Physiologically–based pharmacokinetic (PBPK) modelling of recombinant factor IX Fc fusion protein (rFIXFc) and rFIX to characterize the binding to type 4 collagen

M.E. Cloesmeijer[1], E. Sjögren[2,3], P.J. Lenting[4], M.H. Cnossen[5], R.A.A. Mathôt[1] for SYMPHONY consortium

1) Department of Hospital Pharmacy-Clinical Pharmacology, Amsterdam University Medical Centers, Amsterdam, The Netherlands;
2) Department of Pharmaceutical Bioscience, Translational Drug Discovery and Development, Uppsala University, Uppsala, Sweden;
3) Pharmetheus, Sweden;
4) Laboratory for Hemostasis, Inflammation & Thrombosis, Unité Mixed de Recherche (UMR)-1176, Institut National de la Santé et de la Recherche Médicale (Inserm), Université Paris-Saclay, Le Kremlin-Bicêtre, France;
5) Department of Pediatric Hematology and Oncology, Erasmus University Medical Center - Sophia Children's Hospital Rotterdam, Rotterdam, The Netherlands.

Background

Haemophilia B patients are characterized by a deficiency of coagulation factor IX (FIX) resulting in bleeding, typically in joints and muscles[1]. FIX replacement therapy, such as recombinant factor IX Fc fusion protein (rFIXFc) or recombinant FIX (rFIX) is administered prophylactically in severe cases. FIX is able to distribute in the extravascular space by binding to type IV collagen (Col4)[2]. The concentrations of FIX in the extravascular space seem to be crucial, since its hemostatic effect is present even with no measurable FIX concentrations in plasma[3].

Objectives

The aim of this study was to develop a PBPK model of rFIXFc in haemophilia B patients and to quantify the binding of rFIXFc to Col4. We also wanted to investigate the predictive performance of the PBPK model of rFIXFc for other FIX concentrates such as rFIX.

Methods

The whole-body scale PBPK modelling of rFIXFc and rFIX was performed using PK-Sim (version 11 – build 150, Open Systems Pharmacology) and using the base model for large molecule drugs [4]. The workflow followed to developed and validate the model is illustrated in figure 1. A schematic overview of the model is displayed in figure 2.

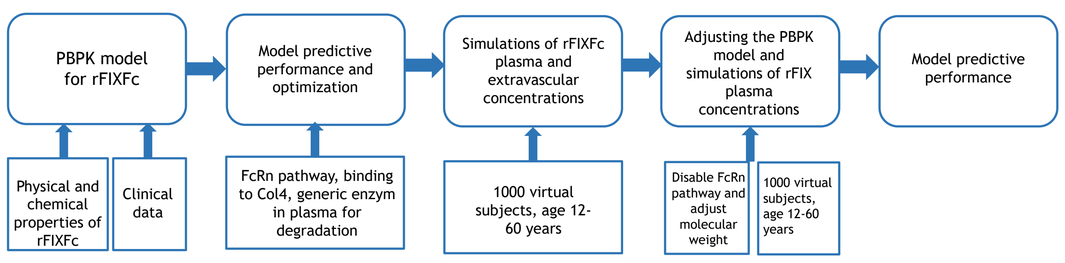

Figure 1. rFIXFc and rFIX PBPK modelling workflow

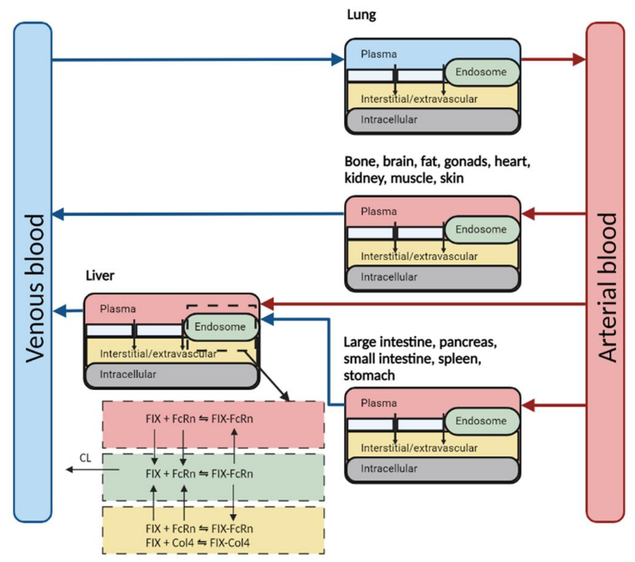

Figure 2. Schematic overview of the rFIXFc PBPK model

Results

A PBPK model for rFIXFC was developed and could adequately predict the clinical observations (figure 3A). Afterwards, the FcRn pathway was disabled and the molecular weight was adjusted for rFIX in the PBPK model. The rFIXFc PBPK model was also capable of predicting the clinical observations of rFIX (figure 3B).

