A Target-Mediated Drug Disposition model to quantify the relationship between Anti-CD3 monoclonal antibody and CD3/TCR receptors in Patients with autoimmune diseases

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Introduction

Otelixizumab is a monoclonal antibody (mAb) directed against human CD3ε, which forms part of the CD3/T-cell receptor (TCR) complex on T lymphocytes.

Attempts have been made to model the relationships between Otelixizumab, receptor binding and changes in lymphocytes count [1].

Based on the observed short half-life for Otelixizumab and other anti-CD3 mAbs relative to endogenous Immunoglobulin G it is hypothesised that the antibody is subject to target-mediated drug disposition (TMDD) at clinically relevant doses.

Objectives

The aim of the present work was to develop a mechanistic target-mediated drug disposition (TMDD) model for Otelixizumab using published clinical data.

Methods

Data were obtained from 3 clinical trials of Otelixizumab in psoriatic and diabetic patients. Free drug in serum (Cp) and free (FR), bound (DR) and total (TR) receptors on both CD4+ and CD8+ lymphocytes were measured using immunoassay and flow cytometry, respectively.

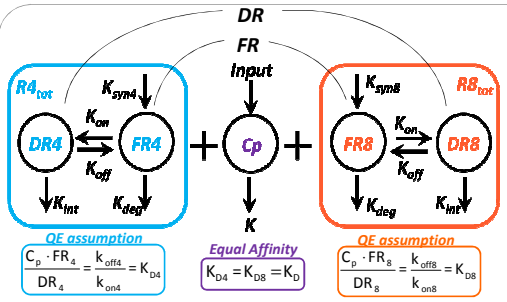
A general TMDD model [2] and its Quasi Equilibrium (QE) approximation [3] were implemented. The QE TMDD model was also extended as in [4] to account for the two different lymphocytes populations, under the assumption of equal affinity between drug and receptors on CD4+ and CD8+ (**FIG 1**).

The analysis of clinical data anticipates potential complexities in model development:

- Different targets (CD4+ and CD8+)
- Different Studies
- Conversion factors between FR, DR and TR and their actually measured quantities

Conclusion

- General and extended TMDD models and their QE approximations were proposed in the attempt to describe Otelixizumab binding to CD3/TCR on T lymphocytes.
- An extended QE approximation was successfully estimated including receptors on both CD4+ and CD8+.
- Simulations provided additional evidence about model robustness in the context of additional complexities as different conversion factors for different studies.



$$\frac{dC_{tot}}{dt} = \frac{dC_p}{dt} + \frac{dDR}{dt} = \frac{Input}{V} - k \cdot C_p - k_{int} \cdot DR$$

$$\frac{dR8_{tot}}{dt} = \frac{dFR_8}{dt} + \frac{dDR_8}{dt} = k_{syn8} - k_{deg} \cdot FR_8 - k_{int} \cdot DR_8$$

$$\frac{dR4_{tot}}{dt} = \frac{dFR_4}{dt} + \frac{dDR_4}{dt} = k_{syn4} - k_{deg} \cdot FR_4 - k_{int} \cdot DR_4$$

$$C_{tot} = C_p + DR_4 + DR_8 = C_p + \frac{R4_{tot} C_p}{K_D + C_p} + \frac{R8_{tot} C_p}{K_D + C_p} = C_p + \frac{R_{tot} C_p}{K_D + C_p}$$

$$C_p = \frac{1}{2}[(C_{tot} - R_{tot} - K_D) + \sqrt{(C_{tot} - R_{tot} - K_D)^2 + 4K_D \cdot C_{tot}}]$$

FIGURE 1. Extended TMDD Model diagram and its QE approximation equations

Results

- Both the general and extended TMDD models and their QE approximations were fit to the available data. The sum of measured quantities on CD4+ and CD8+ was used in general models (both QE and TMDD) estimation, while each target was considered singularly for the extended ones. The different studies were fit first individually and then simultaneously. Explored model are summarised in **TABLE 1.**

- The TMDD models (both general and extended) showed higher instability and, even when converged, Kon and Koff were estimated with very high RSE.

