An integrated semi-mechanistic model to predict the outcome of drug-target effects on the erythropoietic system

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Introduction

- Target-related effects of investigational drugs may lead to clinical efficacy but also safety concerns if the target is also expressed elsewhere
- **Bitopertin (BTP)** is a specific inhibitor of the glycine type 1 transporter (GlyT1), a transporter known to control extracellular levels of the neurotransmitter glycine in the brain, and was initially intended to be developed for psychiatric indications
- The GlyT1 transporter is also expressed on erythroid cells and its inhibition leads to a decreased **haemoglobin (Hb)** synthesis within erythrocyte precursors due to reduced availability of glycine for the heme synthesis
- As a consequence, **reticulocytes (RET)** with reduced Hb content are released into the blood, and Hb blood concentrations gradually decrease with a delay corresponding to the **red blood cell (RBC)** lifespan
- Homeostatic feedback stimulates the production of new RBCs to compensate for the decreased Hb concentrations

Methods

- Haematological biomarker data were available from 62 healthy male and female subjects
  - 10, 30, or 60 mg of BTP or placebo QD for 120 days + 120 days follow-up
- A previously developed model [1] was used as a starting point to build a more generalised erythropoiesis model
  - The inhibitory effect of BTP on Hb synthesis was assumed to be driven by individual AUC_{ss}
- The model was fitted simultaneously to cell count data (RBC, RET, and **immature reticulocyte fraction** [**IRF**]), as well as **mean corpuscular Hb (MCH)**, ensuring steady-state baseline conditions
- The framework was used to simulate the inhibitory effect that hypothetical compounds would have when interacting with specific pathways of the erythropoiesis system
  - Assumed 120 days treatment with a dose corresponding to ½ and 2x AUC_{50} of BTP, i.e. ~20% and ~40% inhibition of pathway, respectively
- NONMEM 7.4.3, PsN 4.9.3, Improve 2.5.1-5. Simulations were performed in mrgsolve 1.0.3.

Objectives

1) To expand a previously developed semi-mechanistic model of erythropoiesis
2) To predict the downstream outcome of hypothetical drug-target interactions on different stages of erythropoiesis and Hb production

Results

- The final model structure (Figure 1) consisted of a transit-compartment structure describing: (i) the formation of erythroid precursors in the bone marrow, (ii) the progression of precursors into immature and mature RET and release into the blood depending on the IRF (as inspired by Thorsted *et al.* [2]), (iii) the maturation of RET to RBC in blood, and (iv) the dynamics of RBC in blood. In addition, the Hb content inside the RBC was described by means of a parallel chain. The predictive performance of the integrated model was found to be adequate (Figure 2).

