Rituximab target-mediated elimination is influenced by both baseline antigenic burden and *FCGR3A*-158V/F polymorphism in chronic lymphocytic leukemia

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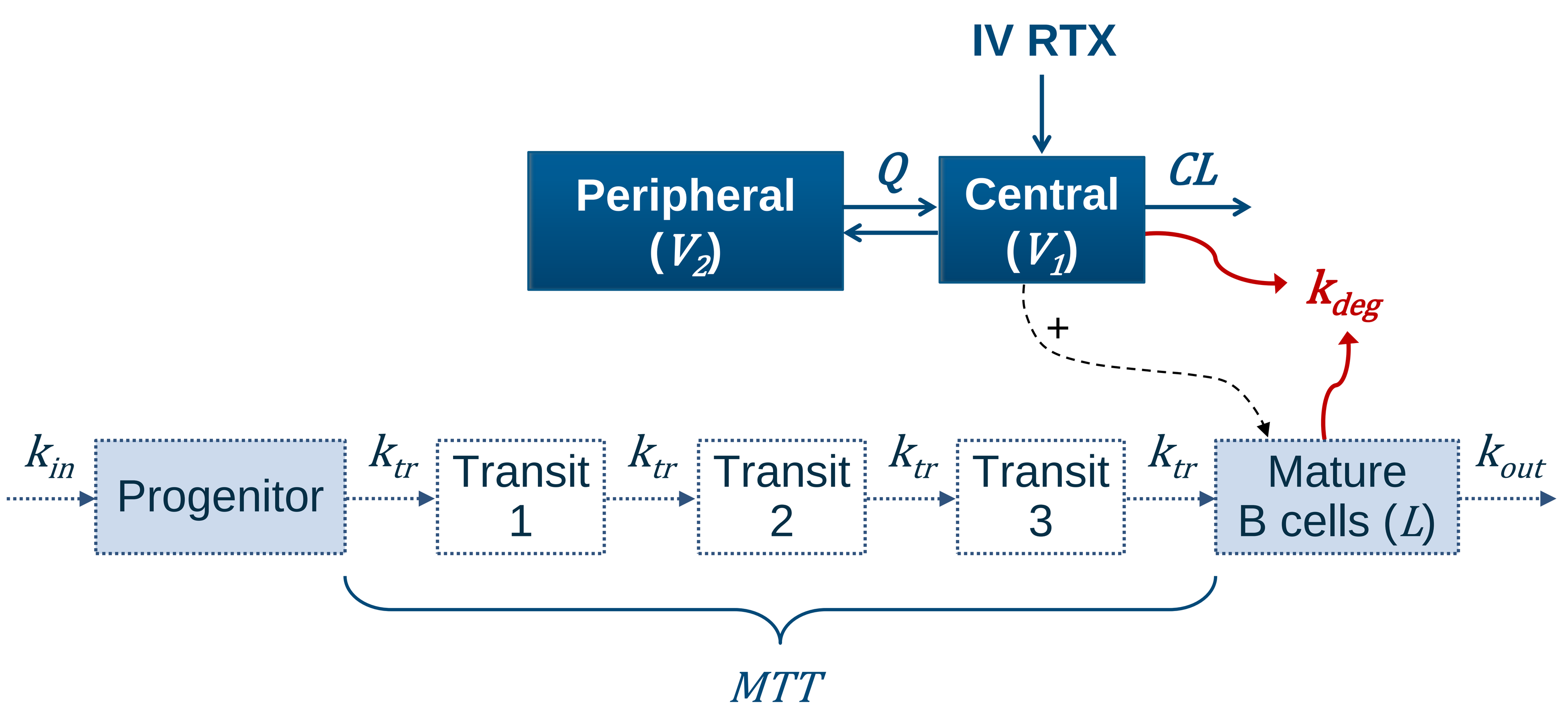
Background

The anti-CD20 monoclonal antibody rituximab (RTX) is indicated as first-line treatment in chronic lymphocytic leukemia (CLL). Rituximab exhibits time-dependent clearance in CLL [1], possibly because of treatment-related decrease in B-cell antigenic burden over time. The aim of this study was to quantify the effects of CD20 antigenic mass and FcγRIIIA gene polymorphism on rituximab PK in CLL patients.

