Semi-mechanistic thrombocytopenia model of a new histone deacetylase inhibitor (HDACi) in development, with a drug-induced apoptosis of megakaryocytes.

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Introduction

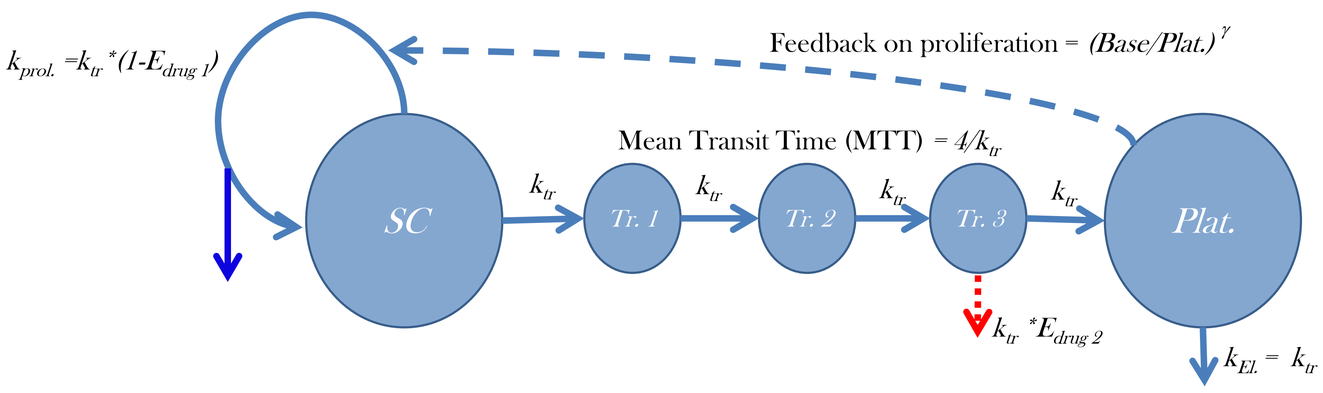
The ability to anticipate haematological toxicity is of great value for optimizing treatment and predicting complications for patients who undergo prolonged periods of myelosuppression. Our work aims at developing a semi-mechanistic thrombocytopenia model of a new HDACi in development, taking into account the pharmacological knowledge on the molecule. Therefore, the aim is to assess the compound effect on both stem cells and megakaryocytes (MK) using modelling and simulation. A second objective is the evaluation of structural and experimental identifiability of these models, in particular the final extended one.

Materials & Methods

Data: **Phase I** clinical trial
35 patients treated over 4-week cycles, 3 dosing regimens tested
Oral multiple doses administration
- 5 days a week, 3 weeks/4 (n=21)
- 7 days a week, every other week (n=6)
- 5 days a week, every other week (n=8)

180 platelets samples (first cycle only, 0-1150.9 hours follow-up period) with a **median of 5 samples by patient** (range 3-12)

Model building: A ***BASIC*** model was first developed to describe the time course of platelets using the original model structure from Friberg *et al.* [1,2], with a drug effect on progenitor compartment (E_{drug1}). Several *in vitro* studies show that the mechanism of action of this drug is not only an inhibition of stem cell proliferation, but also an apoptosis of MK, leading to our suggestion of an ***EXTENDED*** model. A linear drug effect (E_{drug2}) was added on a final transit compartment, as MK are final precursors in the ***thrombopoiesis***. Internal evaluations were performed using Normalized Prediction Distribution Errors (NPDE) graphs.



