Development and Evaluation of a Population PK/PD Model for Fc-OPG in Healthy Postmenopausal Women

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ABSTRACT

Osteoporosis is a disease characterized by low bone mass and deterioration of bone tissue. This leads to increased bone fragility and risk of fracture, particularly of the hip, spine and wrist. Osteoprotegrin (OPG) is a promising alternative medication for osteoporosis. It is a member of the tumor necrosis factor (TNF) family, and works to decrease bone resorption by inhibiting osteoclast differentiation and survival through the RANKL/RANK/OPG pathway. We describe the development of a PK-PD model for the fusion protein, Fc-osteoprotegrin (Fc-OPG), in healthy postmenopausal women. The model describes data from 8 cohorts (n = 13 subjects/cohort; Fc-OPG:placebo = 10:3) classified by dose level (0.1, 0.3, 1.0, or 3.0 mg/kg) and route of administration (intravenous (IV) or subcutaneous (SC) injection). Fc-OPG serum concentrations following IV or SC administration and urinary N-telopeptide (NTX) levels were available. The model was developed in a stepwise fashion and results in an adequate fit to the data and physiologically plausible parameter estimates. Model robustness was tested via a posterior predictive check with the model performing well in almost all cases. Clinical trial simulations with the model clearly showed that a single 3 mg/kg SC dose of Fc-OPG produces a median urinary NTX percent change (w.r.t. baseline) of -45% (with a 95% confidence interval ranging from -34 to -60%). Simulations were evaluated using local and global sensitivity analysis methods. The model selection and simulation strategies we applied are rigorous, useful and easily generalizable.

INTRODUCTION

Osteoporosis is a disease characterized by low bone mass and deterioration of bone tissue. There are a variety of drug treatments available, including: bisphosphonates[6], hormone replacement therapy[9], selective estrogen receptor modulators[5], and anabolic parathyroid hormone[8].

Osteoprotegerin (OPG) is a promising alternative medication[3]. OPG is a member of the tumor necrosis factor (TNF) family, and works to decrease bone resorption by inhibiting osteoclast differentiation and survival through the RANKL/RANK/OPG pathway[4] (Figure 1). It has been recently shown[2] that a single SC injection of genetically engineered Fc-OPG fusion molecule (Fc-fragment of IgG_1) was effective in rapidly and profoundly reducing bone turnover for a sustained period of time.

This study summarizes our work in developing an integrated PK-PD model of Fc-OPG and applying the model through simulation to address questions of interest. The approach we have taken is general, and can likely be applied to other compounds at a similar stage of development.

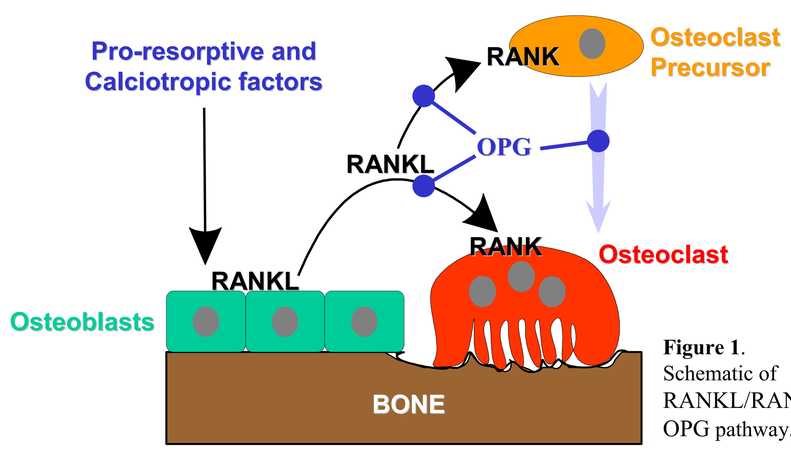

Figure 1. Schematic of RANKL/RANK/OPG pathway.

STUDY DESIGN

This was a randomized, double blind, placebo-controlled, single-dose, dose escalation, phase I study.

