Target-Mediated Drug Disposition (TMDD): Indirect-Response Models Can Be Used to Estimate Unobservable Unbound Target Concentrations

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ABSTRACT

Purpose

a. To derive relationships between the parameters of TMDD and indirect response models (IRM); b. To demonstrate that IRM can be used to estimate the TMDD parameters and unobservable unbound target concentrations.

Methods

The TMDD equations and its quasi-steady-state (QSS) approximation were used to derive the IRM equations for total target concentrations. The ability of IRM to estimate the TMDD parameters and to predict unobservable unbound target concentrations were investigated using population PK-PD simulations in NONMEM6. The dataset included rich data from two studies (mimicking typical Phase 1 and Phase 2 studies). The PK parameters of the simulation model were typical for monoclonal antibodies. The TMDD binding and target turnover parameters were similar to those estimated for omalizumab. The unbound drug and total target concentrations were simulated from the TMDD model. The QSS approximation and IRM were used for estimation.

Results

The direct correspondence between the parameters of the TMDD and IRM was established. This correspondence allows estimating the TMDD parameters (production and degradation rate constants of the unbound target, quasi-steady state constant, and degradation rate constant of the drug-target complex) and unobservable unbound target concentrations from the estimated IRM parameters. In the simulation, IRM precisely estimated the TMDD population parameters with less than 7% bias and less than 5% relative standard error, and provided unbiased population and individual predictions of the total and unbound target concentrations.

Conclusions

The equation for the total target concentration of the QSS approximation coincides with the indirect-response model with inhibition (when $k_{deg} > k_{int}$) or stimulation (when $k_{int} > k_{deg}$) of elimination. The simulated population PK-PD study demonstrated that for drugs with TMDD, IRM are in fact mechanistic models that can be used to estimate TMDD model parameters and unobservable unbound target concentrations that are important for pharmacodynamic modeling.

OBJECTIVES

- To derive indirect response models (IRM) from the target-mediated drug disposition (TMDD) equations [1-4]
- To demonstrate (on the example of the simulated PK-PD data) that IRM can be used to estimate the TMDD parameters and unobservable unbound target concentrations.

METHODS

- The TMDD equations and its quasi-steady-state (QSS) approximation were used to derive the IRM equations for total target concentrations.
- The ability of IRM to estimate the TMDD parameters and predict unobservable unbound target concentrations were investigated using population PK-PD simulations in NONMEM.
  - ✓ The simulated dataset included rich data from two studies. Study 1 had 4 cohorts of six subjects administered single 100 nmol IV, 300 nmol SC, 1000 nmol IV, or 3000 nmol SC doses. Study 2 had two 100-subject arms administered multiple 1000 or 3000 nmol SC doses at 4 week intervals.
  - ✓ The PK parameters of the simulation model were typical of monoclonal antibodies.

METHODS (Continued)

- ✓ TMDD binding and target turnover parameters were similar to those estimated for omalizumab [5,6] with the elimination rate of the drug-target complex (k_{int}) 5 times lower than the elimination rate of the unbound target (k_{deg}).
- ✓ The unbound drug and total target concentrations were simulated from the TMDD model.
- ✓ The QSS approximation and IRM were used for estimation.

RESULTS: Comparison with Indirect Response Models

Direct correspondence between the parameters of the TMDD (QSS) equation for the total target concentration

$$\frac{dR_{tot}}{dt} = k_{syn} - k_{deg} R_{tot} - (k_{int} - k_{deg}) \frac{R_{tot} C}{K_{SS} + C}; \qquad R_{tot}(0) = \frac{k_{syn}}{k_{deg}}$$

and IRM was established:

$$\frac{dR_{tot}}{dt} = k_{syn} - k_{deg} R_{tot} \left(1 + E_{max} \frac{C}{K_{SS} + C}\right); \qquad E_{max} = \frac{k_{int}}{k_{deg}} - 1;$$

$$\frac{dR_{tot}}{dt} = k_{syn} - k_{deg} R_{tot} \left(1 - E_{max} \frac{C}{K_{SS} + C}\right); \qquad E_{max} = 1 - \frac{k_{int}}{k_{deg}}.$$

This correspondence allows estimating TMDD parameters (production rate k_{syn} of the unbound target, degradation rate k_{deg} of the unbound target, quasi-steady state constant KSS, and degradation rate of the drug-target complex k_{int}). Then, the drug-target complex concentration RC and the unobservable unbound target concentration R can be computed as

$$RC = \frac{R_{tot} C}{K_{SS} + C}, \qquad R = \frac{R_{tot} K_{SS}}{K_{SS} + C}$$

In the simulation study, IRM (that utilized individual predictions of free drug concentrations provided by the empirical PK model) precisely estimated the TMDD population parameters with less than 7% bias and less than 5% relative standard error, and provided unbiased and precise population and individual predictions of the total and unbound target concentrations.

