A Mechanism Based Population Pharmacokinetic-Pharmacodynamic Model for Epoetin Alfa and Darbepoetin Alfa in Chronic Kidney Disease Patients

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Objectives

The purpose of this analysis was to develop a mechanistic longitudinal pharmacokinetic / pharmacodynamic (PK/PD) model for the characterization of the erythropoietic effects of epoetin alfa and darbepoetin alfa in chronic kidney disease patients on hemodialysis and to enable switching of one agent to another.

Methods

DATA:

- Long term dialysis data in CKD patients obtained from dialysis center
- Darbepoetin and Epoetin treatments
- ~ 1100 subjects (52% males and 48% females)
- Laboratory values:
  - Hemoglobin, reticulocytes, records of dose adjustments
  - Patient demographics (body weight, age, sex, BMI etc.)
  - Creatinine clearance, concomitant medications, etiology of CKD etc.
- Treatment duration of 3-12 months per patient (2002 - 2008)

ANALYSIS:

- PK/PD model to describe time-course of red blood cell production (reported as hemoglobin concentration) based on the hematopoiesis processes and effect of epoetin and/or darbepoetin
- Darbepoetin and epoetin PK parameters from published literature [1, 3].
- Population analysis: Non-linear mixed effects modeling approach implemented in NONMEM® V

PREDICTIVE PERFORMANCE ASSESSED BY:

- Posterior predictive check (PPC):
  - PPC was conducted to assess the predictability of the PK/PD model. Specifically, 250 simulated trials were created conditioned upon the observed design including doses/sampling times for the dialysis center data.
- External predictive check:
  - Predictability of the PK/PD model was further assessed by comparing model-simulated data with external clinical data (protocols 960245 and 980211 from the development program for darbepoetin alfa). Specifically 1000 clinical trial simulations were conducted based on the study design and compared with observed data.

Results

Figure 1: Distribution of number of hemoglobin values in the dialysis center data

Total Number of Subjects: 1183

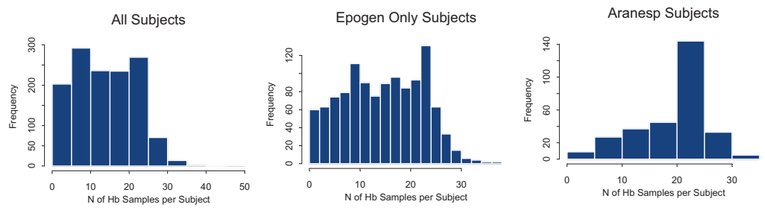
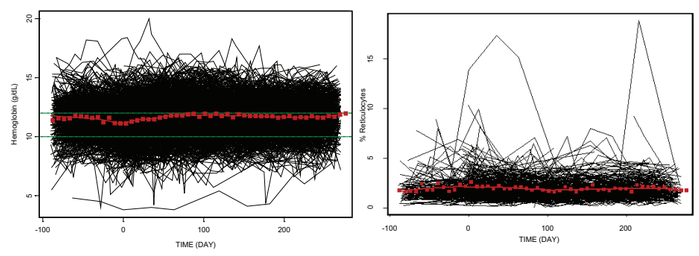


Figure 2: Individual subject hemoglobin and reticulocyte data in dialysis center dataset. Red symbols represent median values at each time point



PK/PD Model for Epoetin Alfa and Darbepoetin Alfa

The PK/PD model was modified from literature (2,3). The pharmacodynamic model for the erythropoiesis-stimulating effects of erythropoietin is described by a combination of cell production and loss model (cell life span concept) and indirect response model (Figure 3). The first precursor compartment represents progenitor cells (PRO), which are generated at a constant rate, R0. R0 is modeled as a function of individual subject's baseline hemoglobin values. Progenitor cells are transformed into normoblasts (NOR) by a first-order rate constant, KP. It is further assumed that normoblasts are transformed into reticulocytes (RETI) after their maturation time TNOR. Similarly, reticulocytes are transformed into mature RBC after their life span of TRET, which in turn are removed from the circulation after their maturation time of TRBC. Hemoglobin (Hb) levels were assumed to be directly proportional to the RBC count. A linear concentration-response model was selected to describe the effects of epoetin and darbepoetin on erythropoiesis, as data didn't support nonlinear relationships such as Emax and Power models.

Figure 3: Final PK/PD Model for the Effects of Darbepoetin and Epoetin alfa on Hb Concentration

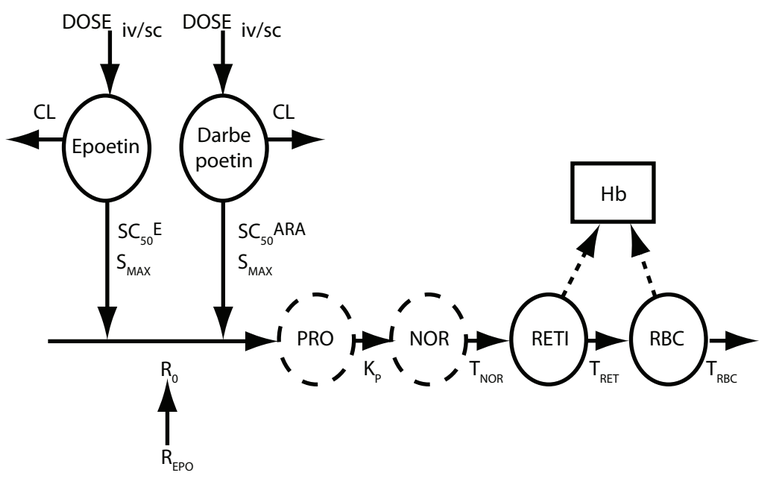


Table 1: Final population PK/PD parameters

Parameters	Estimates	SE	IIV (%)
R'0	0.567	0.0087	23.2
SLP-Epogen	0.282	0.0148	62.5
EPO Dose on SLP	-0.979	0.0396	
SLP- Aranesp	0.472	0.0462	40.7
ARA Dose on SLP	-0.874	0.0555	
Kp	0.114	0.0152	
TNOR	1.14	FIXED	
TRET	3.13	FIXED	
TRBC	120	FIXED	
Kc	1.52	0.0339	29.1
Residual	0.837	0.0229	
OFV	8204.416	CN	**1265**