- 104 healthy postmenopausal women between 41 and 71 years of age
- 8 cohorts - 0.1, 0.3, 1.0, or 3.0 mg/kg administered either intravenous (IV) or subcutaneous (SC)
- 13 subjects per cohort received Fc-OPG:placebo (10:3 ratio)

MATERIALS AND METHODS

- NONMEM, version V, level 1.1, ADVAN8, TRANS1[1]
- Intel-based PC with the Compaq Visual Fortran Compiler, version 6.6A
- S-Plus 2000 Professional Release 3 (Insightful, Seattle, WA)

- PK Data
  - Serum samples obtained and measured for Fc-OPG concentration pre-dose and through 28 days post-dosing
    - nOPG-Ab ELISA method – R&D Systems
    - limit of quantification = 0.039 ng/mL

- PD Data
  - Urine collected for measurements of urinary N-telopeptide/creatinine (NTX (nM BCE/mM Creatinine)) up to 33 days prior to and through 84 days after dosing
    - Osteomark®, Urine ELISA Kit, Seattle, WA

PHARMACOKINETIC ANALYSIS

- IV data used for structural model (Naïve pool and First Order Estimation)
  - 2 and 3 compartment models, with various types of elimination from central compartment, compared using minimum objective function values (MOFV) and diagnostic plots
  - A minimum difference in MOFV (α=0.01 – chi square distribution) used as final selection criteria, but not for hypothesis testing

- First Order Conditional Estimation and interaction used to build OMEGA matrix
  - Stepwise approach, similar in technique to many common covariate selection approaches[7], adding non-zero between-subject variances to specific pharmacokinetic parameters one at a time
  - The variance term with the largest contribution to the MOFV (α=0.01) permanently added to the model
  - Repeated process until all 8 variance terms were added
  - Final PK model for IV data was selected based on:
    - Parsimony principles
    - A required minimum difference in MOFV (α=0.01),
    - The availability of NONMEM $COV matrix

- Fix IV PK parameters for SC model; fit all SC first-order absorption parameters

- With superior diagnostic plots and an acceptably lower MOFV, the 3-compartment, parallel elimination model was selected as the structural model of choice (Figures 2 and 3).

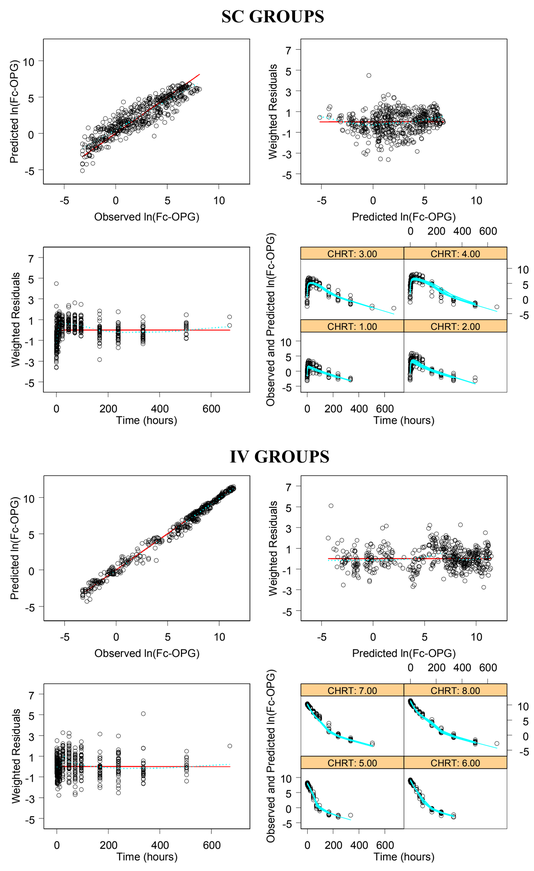

Figure 2. PK model diagnostic plots for SC (top) and IV (bottom) administered compound. Both predicted and observed concentrations have been log-transformed for analysis. Plots are, clockwise from top left: typical population model predicted Fc-OPG plasma concentration (PRED) vs. observed Fc-OPG plasma concentration (DV); weighted residuals of model prediction (WRES) vs. PRED; PRED and DV vs. TIME (split by cohort); WRES vs. elapsed time after injection (TIME). For all plots except PRED and DV vs. TIME, the red identity line represents a perfect model fit, and the dotted line is the Loess fit of the plot data points. For the PRED and DV vs. TIME graph, the continuous line is the typical population model predicted fit to the IV data points

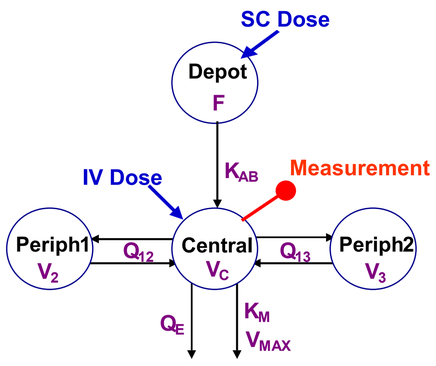

Figure 3. Final compartmental model for Fc-OPG pharmacokinetics. V_C is the central compartment volume of distribution, V_2 and V_3 are the peripheral compartments' volumes, Q_{np} is the intercompartmental clearance between n and p, Q_E is the linear clearance from plasma, and V_{max} and K_M describe Michaelis-Menten elimination. Subcutaneously injected compound had a first-order absorption rate of K_{AB} and a bioavailability of F.

