Influence of immunization on the pharmacokinetics of monoclonal antibodies : anti-drug antibody-mediated drug disposition (ADAMDD) of rituximab (RTX) in mice

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INTRODUCTION

- Immunisation against monoclonal antibodies (mAbs) lead to the development of **anti-drug antibodies (ADA)** responsible of **increase in mAb clearance** by approximately 1.5 fold [1].
- Big challenge in human mAb therapy
- Joint kinetics of both mAbs and anti-mAb ADA in previous works suggested:
  - nonlinear elimination of mAbs [2]
  - mechanism of mAb elimination similar to target-mediated drug disposition (TMDD) [3]
- **Objectives.** To describe the kinetics of immunisation and interactions of rituximab (RTX), an anti-CD20 mAb, and anti-drug antibodies (ADA) in mice using TMDD-derived models [4,5] defined as ADA-mediated drug disposition (ADAMDD)

METHODS

- **129 male mice** of 9 different lines administered a single 50 µg dose of rituximab in tail vein
- 829 blood samples were collected at hours 1, 6 and 24, and days 3, 7, 15 and 25 after administration
- Concentration measurements using in-house ELISA techniques
  - RTX concentrations at each sampling time
  - ADA concentrations at day 25
- Pharmacokinetic modeling: two-compartment model, RTX–ADA interactions with irreversible binding (IB) model
- ADA concentrations, body weight (WT) and line tested as covariates

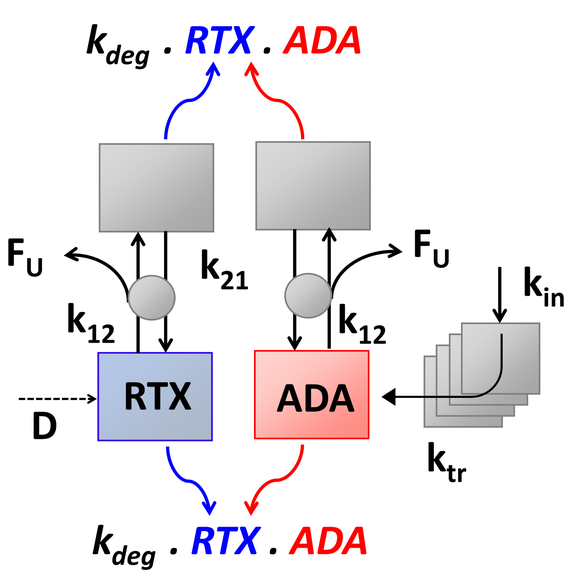


Figure 1: PK–ADA model

Legends. The kinetics of ADA input was described using 4 transit compartments, and zero and first-order rate constants for ADA production and transit, respectively. The kinetics of ADA was then tested as a two-compartment irreversible binding model, assuming that both rituximab and ADA share the same values for central volume of distribution, and transfer and elimination rate constants. Rituximab ADA-mediated elimination was assumed as ocuring in both central and peripheral compartments.
Parameters. V_1 central volume of distribution, k_{12} first-order central-to-peripheral (=2.3) and k_{21} peripheral-to-central transfer rate constants, k_{in} zero-order ADA input rate constant k_{tr} first-order transit and elimination rate constant and F_U antibody fraction unbound to neonatal Fc Receptor (FcRn) and eliminated.

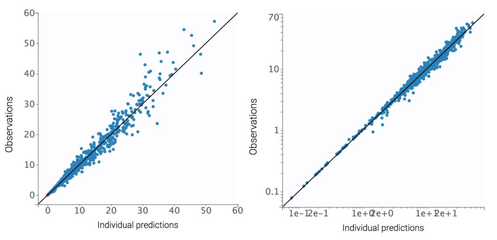
- Modeling was carried out using nonlinear mixed-effect modeling software **Monolix Suite 2019** and **Simulx** (Lixoft®, Antony, France)

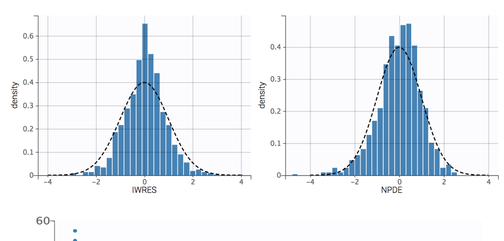
RESULTS

- Satisfactory description of concentration-time data with 2-compartment IB model
- Nonlinear elimination shape of concentrations observed in 2/3 mice
- Strong association between increasing ADA concentrations and increased k_{in} (ΔAIC = -114.79)
- Mice lines presented different PK (V_1, F_U) and ADA production (k_{in}) parameter values
- Onset of ADA-mediated elimination starting 7-10 days after rituximab injection