Generalization: TMDD systems with cooperative or allosteric binding.

$$\frac{dR_{tot}}{dt} = k_{syn} - k_{deg} R_{tot} - (k_{int} - k_{deg}) \frac{R_{tot} C^{\gamma}}{K_{SS}^{\gamma} + C^{\gamma}}; \qquad R_{tot}(0) = \frac{k_{syn}}{k_{deg}}$$

$$\frac{dR_{tot}}{dt} = k_{syn} - k_{deg} R_{tot} \left(1 + E_{max} \frac{C^{\gamma}}{K_{SS}^{\gamma} + C^{\gamma}}\right); \qquad E_{max} = \frac{k_{int}}{k_{deg}} - 1;$$

$$\frac{dR_{tot}}{dt} = k_{syn} - k_{deg} R_{tot} \left(1 - E_{max} \frac{C^{\gamma}}{K_{SS}^{\gamma} + C^{\gamma}}\right); \qquad E_{max} = 1 - \frac{k_{int}}{k_{deg}}.$$

Then, the drug-target complex concentration RC and the unobservable unbound target concentrations R can be computed as

$$RC = \frac{R_{tot} C^{\gamma}}{K_{SS}^{\gamma} + C^{\gamma}}, \qquad R = \frac{R_{tot} K_{SS}^{\gamma}}{K_{SS}^{\gamma} + C^{\gamma}}$$

RESULTS: Simulated PK-PD Study

- PK and PD data were simulated from TMDD model (Table 1: True Value);
- QSS approximation was able to recover the true model parameters (Table 1: QSS) and correctly estimate the drug, target, and complex concentrations;
- The empirical PK model with Michaelis-Menten elimination (Table 1: MM model) was able to describe the individual concentration-time profiles, but the parameter estimates and the population predictions were strongly biased and dose-dependent;
- The indirect-response PK-PD model (that used individual predictions of drug concentrations) precisely estimated the relevant TMDD model parameters (Table 1: Indirect Response Model), providing unbiased population and individual predictions of the total and free target concentrations (Figure 1).

Figure 1: Free and Total Target Concentrations Predicted using Indirect Response Model versus True Values (Simulated from the TMDD Model)

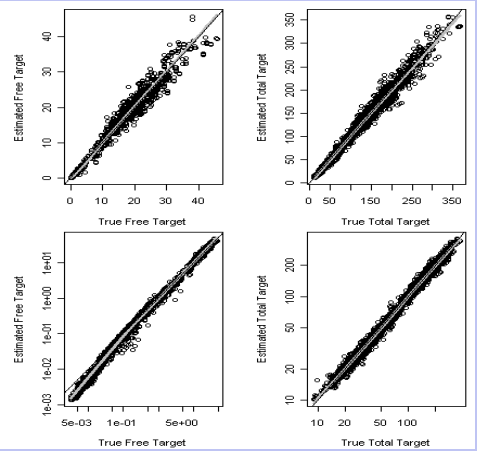

Table 1 Parameters of the "True" Model, and the Estimated Parameters of the QSS, and MM/Indirect-Response Models

Parameter	Definition	True	QSS			MM/Indirect Response		
		Value	Value	Bias (%)	RSE (%)	Value	Bias (%)	RSE (%)
CL (L/day)	Linear clearance	0.15	0.160	6.4	2.9	0.152	1.3	11
V_c (L)	Central volume	3.00	3.34	11.3	3.4	5.46	82	13
Q (L/day)	Inter-compartment clearance	0.45	0.453	0.6	14.3	0.0502	-89	11
V_p (L)	Peripheral volume	1.5	1.59	6.0	4.6	1.31	-13	8.9
F_a	Bioavailability	0.6	0.653	8.8	3.1	0.787	31	12
k_a (1/day)	Absorption rate	1.0	1.01	0.6	1.8	1.29	29	1.9
k_{on}(nmol/L)$^{-1}$/day	Association rate	8.0	-	-	-	-	-	-
k_{off}(1/day)	Dissociation rate	8.0	-	-	-	-	-	-
k_{int}(1/day)	Internalization rate	0.04	0.0399	-0.4	1.4	0.0406	1.5	-
k_{syn} (nmol/day)	Target production rate	1	1.01	0.6	2.1	1.0	0.0	3.2
k_{deg}(1/day)	Degradation rate	0.2	0.191	-4.3	2.1	0.189	-5.6	3.7
σ^2_{prop}	Variances of the exponential residual errors	0.0225	0.0222	-1.3	2.6	0.0238	19	3.1
σ^2_{prop2}		0.04	0.0414	3.5	2.8	0.422	5.5	2.5
$R_{ss}=k_{syn}/k_{deg}$ (nmol/L)	Baseline target concentration	5.0*	5.26	5.2		5.3*	6.0	-
$K_{SS}=k_{off}/k_{on}$ (nmol/L)	Equilibrium dissociation constant	1.0*	0.992	-0.8	Was fixed at estimated value	1.06	6.1	4.8
$K_{SS}=(k_{int}+k_{off})/k_{on}$ (nmol/L)	Steady-state constant	1.0*						
$E_{max}=1-k_{int}/k_{deg}$	Maximum inhibition	0.8*	0.792*	-1.0		0.785	-1.9	0.6
$k_{el}=CL/V_c$ (1/day)	Elimination rate	0.05	0.048	-4.0		0.0278	-44.4	-
$k_{12}=CL/V_c$(1/day)	Inter-compartment rate constants	0.15*	0.136	-9.3		0.009*	-94	-
$k_{21}=Q/V_p$ (1/day)		0.3*	0.285*	-5.0		0.0384*	-87	-
$K_m=(k_{int}+k_{off})/k_{on}$ (nmol/L)	Michaelis-Menten rate constant	1.0	-	-	-	16.2	1520	15
V_{max} (nmol/L/day	Maximum elimination rate	-	-	-	-	1.71	-	6.4

*The parameter was derived from the values of the other parameters.

CONCLUSIONS

- The equation for the total target concentration of the QSS approximation coincides with the indirect-response model with inhibition (when $k_{int} < k_{deg}$) or stimulation (when $k_{int} > k_{deg}$) of elimination.
- For drugs with TMDD, Indirect Response Models are in fact mechanistic models that can be used to estimate the TMDD model parameters and the unobservable unbound target concentrations that are important for pharmacodynamic modeling.

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