PHARMACODYNAMIC ANALYSIS

- An indirect inhibition of synthesis model described the observed data:

$$\frac{dU_{NTX}(t)}{dt} = K_{syn}\left(1 - \frac{C_{OPG}(t)}{IC_{50} + C_{OPG}(t)}\right) - K_{deg}U_{NTX}(t)$$

- $C_{OPG}(t)$: PK model-predicted Fc-OPG serum concentration (ng/mL)
- $U_{NTX}(t)$: Predicted value of urinary NTX (nm BCE/mM Creatinine)
- K_{syn}: Systhesis rate of U_{NTX}
- K_{deg}: Degradation rate constant for U_{NTX}
- IC_{50}: 50% inhibition concentration
- Between-individual variance terms were estimated for all parameters

PK Model Parameter (units)	Estimated Value	% Relative Standard Error
K_M (ng/mL)	6.74	11
V_{MAX} (ng/hr)	13300	13
V_C (mL)	2800	2
V_2 (mL)	443	16
V_3 (mL)	269	14
Q_E (mL/hr)	168	3
Q_{12} (mL/hr)	15.5	16
Q_{13} (mL/hr)	3.02	13
F (%)	7.19	9
K_{AB} (hr^{-1})	0.0131	4
ω^2_{VC}	0.0102	39
ω^2_{V2}	0.0144	52
ω^2_{V3}	0.0333	124
ω^2_{QE}	0.0391	20
ω^2_{Q12}	0.0379	71
ω^2_{F}	0.263	20
ω^2_{KAB}	0.0457	31
$cov_{F\text{-}KAB}$	0.0577	48
$\sigma^2_{IV\text{-}prop}$	0.0193	13
$\sigma^2_{SC\text{-}prop}$	0.733	11

Table 1. Final population PK model parameters (fixed and random effects), including % relative standard error.

PD Model Parameter (units)	Estimated Value	% Relative Standard Error
Ksyn ([nM BCE/mM Creatinine]/hr)	0.864	8
Kdeg (hr^{-1})	0.0204	6
IC_{50} (mL/hr)	5.38	21
ω^2_{Ksyn}	0.281	28
ω^2_{Kdeg}	0.0325	88
$cov_{Ksyn\text{-}Kdeg}$	0.0867	59
ω^2_{IC50}	1.18	43
σ^2_{prop}	0.0407	13
σ^2_{add}	20.7	19

Table 2. Final population PD model parameters (fixed and random effects), including % relative standard error.

POSTERIOR PREDICTIVE CHECK

To assess whether the model provided an adequate description of the observed data:

- 1000 simulations of the original data set
- Estimated parameter uncertainty (NONMEM $COV matrix) used for between-trial variability
- Conducted for both PK and PD models (Figure 4)

SIMULATION AND SENSITIVITY ANALYSIS

- *Population Characteristics*
  - 200 subjects
  - SC doses of 210 mg to 70 kg subjects (reflecting cohort 4 dosage; 3 mg/kg)

- *Simulation*
  - Is cohort 4 dosing regimen effective every two weeks?
    - 200 replicate simulations
    - Display the variation in the population PD profile (%change from baseline U_{NTX} versus time) (Figure 5)

- *Global Sensitivity Analysis*
  - How do parameter uncertainties affect simulation conclusions?
    - 1000 simulation replications
    - Endpoint = %change from baseline U_{NTX} at 2 weeks
    - Illustrates simulation outcome dependencies on model parameters, taken over the uncertainty in all model parameters simultaneously (Figure 6).

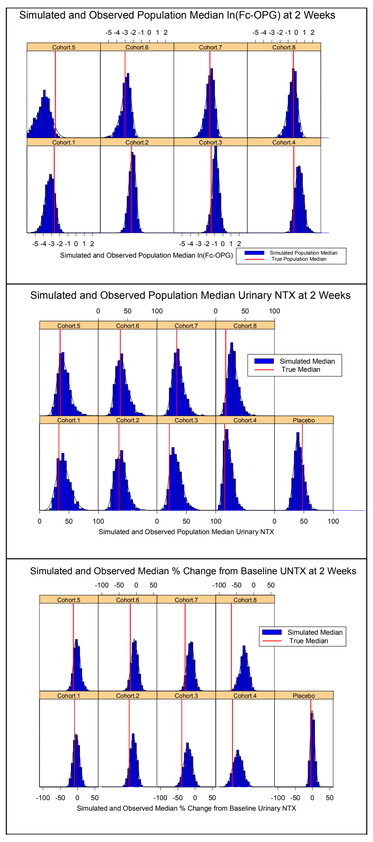

Figure 4. (Left) Posterior predictive check plots. From top to bottom: Fc-OPG log-transformed concentration (eight cohorts); urinary NTX values (eight cohorts with placebo); percent change from baseline urinary NTX (eight cohorts with placebo). The plots show the distribution of simulated population median values (histogram; 1000 populations) and actual population median from the available data (vertical line) at 2 weeks post drug administration.

