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Population Pharmacokinetic Modeling of Factor IX Activity After Administration of Nonacog Alfa in Patients With Hemophilia B

Akiyuki Suzuki, MS; Yoshiro Tomono, BS; Joan Korth-Bradley, PharmD, PhD
Department of Clinical Pharmacology, Pfizer Inc

ABSTRACT

Introduction and Objectives: Assessment of factor IX (FIX) activity trough levels and half-life after administration of recombinant FIX replacement therapy is one approach to optimizing prophylactic dosing schedules in the absence of frequent bleeding episodes in patients with hemophilia B. Our objective was to develop a pharmacokinetic (PK) model for FIX activity after nonacog alfa to help individuals optimize dosing in the absence of patient-specific PK data.

Materials and Methods: A population pharmacokinetic model was developed using all available clinical data collected during the development of nonacog alfa, including: data from 8 estimation studies (4936 observations from 201 patients; mean ± SD weight 45.4±34.8 kg; age 16.7±17.5 yr) and 2 additional reference studies (385 observations from 72 patients; weight 70.0±20.7 kg; age 29.6±13.6 yr) were evaluated. PK samples were collected when patients were stable and non-bleeding and were given single doses after at least 72 hours washout. The population pharmacokinetic analysis was conducted using the nonlinear mixed-effects modeling software package NONMEM (version 7.2; ICON Development Solutions, Hanover, MD, USA), using first-order conditional estimation with interaction.

Results: The final model was a 2-compartment model, parameterized for clearance (CL), volume of distribution of the central (V1) and peripheral (V2) compartments, and intercompartmental clearance (Q). Weight was incorporated as a power function for each parameter, with estimates close to allometric scaling. Decreases in objective function were observed when inter-occasional variability (IOV) on CL and V were included. Investigations of a full-block omega matrix led to the retention of a correlation between V2 and Q. Age was not a significant covariate once weight was included in the model. Observations in the reference studies were found to be higher than model-simulated values immediately after dose administration and 1 week after dosing. The differences may be attributable to older subject age (all were adults) and longer sample collection time in the reference studies.

Conclusions: FIX activity is appropriately modeled as a 2-compartment model after nonacog alfa administration. When weight is included, no additional effect of age is observed; thus, current dosing recommendations that are consistent for patients of all ages appear to be supported by the model. Longer times of observation after dosing may be helpful in refining the model.

INTRODUCTION

- The goal of factor IX (FIX) replacement therapy in patients with hemophilia B is to control bleeding episodes or to minimize the number of spontaneous bleeding episodes
- Target trough FIX activity may be guided by individual pharmacokinetics (PK)
- A population PK model would be helpful to identify important determinants of individual PK and provide prior distribution for predictions

OBJECTIVE

- To develop a pharmacokinetic model for FIX activity after administration of nonacog alfa to help individuals optimize dosing in the absence of patient-specific PK data

METHODS

Patients

- Data from 8 completed studies (4936 observations from 201 patients) were used to develop the model
- Data from 2 recently completed studies (385 observations from 72 patients) were used to evaluate the model
- PK samples were collected when patients were stable and non-bleeding and were given single doses of nonacog alfa after at least 72 hours washout

Sampling

- Dense sampling (0, 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 72 hr) and sparse (0, 0.5 hr) schemes used for 106 (development data set)/95 (evaluation data set) patients
- Only sparse sampling was available for the 72 patients in the evaluation data set

FIX Activity Assay

- One-stage activated partial thromboplastin time (APTT) clotting assay
- Lower limit of quantification was 1 IU/dL
- FIX activity reported below limit were excluded from analysis
- Post-dose FIX activity were corrected for observed FIX activity above limit of quantification

Population Pharmacokinetic Modeling

- NONMEM (version 7, level 2, ICON Development Solutions, Hanover, MD)
  - First-order conditional estimation with interaction
  - R v2.15.2 (R project)
  - Perl-speaks-NONMEM (PsN) v 3.5.4
  - R package Xpose v4.3.2
- Base model developed, then covariates added using stepwise testing in forward inclusion (ΔOFV 3.84, P<0.05 for 1DF) and backward inclusion (ΔOFV 6.63, P<0.01 for 1DF)
- Diagnostic plots evaluated adequacy of final model
- Non-parametric bootstrapping without stratification used to generate 95% CI probability curves for final models
- Visual predictive checks (VPCs; PsN without automatic truncation) simulated 100 data sets to evaluate final model

RESULTS

- The data sets used to develop and evaluate the model are shown in **Table 1**
- The final model was a two-compartment model parameterized for clearance (CL), volume of distribution of the central (V1) and peripheral (V2) compartments, and intercompartmental clearance (Q)