$$\frac{dSC}{dt} = k_{prol} \cdot (1 - E_{drug1}) \cdot \left(\frac{Base}{Plat}\right)^{\gamma} - k_{tr} \cdot SC$$
$$\frac{dTr1}{dt} = k_{tr} \cdot SC - k_{tr} \cdot Tr1$$
$$\frac{dTr2}{dt} = k_{tr} \cdot Tr1 - k_{tr} \cdot Tr2$$
$$\frac{dTr3}{dt} = k_{tr} \cdot Tr2 - k_{tr} \cdot Tr3 - k_{tr} \cdot E_{drug2} \cdot Tr3$$
$$\frac{dPlat}{dt} = k_{tr} \cdot Tr3 - k_{El.} \cdot Plat$$

$$E_{drug1} = \frac{I_{max} \cdot Conc^{Hill}}{IC_{50}^{Hill} + Conc^{Hill}}$$

$$E_{drug2} = Slo\,2 \cdot Conc$$

Stem cells → CFU-GEEM → CFU-MK → MK → Platelets (Thrombopoiesis)

Identifiability analyses: Analyses were based on a period corresponding to the cycle 1 only. Expected parameter precision of estimation (*i.e.* relative standard error (RSE)) using mathematical derivation of the Fisher Information Matrix (FIM) was computed, for different sampling designs [3].

Structural identifiability: rich design (14 platelets samples every 50 hours during the period 0-700 hours)
Experimental identifiability: sparse design (4 platelets samples as foreseen in the clinical protocol at 0, 170, 300 & 500 hours)

The administration schedule was set to be close to the clinical trial. FIMs were calculated with respectively 21, 6 & 8 patients, half of whom were treated at 60 mg/m² and half at 140 mg/m² according to the respective dosing regimens cited above.

Software: Data were analyzed with **NONMEM 7.2**, FOCE-I. Sequential Pharmacokinetic/Pharmacodynamic (PK/PD) modelling was performed, where individual Bayesian estimates of PK parameters were fixed from a prior PK analysis for subsequent PD modelling. Identifiability analyses were performed using **PFIM 3.2.2** software [3].

Results

Model building

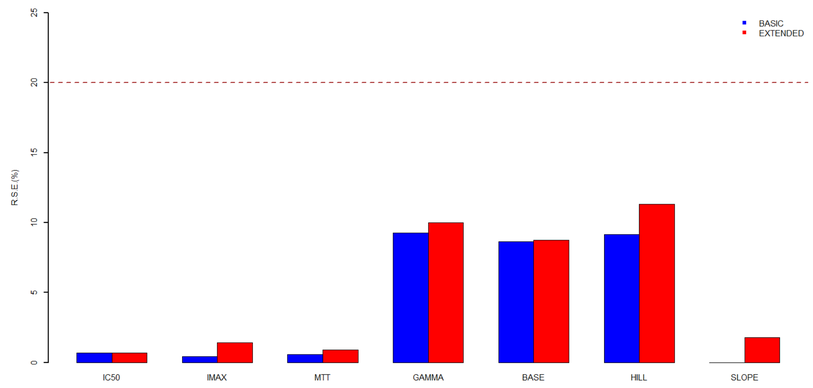
Final parameter estimates of the BASIC and EXTENDED models

Models	Parameters	Estimates	RSE (%)	BSV (%)	RSE (%)	Sh. Std. (%)
BASIC OFV : 1715.205 BIC : 1767.135	IC_{50} (ng/mL)	0.278	34	/	/	/
	I_{max}	1 FIX	/	/	/	/
	MTT (h)	97.1	3.5	/	/	/
	Gamma	0.344	13.7	40.7	28	15.7
	Base (x10^9/L)	268	8.1	39.1	21.1	3.5
	Hill	0.667	29.1	41.8	33.1	36.5
	Add (x10^9/L)	26.6	15.8	/	/	/
	Prop (%)	14.8	24.1	/	/	/
	Eps. shrinkage (%)	21.6				
EXTENDED OFV : 1701.141 BIC : 1758.264	IC_{50} (ng/mL)	0.119	25.7	/	/	/
	I_{max}	1 FIX	/	/	/	/
	MTT (h)	134	5.2	/	/	/
	Gamma	0.494	11.4	45.3	35.4	10.5
	Base (x10^9/L)	268	9.6	40.1	27.2	2
	Hill	0.678	16.4	51.8	41.4	35.2
	Slope (mL/ng)	7.33	27.6	/	/	/
	Add (x10^9/L)	27.9	7.4	/	/	/
	Prop (%)	8.48	33.7	/	/	/
	Eps. shrinkage (%)	22.7				