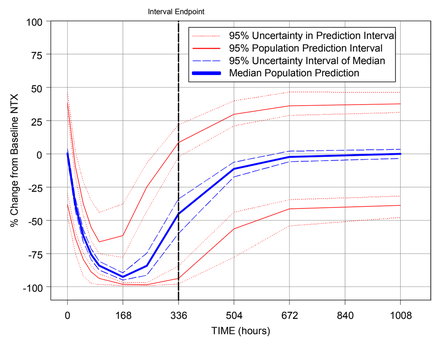

Figure 5. (Above) Simulation of 200 replicate trials, each with 200 subjects. The vertical dashed line intersects the computed profiles at 2 weeks after drug administration, and it helps to gauge visually how effective a biweekly dosing regimen might be. Median population prediction is -45% with a 95% uncertainty interval of -34% to -60%.

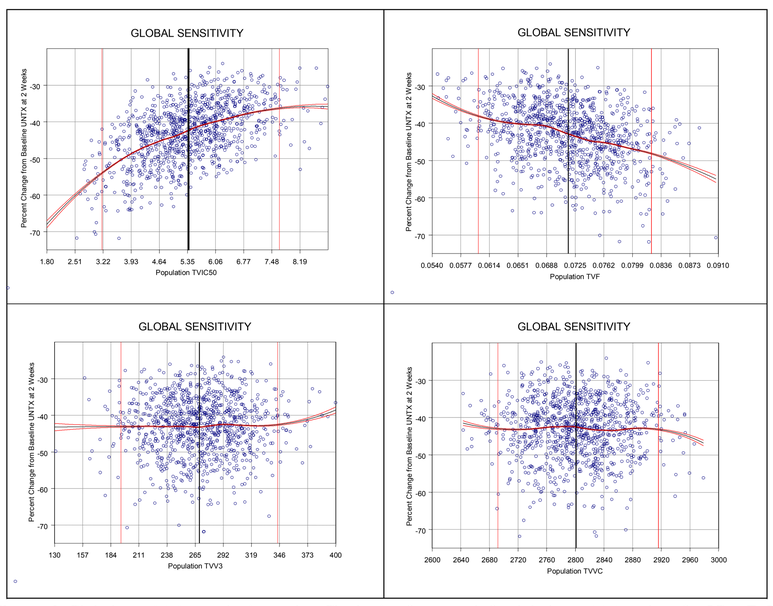

Figure 6. Global sensitivity analysis results. Clockwise from top left, global sensitivity plots for IC_{50}, F, V_C and V_3 are shown. The simulation outcome is highly sensitive to uncertainty in the model parameters IC_{50} and F, for example, while sensitivity to uncertainty in V_C and V_3 is negligible. All plots show U_{NTX} percent change from baseline vs. the typical value of the population parameter (TV*par* in the plots). The open circles show a scatter plot of the simulated predictions together with a Loess-fit curve and its 95% confidence interval (solid lines). The vertical thick line is the final typical value estimate from the original PK or PD model and the vertical red lines represent the 95% uncertainty interval for that parameter estimate (from the NONMEM asymptotic covariance matrix). The steeper the slope of the Loess-fit curve, the more sensitive the simulated outcome is to that particular parameter estimate. These plots were obtained for all 13 fixed effect parameters, and only 5 displayed noticeable sensitivity (IC_{50}, F, V_{MAX}, K_{AB}, and K_M).

CONCLUSIONS

- **Naïve pool analysis dramatically reduced basic model selection time**
- **Piecewise assessment of IV and SC data improved parameter estimation in complex model development**
- **Stepwise construction was useful in identifying estimable between-subject variance components**
- **Between-trial parameter variability in simulations:**
  - **Dramatically speeds up posterior predictive check (no bootstrap)**
  - **Exploits all available information to improve relevance of simulation outcomes**
- **Global sensitivity analysis exposes parameters whose uncertainty may greatly influence the predicted clinical outcome**
- **This generalizable approach for model development and evaluation may be useful for application to other similarly complex systems**

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