- Generally, receptor baseline (BAS) and conversion factors (γ) estimates were also uncertain (**TABLE 1**).

- The extended QE model simultaneously fit on all studies performed best. Its parameter estimates are shown in **TABLE 2** and the corresponding VPCs are illustrated in **FIGURE 2**.

TABLE 1 Explored models

STUDY	TARGET	MODEL	SUCC	COV	COMMENTS
STUD0	SUM	QE	Yes	Yes	High RSE (50% - 100%)
STUD0	SUM	TMDD	Yes	No	R , S sing
STUD0	EXTENDED	QE	Yes	Yes	High RSE on BAS and γ (40%)
STUD0	EXTENDED	TMDD	Yes	No	R , S sing
STUD2	SUM	QE	Yes	Yes	High RSE on BAS and γ (100%)
STUD2	SUM	TMDD	Yes	Yes	High RSE on Kon and Koff (>200%)
STUD2	EXTENDED	QE	Yes	Yes	High RSE on BAS and γ (60%)
STUD2	EXTENDED	TMDD	Yes	Yes	High RSE on Kon and Koff (>500%)
ALL	SUM	QE	Yes	Yes	High RSE on BAS and γ (60%)
ALL	SUM	TMDD	No	-	Rounding error
ALL	EXTENDED	QE	Yes	Yes	Good RSE
ALL	EXTENDED	TMDD	No	-	Rounding error

TABLE 2 Extended QE model – simultaneous fitting: Parameter estimates

Theta	Units	EST	SE	RSE
K	/day	**1.58**	0.0283	1.8%
V	L	**10.5**	0.107	1%
BAS4	nM	**0.0861**	0.0114	13.2%
BAS8	nM	**0.0648**	0.0091	14.1%
KDEG	/day	**0.294**	0.0234	8%
KINT	/day	**1.02**	0.0402	3.9%
KD (KSS)	nM	**0.0816**	0.0094	11.5%
γ_FR STUD0	MESF/nM	**10.8**	1.52	14.1%
γ_DR STUD0	MESF/nM	**45.9**	12.8	27.9%
γ_TR STUD0	MESF/nM	**12.9**	1.86	14.4%
γ_FR STUD2	MESF/nM	**41.7**	6.04	14.5%
γ_DR STUD2	MESF/nM	**96.6**	15.5	16%
γ_TR STUD2	MESF/nM	**6.09**	0.898	14.7%
Omega		**EST**	**SE**	**RSE**
K		**0.921**	0.101	11%
V		**0.475**	0.0615	12.9%
BAS4		**0.0358**	0.0058	16.3%
BAS8		**0.0334**	0.0053	16%

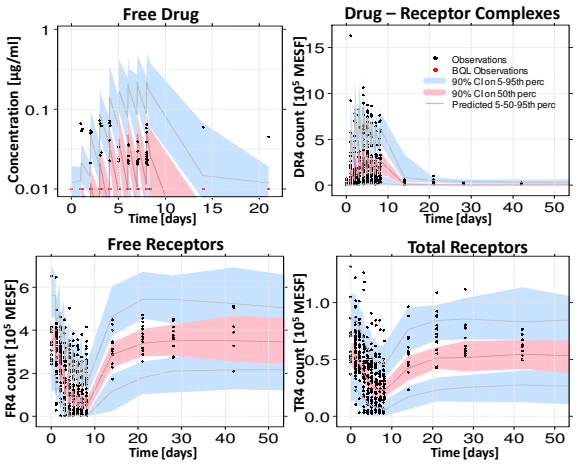


FIGURE 2 Extended QE model – simultaneous fitting: VPCs of Free drug, Free Receptors, Drug-Receptor Complexes and Total Receptors on CD4+

- Finally, simulations were run to better characterise the model behaviour and identify the source of model instability. Data were simulated with the TMDD model (general or extended) and re-estimated using both TMDD and QE (general or extended).

- For both TMDD and QE models, simulations from single studies did not show any identifiability problem related to conversion factors or the estimation of different targets (not shown).

- Joint simulations of multiple studies followed by simultaneous fitting highlighted instability in TMDD model estimation, while the QE one successfully converged providing adequate parameter estimates (not shown).

References

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