Patients and methods

- 118 CLL patients from the CLL 2010 FMP phase II study (1943 RTX serum concentrations)
- Dosing regimens:
  - Standard R-FC arm: **Cycle 1*: IV RTX 375 mg/m^2 + FC (fludarabine, cyclophosphamide); **Cycles 2-6*: IV RTX 500 mg/m^2 + FC; Q 28 days
  - Dense R-FC arm: **Prephase*: IV RTX (500 mg on day 0; 2000 mg on days 1, 8, 15); **Cycles 1-6*: IV RTX 500 mg/m^2 + FC Q 28 days
- Population modelling using Monolix® 4.3.3
- Semi-mechanistic model including two compartments linked to latent target-antigen turnover
- Evaluated covariates: gender, age, body size, treatment arm, baseline CD20 antigen count in circulation (CD20$_{cir}$) and lymph nodes (CD20$_{LN}$), Binet stage, gene polymorphisms (*FCGR3A*-158V/F, *FCGR2A*-131H/R)



$$\frac{dA_1}{dt} = -(CL+Q)\times\frac{A_1}{V_1} + Q\times\frac{A_2}{V_2} - k_{deg}\times A_1\times L$$

$$\frac{dA_2}{dt} = Q\times\left(\frac{A_1}{V_1}-\frac{A_2}{V_2}\right)$$

$$\frac{dProgenitor}{dt} = k_{in} - k_{tr}\times Progenitor, \qquad Progenitor(0) = L_{ini}$$

$$\frac{dTransit1}{dt} = k_{tr}\times Progenitor - k_{tr}\times Transit1$$

$$\frac{dTransit2}{dt} = k_{tr}\times Transit1 - k_{tr}\times Transit2$$

$$\frac{dTransit3}{dt} = k_{tr}\times Transit2 - k_{tr}\times Transit3, \qquad Transit1,2,3(0) = L_{ini}$$

$$\frac{dL}{dt} = k_{tr}\times Transit3 - k_{out}\times L - k_{deg}\times A_1\times L, \qquad L(0) = L_{ini}$$

$$k_{tr} = \frac{n+1}{MTT}, \qquad L_{ini} = \frac{k_{in}}{k_{out}}$$

Results

Table 1: Parameter estimates

Parameter (unit)	Estimate	RSE (%)	*p*
Fixed effects			
CL (L/d)	0.137	4	
Dense R-FC arm on CL	0.197	29	6.7x10^{-4}
V_1 (L)	3.08	2	
BSA on V_1	0.904	21	2.5x10^{-6}
Q (L/d)	0.31	3	
V_2 (L)	2.54	6	
Dense R-FC arm on V_2	0.52	16	2.9x10^{-10}
BSA on V_2	1.31	30	10^{-3}
MTT (d)	57.6	5	
k_{in} (nmol/d)	0.22	6	
k_{out} (d^{-1})	17.6x10^{-5}	8	
Binet stage C on k_{out}	-0.392	27	2.1x10^{-4}
k_{deg} (nmol^{-1}d^{-1})	0.0017	12	
FCGR3A-158VV on k_{deg}	1.47	25	8.6x10^{-5}
CD20$_{cir}$ on k_{deg}	0.32	25	8.1x10^{-5}
Interindividual and residual variability			
ω_{CL} (%)	29.9	7	
ω_{V1} (%)	18	9	
ω_{V2} (%)	34.7	9	
ω_{kout} (%)	46.3	8	
ω_{kdeg} (%)	90.5	10	
σ_{add} (nmol/L)	8.33	12	
σ_{prop} (%)	20.7	2	

