Performance Evaluation of Three Pharmacodynamic Models of ESA-induced Erythropoiesis - Focus on Erythrocyte Lifespan

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OBJECTIVES

Erythrocyte lifespan is markedly shortened in end-stage renal disease patients, contributing to the development of renal anemia[1,2,3]. It is also the key pharmacodynamic parameter of erythropoiesis determining the extent of hematocrit changes under treatment as well as the time needed to achieve a new staedy state[4]. Efficient and useful dosing algorithms imperatively have to include this parameter.

In the present work, we analyzed the predictive and estimative performance of three different pharmacodynamic models applied to real data focusing on erythrocyte lifespan distributions.

METHODS

The transit-compartment model (***Model A***)[5], the piece-wise linear regression (***Model B***)[2] and the lifespan indirect response model using delayed differential equations (***Model C***)[6] were used to analyze a set of original data consisting of 57 rHuEPO-naïve hemodialyses patients with spontaneously low hematocrit levels receiving epoietin alfa s.c. twice or thrice weekly. The stimulatory effect of ESA was modelled with an Emax-function (**EMAX** and $\mathbf{ED_{50}}$). Additional pharmacodynamic parameters included the basal erythropoietic rate (**BASE**) or the basal hematocrit ($\mathbf{HCT_B}$) and the lifespan (**LS**). Random effects included the between-subject variability on $\mathbf{ED_{50}}$, **BASE** or $\mathbf{HCT_B}$, respectively, and **LS** and a proportional or additive residual error. The analysis was performed with NONMEM VI.2, ICON plc, using self-provided differential equations (ADVAN 6) and first-order conditional estimation method (FOCE) with interaction. Empirical Bayes Estimates of the studied parameter were further used for subsequent analysis.

Tab. 1. Summery of estimated model parameters.

		Model A	*Model B*	*Model C*
OFV [Δdf]		2215 [ref.]	2305 [+1]	2341 [-1]
θ_{EMAX}		2.25	0.26	1.05
$\theta_{ED_{50}}$ ($\Omega_{ED_{50}}$)	[IE*10^{-3}]	49.5 (61.5%)	13.5 (81.8%)	21.3 (91.2%)
θ_{BASE} (Ω_{BASE})	[%Hct/d]	-	-	0.331 (17.7%)
θ_{HCT_B} (Ω_{HCT_B})	[%Hct]	24.0 (12%)	24.3 (12.2%)	-
θ_{LS} (Ω_{LS})	[d]	81.7 (48.3%)	65.0 (30.7%)	73.6 (19.3%)
Σ_{prop}	[%]	5.3	-	5.6
Σ_{add}	[%Hct]	-	1.66	-