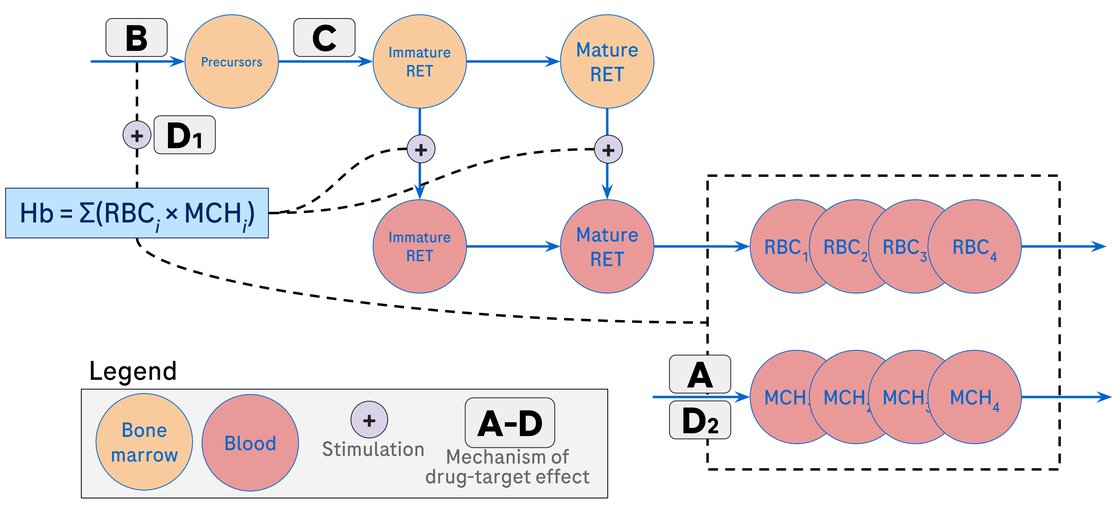

Figure 1 Graphical representation of the integrated semi-mechanistic model.

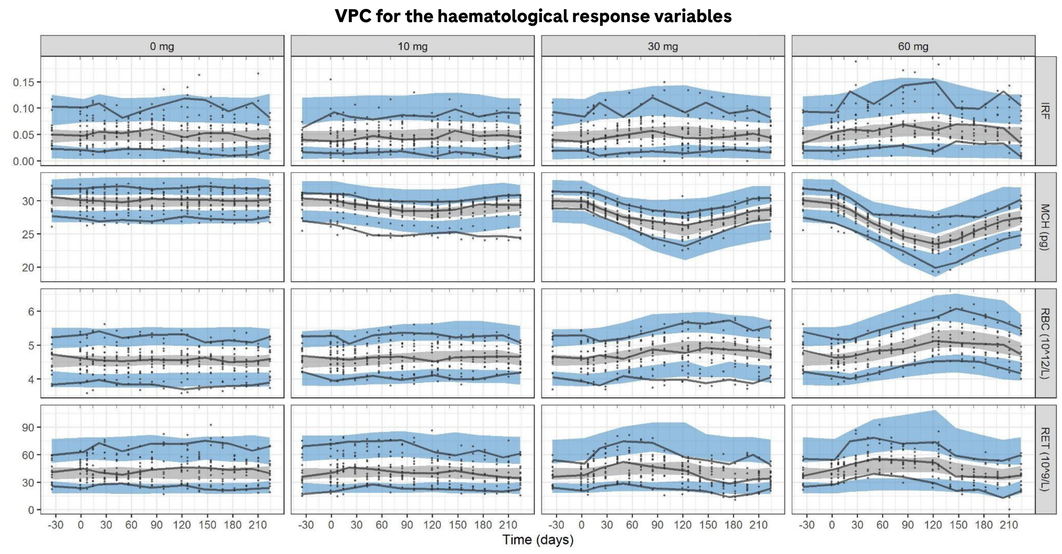

Figure 2 Visual predictive check of the four response variables IRF, MCH, RBC, and RET, that were used in a simultaneous fit of the model. Shaded areas: 90% CI for simulated median, 5th and 95th percentiles. Symbols and lines: observed data with respective quantiles. The patterns of response are well captured, despite the large variability on the reticulocyte related data (RET, IRF).

Simulated drug-target effect mechanisms:
Mechanism A: inhibition of haemoglobin production (BTP-like type of effect)
Mechanism B: inhibition of production of RET precursors
Mechanism C: inhibition of differentiation of precursors to RET
Mechanism D: inhibition of Hb-driven feedback (D1) and inhibition of production of haemoglobin (D2)