Table 1. – Data Summary

Data Set	No. of Subjects	No. of Samples	Median Wt (min–max) (kg)	Median Age (min–max) (yr)	Dose (min–max) (IU/kg)
Development	201	4936	43.5 (1.3–172.5)	12.2 (0–69.2)	54.7 (14.2–205.9)
Evaluation	72	385	74.3 (20.7–127.5)	27.6 (6.1–64.7)	49.6 (14.6–213.3)

- Effect of weight modeled (**Table 2**)
  - Reference 70 kg
  - Power function

Table 2. Effect of Weight and Age on CL

Model	Description	OFV (M)	ΔOFV	Keep in Model?
B1	Two-compartment model	19912.374		
B2	Wt on CL, V1, Q, V2	18851.406	-1061	Yes
Base Model	Wt on CL, V1, Q, V2; IOV on CL and V1, omega block Q-V2, without age effect on CL	16765.790		
1	$TVCL = CL_{pop} \times \left[1 - \theta \times (Age - 24)\right]$ CL_{pop}: the population central tendency for CL in patients with age=24 yr	16764.828 (S)	-0.962	No
2	Age ≤ θ_1 $TVCL = CL_{pop} + \theta_2 \times Age$ Age > θ_1 $TVCL = CL_{pop} + \theta_2 \times \theta_1$ CL_{pop}: the population central tendency for CL in patients with age=0 yr	16759.798 (F)	-5.992	No

OFV (M), OFV (minimization status: S [successful], F [failed]).
ΔOFV, change from base model.

- The final model is shown in **Table 3**

Table 3. Final Model

$$CL_{ij} = \theta_1 \times \left(\frac{WT_i}{70}\right)^{\theta_7} \times e^{\eta_{CL_i} + \kappa_{CL_{ij}}} \qquad Q_i = \theta_4 \times \left(\frac{WT_i}{70}\right)^{\theta_{10}} \times e^{\eta_{Q_i}}$$

$$V1_{ij} = \theta_2 \times \left(\frac{WT_i}{70}\right)^{\theta_8} \times e^{\eta_{V1_i} + \kappa_{V1_{ij}}} \qquad V2_i = \theta_3 \times \left(\frac{WT_i}{70}\right)^{\theta_9} \times e^{\eta_{V2_i}}$$

Residual error $Y_{ijk} = F_{ijk} + w_{ijk} \cdot \varepsilon_{ijk}$

$w_{ijk} = \sqrt{\theta_\varepsilon^2 + \theta_p^2 \cdot F_{ijk}^2}$

here Y_{ijk} denotes the observed concentration for the ith individual in occasion j at time t_k, F_{ijk} denotes the corresponding predicted concentration based on the PK model, and θ_ε and θ_p denote the standard deviations of additive and proportional residual errors, respectively

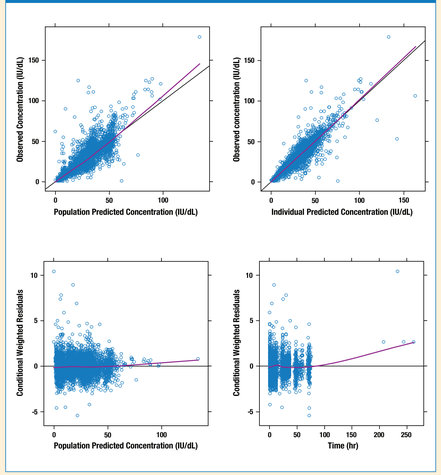
3090A1-200 & 3090A1-201: $\theta_{11}=\theta_{13}$
3090A1-300: $\theta_{12}=\theta_{13}$
Other Study: $\theta_{13}=\theta_5$