Fig. 1

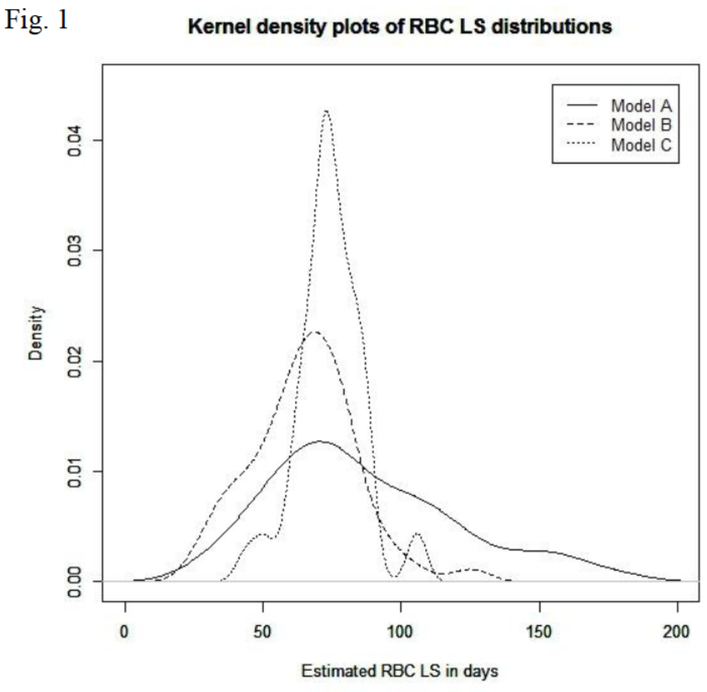


Fig. 2. Predicted versus observed plots

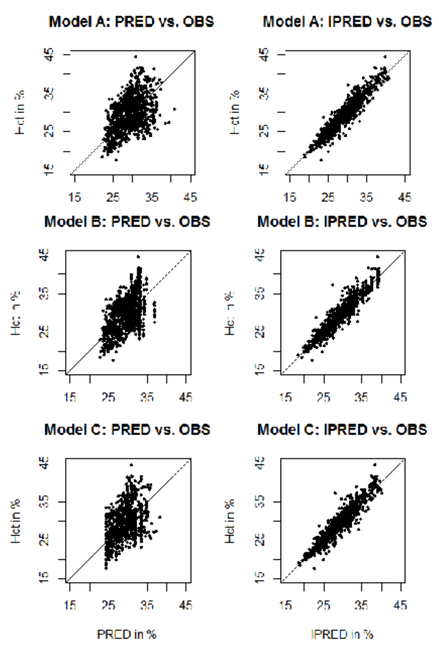
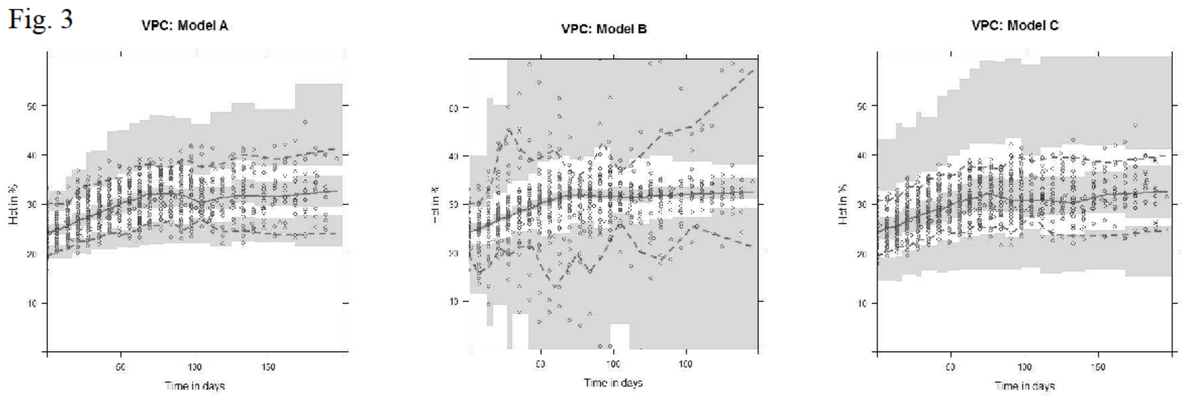


Fig. 3



RESULTS

All three models adequately described the data as shown in *(Fig. 2)*. The estimated PD parameters and their variability are exposed in *(Tab. 1)*. All models adequately exhibited an inverse correlation between $\mathbf{ED_{50}}$ (indirect measure of resistance to ESA) and the initial hematocrit raise. ***(Model A)*** implementing 12 transit compartments performed best in terms of quality of fit (objective function value, OFV) and visual predictive checks *(Fig. 3)*. However, the estimated erythrocyte lifespan showed an unrealistic distribution, centered at 81.7 days, characterized by a high inter-individual variability of 48%. ***(Model B)*** yielded a better estimate of the erythrocyte lifespan with a population mean of 65.0 days and an inter-individual variability of 31%. The minimum and the maximum were 28 and 125.2 days respectively with 5-95% CI of 59.8 to 70.5 days. ***(Model C)*** performed best in term of estimated lifespans with a mean of 73.6 days and a rather small inter-individual variability of 19% *(Fig. 1)*. Only***(Model C)*** showed a correlation between the estimated lifespan and the initial hematocrit ($HCT_0 = -13.32 + 0.151 \cdot LS$, r^2=0.23, p=0.0003) as well as with the basal erythrocyte production rate since the relationship *BASE~HCT0/LS* is given by the model.

CONCLUSIONS

The three models showed heterogeneous results. Despite better fit and predictive performance, the transit compartment model ***(Model A)*** yielded an unrealistically large range of lifespans with mostly unphysiological individual values. The lifespan indirect response model ***(Model C)*** was the only one to provide realistic estimates of the lifespans and to link basal hematocrit with basal erythropoiesis and lifespan. These differences in estimative and discriminative properties should be considered for further development of dosing algorithms.

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487--MP
M) Dialysis. M5) Anaemia in CKD 5D.
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