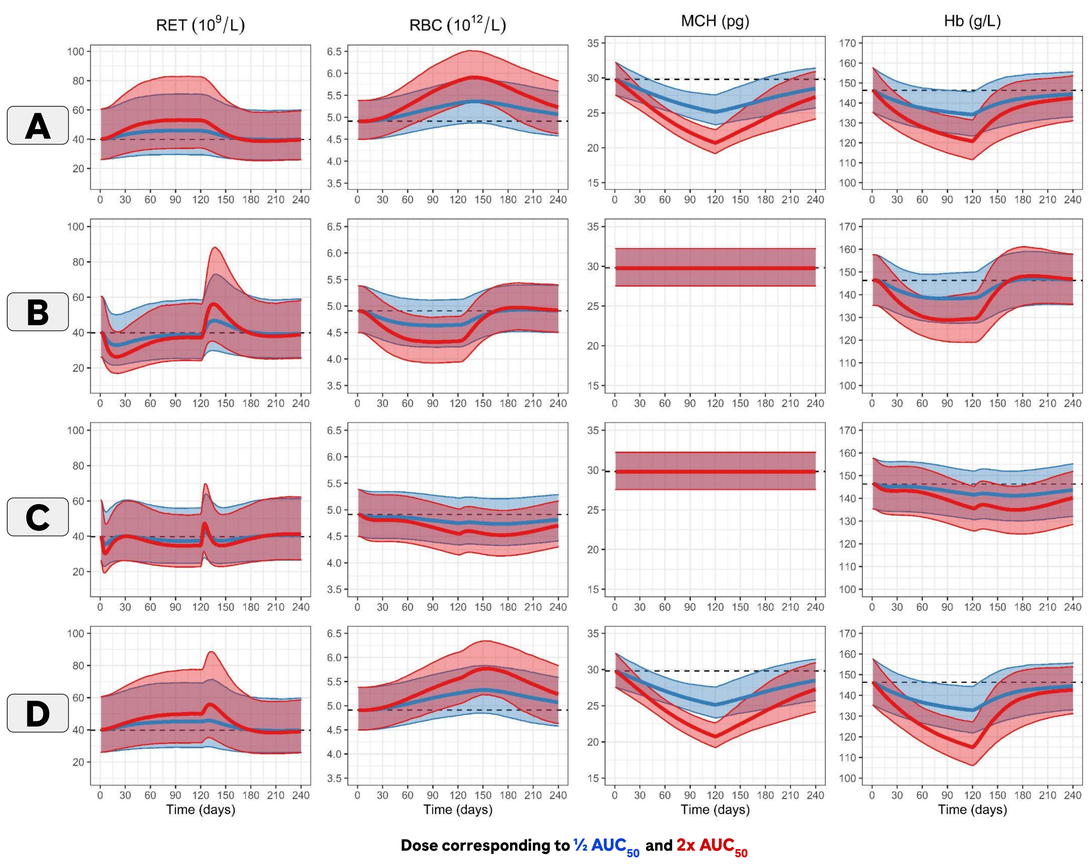

Figure 3 Simulated outcome of hypothetical drug-target interactions for mechanisms A-D following 120 days of treatment in 2000 males. The thick lines represent the median, and the shaded area the 90% prediction interval which reflects inter-individual variability. The horizontal dashed lines represent baselines in the absence of drug effect.

Table 1 Model parameters estimates

Parameter	Description	Estimate	Units	IIV (%CV)
LS RBC	Lifespan of RBC	125	days	28.0
MCH_0	Baseline MCH	29.8	pg	4.82
RBC_0	Baseline RBC for males	4.91	10^{12}/L	5.34
	Baseline RBC for females	4.32		
RET_0	Baseline RET	39.8	10^9/L	26.0
IRF	Immature reticulocyte fraction	4.71	%	32.0
FDB	Feedback term (driven by haemoglobin relative change from baseline using a exponential function)	2.42	-	-

All model parameters were estimated with good precision (relative standard error <9 % for fixed effects, and <18% for random effects). Correlation between all inter-individual variability parameters estimated (not shown). CV: coefficient of variation, IIV: inter-individual variability.

Conclusion

- An integrated semi-mechanistic population pharmacokinetic-pharmacodynamic model was developed to describe the process of erythropoiesis
- Simulations of hypothetical drug-target effects on different stages of erythropoiesis and Hb production (Figure 3) illustrated the influence of the assumed mechanism of action of compounds on the haematological response
- Combining this integrated model framework with mechanistic understanding from other experiments can be used to inform decision making in drug development

References

[1] Schaedeli Stark *et al.* PAGE 21 Abstr 2553, 2012. [www.page-meeting.org/?abstract=10044]
[2] Thorsted *et al.* ACoP12, PMX-125, 2021. [www.go-acop.org/?abstract=125]