. The novel model better describes the real world PK as opposed to the published model, underlining the necessity to strive for representative population PK models and avoiding extrapolation when performing PK-guided dosing.

ACKNOWLEDGEMENTS

SYMPHONY consortium

The SYMPHONY consortium which aims to orchestrate personalised treatment in patients with bleeding disorders, is a unique collaboration between patients, health care professionals and translational & fundamental researchers specialised in inherited bleeding disorders, as well as experts from multiple disciplines. It aims to identify best treatment choice for each individual based on bleeding phenotype. In order to achieve this goal, workpackages have been organized according to three themes e.g. Diagnostics (workpackages 3&4); Treatment (workpackages 5-9) and Fundamental Research (workpackages 10-12). This research receives funding from the Netherlands Organisation for Scientific Research (NWO) in the framework of the NWA-ORC Call grant agreement NWA.1160.18.038. Principal investigator: Dr. M.H. Cnossen. Project coordinator: Dr. S.H. Reitsma.

Beneficiaries of the SYMPHONY consortium: Erasmus University Medical Center-Sophia Children’s Hospital, project leadership and coordination; Sanquin Diagnostics; Sanquin Research; Amsterdam University Medical Centers; University Medical Center Groningen; University Medical Center Utrecht; Leiden University Medical Center; Radboud University Medical Center; Netherlands Society of Hemophilia Patients (NVHP); Netherlands Society for Thrombosis and Hemostasis (NVTH); Bayer B.V.; CSL Behring B.V.; Swedish Orphan Biovitrum (Belgium) BVBA/SPRL. Additional beneficiaries, not included in the SYMPHONY consortium, currently funding parallel projects are: Novonordisk (OPTI-CLOT TARGET), Roche (Partitura), Stichting Haemophilia (patient-reported outcomes project).

OPTI-CLOT study group

OPTI-CLOT/To WiN study group aims to implement personalized treatment by pharmacometric-guided dosing of factor concentrates, desmopressin and non-factor therapies in patients with bleeding disorders.


Trial bureau: I. van Vliet, Rotterdam.

Local collaborators the Netherlands : M.J.H.A. Kruip, S. Polinder, Rotterdam; P. Brons, Nijmegen; F.J.M. van der Meer, Leiden; K. Fischer, K. van Galen, Utrecht

Principal investigators and local collaborators in the United Kingdom: P. W. Collins, Cardiff; M. Mathias, P. Chowdary, London; D. Keeling, Oxford.
OPTI-CLOT-To WiN, DAVID and SYMPHONY PhDs:


CONFLICTS OF INTEREST

Dr. M.H. Cnossen’s institution has received investigator-initiated research and travel grants as well as speaker fees over the years from the Netherlands Organisation for Scientific Research (NWO) and Netherlands National research Agenda (NWA), the Netherlands Organization for Health Research and Development (ZonMw), the Dutch Innovatiefonds Zorgverzekeraars, Stichting Haemophilia, Baxter/Baxalta/Shire/Takeda, Pfizer, Bayer Schering Pharma, CSL Behring, Sobi Biogen, Novo Nordisk, Novartis, Roche, and Nordic Pharma, and for serving as a steering board member for Roche, Bayer and Novartis. All grants and fees go to the Erasmus MC as an institution. She is coordinator of Erasmus MC as a Health Care Provider within the European Reference Network (ERN) for rare hematological diseases EuroBloodNet and (co)leader of the local Erasmus MC Expert Centers for Rare Bleeding Disorders and Sickle Cell and Thalassemia Comprehensive Care Center.

R.A.A.M. has received grants from governmental and societal research institutes such as NWO, ZonMW, Dutch Kidney Foundation and Innovation Fund and unrestricted investigator research grants from Baxter/Baxalta/Shire/Takeda, Bayer, CSL Behring, Sobi and CelltrionHC. He has served as advisor for Bayer, CSL Behring, Merek Sharp & Dohme, Baxter/Baxalta/Shire/Takeda. All grants and fees paid to the institution.

F.W.G. Leebeek has received unrestricted grants from CSL Behring, Takeda, Sobi and uniQure. He is a consultant for CSL Behring, Takeda, Biomarin and uniQure, of which the fees go to the University. He was DSMB member of a study sponsored by Roche.

M. Coppens has received financial support for research from Bayer, CSL Behring, Roche and Novo Nordisk, and honoraria for lecturing or consultancy from Alexion, Bayer, CSL Behring, Daiichi Sankyo, Sobi and Viatris.

Other authors have no conflict of interest to declare for this paper.

AUTORSHIP CONTRIBUTIONS

T.M.H.J.G. enrolled patients, performed blood sampling for PK analysis and validation and collected in the OPTI-CLOT TARGET study. Patient inclusion in the UK EHL registry was monitored by M.M., P.W.C., C.R.M.H., R.C.T., C.B., S.M., B.M., G.E., B.B., N.C., J.P., and S.A. T.M.H.J.G. collected data from the UK-EHL registry and checked all clinical data from the EHL registry. S.F.K. and R.A.A.M. performed the analysis and developed the population pharmacokinetic model. S.F.K. and T.M.H.J.G. wrote the manuscript. L.H.B., M.H.C. and R.A.A.M. supervised the study. All authors contributed substantially to the critical revision of the manuscript and approved the final draft.

REFERENCES


Hosted file