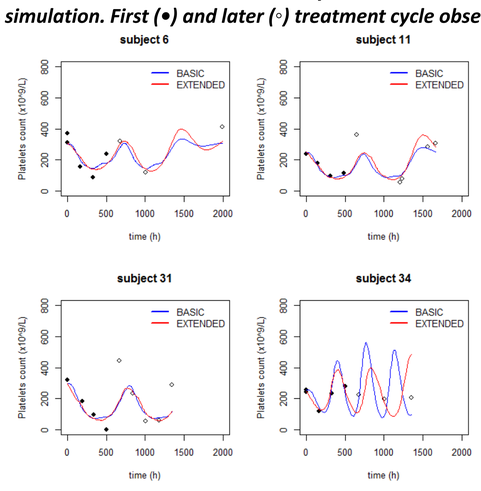
RSE (%) Relative Standard Error
BSV (%) Between Subject Variability
Sh. Std. (%) Shrinkage calculated on standard deviation

Identifiability analyses

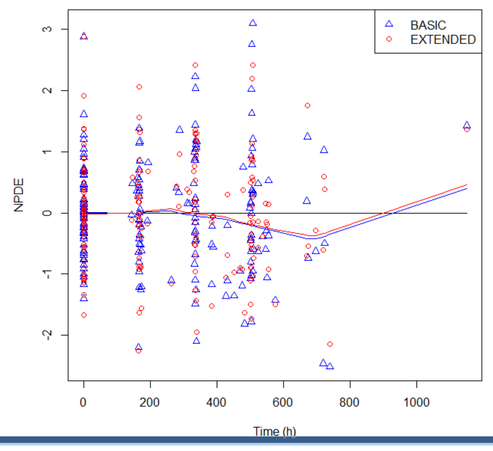
Structural identifiability



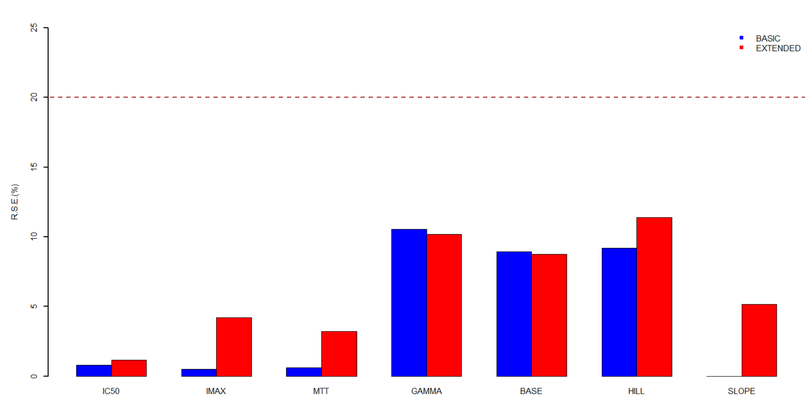
Individual predictions versus time. For treatment cycle later than 1 individuals predictions were based on simulation. First (•) and later (◦) treatment cycle observations.



Internal evaluation by NPDE versus time



Experimental identifiability



Conclusion

Models were evaluated using individual fits analyses, goodness-of-fit plots and NPDE graphs [4], as these methods are particularly adapted in situations such as these with huge data heterogeneity (schedule administration, dosing regimens,…). We showed that both models adequately describe the time-course of platelets following administration of drug S. All these models were shown to be structurally and experimentally identifiable (RSE < 20%), therefore one can expect a good precision of estimation of model parameters for both an experimental and a richer sampling design. ***EXTENDED*** model described available data as well as the ***BASIC*** one and consequently a semi-mechanistic thrombocytopenia model which increased pharmacological description of drug effect by mimicking the thrombocytopenic mechanism of drug S was proposed. Although an internal evaluation was done, before endorsing the ***EXTENDED*** model for this drug, this model must be evaluated on other data (cycle>1, external evaluation with data from others studies).

References

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