Parameter	NONMEM Estimation, Estimates (RSE%)	Bootstrap[a], Median (RSE%b)	95% Confidence Interval
CL (θ_1)	5.51 dL/hr (2.2%)	5.50 dL/hr (2.5%)	(5.23, 5.78 dL/hr)
V1 (θ_2)	97.7 dL (4.0%)	97.0 dL (2.6%)	(92.4, 102 dL)
V2 (θ_3)	46.2 dL (4.1%)	46.2 dL (4.1%)	(43.1, 50.4 dL)
Q (θ_4)	5.77 dL/hr (12.6%)	5.97 dL/hr (17.1%)	(4.74, 8.31 dL/hr)
Power for WT on CL (θ_7)	0.799 (3.6%)	0.800 (4.1%)	(0.739, 0.872)
Power for WT on V1 (θ_8)	0.881 (3.9%)	0.879 (2.9%)	(0.828, 0.927)
Power for WT on V2 (θ_9)	1.02 (9.9%)	1.03 (9.8%)	(0.793, 1.18)
Power for WT on Q (θ_{10})	0.741 (22.1%)	0.732 (18.3%)	(0.422, 0.950)
Inter-individual variability (IIV)			
IIV_{CL}	25.6% (18.9%)	25.4% (19.2%)	(16.3, 34.8%)
$IIV\omega_{V1}$	23.2% (10.2%)	22.7% (11.0%)	(18.5, 28.0%)
$IIV\omega_{V2}$	35.7% (13.7%)	35.0% (15.4%)	(25.5,45.7%)
$IIV\omega_{Q}$	69.1% (17.6%)	73.4% (22.5%)	(41.7, 102.2%)
$\rho_{Q\text{-}Q}$	0.481	0.505	(0.0711, 0.841)
Interoccasion variability (IOV)			
IOV_{CL}	24.7% (14.3%)	23.8% (16.4%)	(17.4, 31.1%)
IOV_{V1}	18.9% (8.6%)	18.8% (9.8%)	(16.2, 23.0%)
Residual variability:			
Proportional error			
3090A1-200 & -201 (θ_{11})	0.122 (5.4%)	0.120 (5.6%)	(0.109, 0.135)
3090A1-300 (θ_{12})	0.260 (11.7%)	0.260 (15.4%)	(0.182, 0.338)
Other studies (θ_5)	0.117 (16.2%)	0.114 (17.3%)	(0.0809, 0.151)
Additive error (θ_6)	0.614 IU/dL (8.4%)	0.639 IU/dL (12.0%)	(0.480, 0.769 IU/dL)

η_1-shrinkage:η_{CL}: 20.2%, η_{V1}: 14.9%, η_{Q}: 30.8%, η_{V2}: 25.8%
ε-shrinkage: 13.0%
[a] 409 of 500 runs converged successfully.
[b] RSE% for bootstrap = standard error/median x100.

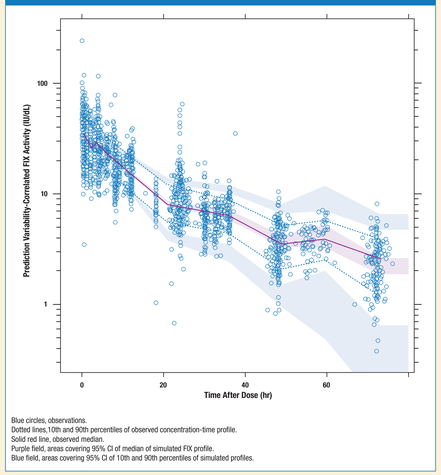
- **Figure 1** shows diagnostic plots for the final model
  - No influential outliers

Figure 1. Diagnostic Plots



- **Figure 2** shows VPC for the development data set

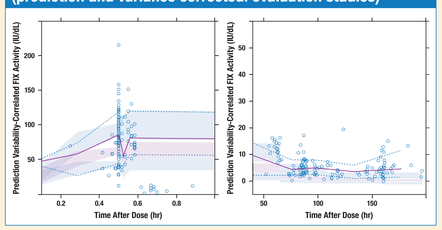
Figure 2. Visual Predictive Checks From the Final Model (prediction and variance corrected)



Blue circles, observations.
Dotted lines,10th and 90th percentiles of observed concentration-time profile.
Solid red line, observed median.
Purple field, areas covering 95% CI of median of simulated FIX profile.
Blue field, areas covering 95% CI of 10th and 90th percentiles of simulated profiles.

- **Figure 3** shows bias of simulations using evaluation data sets, both early and later, after dose administration

Figure 3. Visual Predictive Checks From the Final Model (prediction and variance corrected: evaluation studies)



- **Figure 4** shows maximum a posteriori evaluation, showing similar bias

Figure 4. Results of a Maximum a posteriori Evaluation

Blue circles: estimated data; purple circles: evaluation data.

DISCUSSION

- Previously developed population PK analyses
  - Small subset of data (n=56)[1]
    - 3-compartment model
- Most of development data set (n=191)[2]
  - Alternative parameterization
- Bias observed
  - One evaluation study had high recovery[3]
  - Evaluation data sets had longer postdose data, supporting observed impact of longer sampling times on half-life estimates

CONCLUSIONS

- Two-compartment model for FIX activity after nonacog alfa administration appropriate
- Weight was the only covariate
- No additional effect of age was observed when weight was included in the model
- Longer sampling times postdose may be useful in refining the model

References

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Author Disclosures

All authors are employees of Pfizer Inc and own stock in that company.

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