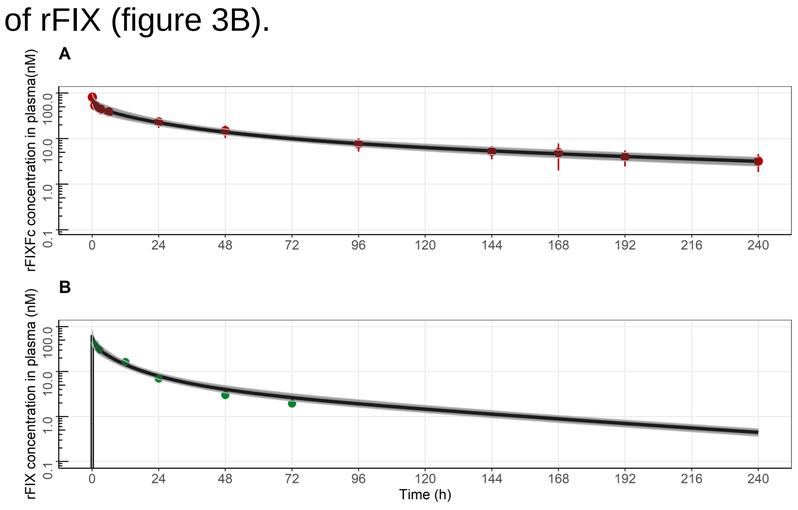

Figure 3. Predictions of rFIXFc and rFIX plasma concentrations over time in a virtual male population of >12 years. A) observed and predicted plasma rFIXFc concentrations over time after single bolus dose of 50 IU/kg (0.6 mcg/kg) B) rFIX observed and predicted plasma rFIX concentrations over time after single bolus dose of 50 IU/kg (0.3 mg/kg). Black solid line: median predictions, red circles: median observed rFIXFc concentrations and standard deviation, green circles: median observed rFIX concentrations, grey shaded area: 95% prediction interval.

The rFIXFc PBPK model quantified the binding of rFIXFc to Col4 in the extravascular spaces of various tissues (figure 2) the pharmacokinetic parameters in plasma and tissues. The results showed that the AUC of rFIXFc to Col4 in the extravascular space was approximately 14 times higher compared to the plasma concentration. The highest concentrations of extravascular rFIXFc bound to Col4 were to be found in the spleen and lungs.

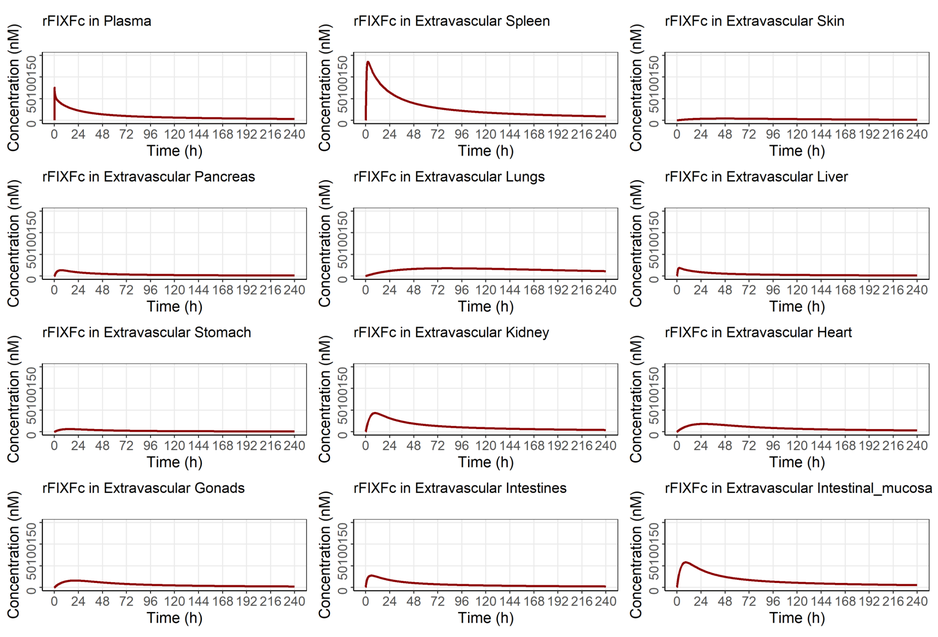

Figure 4: Predicted rFIXFc concentrations over time in plasma or extravascular tissues. *An IV bolus of 50 IU/kg rFIXFc (0.6 mcg/kg) was administered in a virtual male patient of 30 years. Red solid line: predicted population median curve.*

Conclusions

- A PBPK model was developed that adequately predicts rFIXFc and rFIX concentrations in plasma.
- The extravascular rFIXFc AUC was estimated 14 times higher compared to the plasma, suggesting extravascular rFIXFc may play an important role in achieving haemostasis.
- Further studies and measurements on extravascular distribution are needed to evaluate the predictions of the model.

Contact via m.e.cloesmeijer@amsterdamumc.nl or via LinkedIn (QR code)

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