Table 1 : pharmacokinetic parameter estimates

Parameter	Unit	Base model		Final model	
		Estimate	RSE%	Estimate	RSE%
V_1	mL	1.8	2.8	1.7	2.9
Line(1)_V_1	–	–	–	0.18	26
Line(2)_V_1	–	–	–	-0.17	39
BW_V_1	–	–	–	0.34	30
F_U	–	0.09	5.5	0.097	4.1
Line(1)_F_U	–	–	–	-0.33	11
Line(2)_F_U	–	–	–	0.46	13
k_{12}	day^{-1}	2.2	4.7	2.3	3.7
k_{21}	day^{-1}	1.1	4.8	1.2	1.3
k_{in}	day^{-1}	13.1	33	46.2	23
Ln(ADA)_k_{in}	–	–	–	1.1	7.6
Line_k_{in}	–	–	–	2.2	13
k_{tr}	day^{-1}	0.24	6.6	0.21	2.4
k_{deg}	day^{-1}	0.11	2.8	0.83	1.6
ω_{V1}	–	0.28	6.7	0.18	7.3
ω_{Fu}	–	0.19	11	0.092	16
ω_{Kin}	–	3.3	9.8	1.24	9.3
σ_{prop}	–	0.14	3.5	0.14	3.4





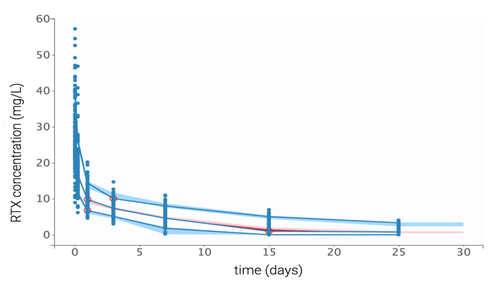


Figure 2: Diagnostic plots of final model

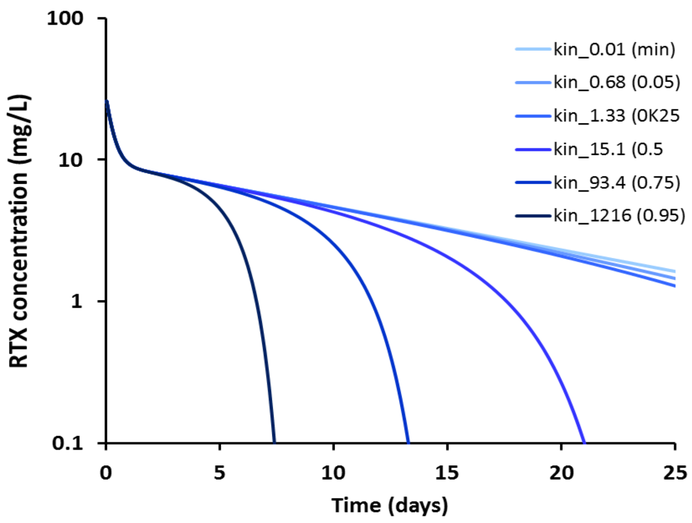


Figure 3: Influence of ADA input on RTX pharmacokinetics

Legends.
Table1. V_1 central volume of distribution, k_{12} first-order central-to-peripheral (=2.3) and k_{21} peripheral-to-central transfer rate constants, k_{in} zero-order ADA input rate constant k_{tr} first-order transit and elimination rate constant and F_U antibody fraction unbound to neonatal Fc Receptor (FcRn) and eliminated, RSE relative standard ratio, ADA, anti-drug antibodies, BW body weight, ω interindividual standard deviation, σ_{prop} proportional residual standard deviation.
Figure 2. Top: observed vs. model-fitted RTX concentrations values in linear (left) and logarithmic (right) scales. Middle: individual reweighted (IWRES, left) and normalized prediction distribution error (NPDE, right) vs. Gaussian law. Bottom: Visual predictive checks (VPC) for 25, 50 and 75th concentration percentiles.

CONCLUSION

- Nonlinear elimination may be imputable to immunization against rituximab only
- Interactions of mAbs and ADA may be
  - similar to mAb-target interactions
  - described using TMDD modeling strategies

Main issues may be the description of the onset of ADA production, hardly predictible in human therapy

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