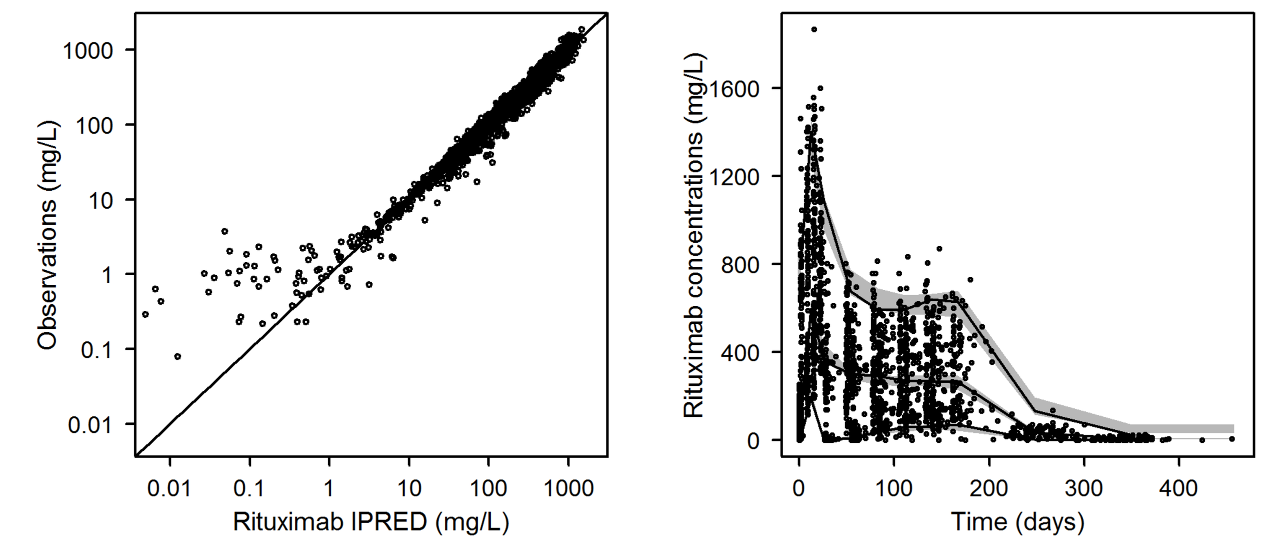
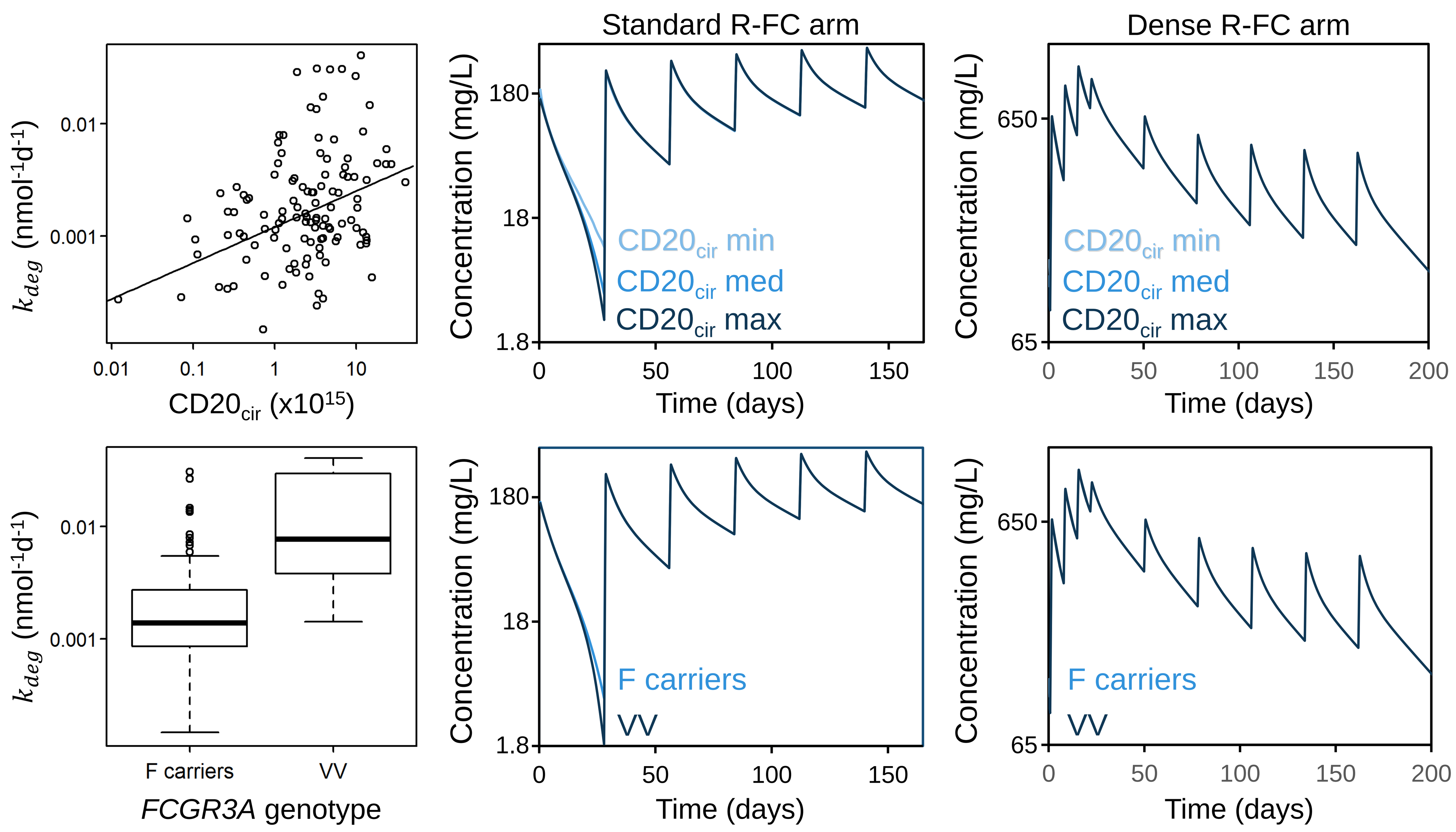


Figure 1: Model diagnostics: Observed vs model-predicted RTX concentrations (*left*); Visual predictive checks (*right*)

Model-based simulations



Conclusions

- The developed semi-mechanistic model accurately predicted RTX concentrations
- RTX target-mediated elimination, hence its "consumption", increased with CD20 target antigen count on circulating B-cells (CD20$_{cir}$) and in FcγRIIIA-158VV patients
- This influenced RTX concentrations in the first treatment cycle of the standard R-FC arm

References

[1] Li J. et al. Population pharmacokinetics of rituximab in patients with chronic lymphocytic leukemia. J Clin Pharmacol (2012) 52,1918–26