SLP-Epogen=THETA*(EPODOSE PER WK/25000)$^{-0.979}$
SLP-Aranesp=THETA*(ARADOSE PER WK/10)$^{-0.874}$
Kc = Parameter used to account for RBC lifespan differences among individuals (TRBCIndividual = TRBCPopulation Mean / Kcindividual)
IIV was described using exponential error model

Figure 4: Model Predicted vs. Observed Hemoglobin

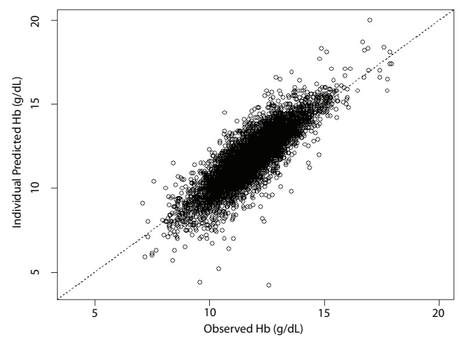
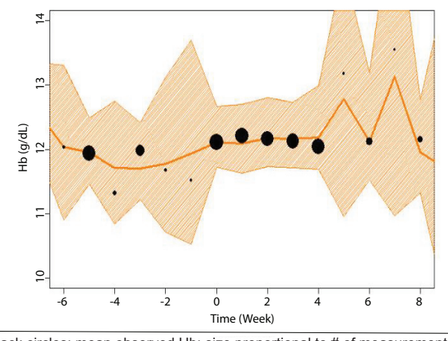


Figure 5: Posterior Predictive Check (PPC): Overall mean response in dialysis center patients. Observed versus simulated mean weekly hemoglobin



- Black circles: mean observed Hb; size proportional to # of measurements.
- Mean Hb values for each timepoint from 250 simulated trials.
- Data summarized as median of 250 mean Hb values (orange line) and associated 90% CI (hatched area).

External Predictive Check

The model was used to simulate protocols 960245 and 980211 from the development program for darbepoetin alfa using the clinical study design in Table 2. Table 3 shows the results of 1000 clinical trial simulations. In general, there was good agreement between the 95% confidence interval of the observed results and the 95% CI for the simulations, although the prediction of the simulation at the 0.225 dose level was slightly lower than the observed result.

Table 2: Clinical Study Parameters for Simulations of Darbepoetin Protocols 960245 and 980211

	Protocol 960245	Protocol 980211
N (by dose level)	4, 8, 10, 56	90
Dose (µg/kg/week)	0.225, 0.45, 0.75	0.45
Route	IV	IV (71%)/SC (29%)
Population	Hemodialysis, no EPO therapy	Peritoneal or hemodialysis, no EPO therapy for 3 months
Baseline Hb (g/dL) Median (range)	8.4 (5.2 – 10.6)	8.60 (5.6 – 9.9)
Hb measurements	Weekly	Weekly

Table 3: Observed and Simulated Mean Change from Baseline Hb at 4 Weeks

Dose (ug/kg/wk)	N	Chg Hb (95% CI) (g/dL) at 4 weeks	
Amgen Study 960245		**Observed**	**Predicted***
0.075	4	0.01 (-1.13,1.16)	-
0.225	8	1.19 (0.38,2.00)	0.57 (0, 1.4)
0.45	10	1.27 (0.55,2.00)	1.08 (0.3, 1.9)
0.75	56	1.71 (1.41, 2.02)	1.64 (1.3, 2.1)
Amgen Study 980211			
0.45	90	1.1 (0.82,1.37)	1.07 (0.8, 1.4)

*Lowest 10% of the responders were excluded from analysis to represent clinical study population and inclusion/exclusion criteria

Conclusions

- **The PK/PD model adequately described the longitudinal hemoglobin-time data in chronic kidney disease patients.**
- **The PK/PD model has the potential to inform future clinical trial design(s) including switching from one agent to the other and to evaluate dose titration strategies.**

1. Agoram B, Sutjandra L, and Sullivan JT. Population pharmacokinetics of darbepoetin alfa in healthy subjects. Br J Clin Pharmacol. (2007) 63(1): 41-52.
2. Ramakrishnan R, Cheung WK, Wacholtz MC, Minton N, Jusko WJ. Pharmacokinetic and pharmacodynamic modeling of recombinant human erythropoietin after single and multiple doses in healthy volunteers. J Clin Pharmacol. (2004) 44(9): 991-1002.
3. Krzyzanski W, Jusko WJ, Wacholtz MC, Minton N, Cheung WK. Pharmacokinetic and pharmacodynamic modeling of recombinant human erythropoietin after multiple subcutaneous doses in healthy subjects. Eur J Pharm Sci. (2005) 26(3-4): 295-306.