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Extending TMDD Models to Simulate the PK of mAbs that Bind to Both a Cell Surface Antigen on Leukocytes and Shed Antigen in the Circulation

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OBJECTIVE

- The impact of target-mediated drug disposition (TMDD) on PKPD of therapeutic proteins has been well appreciated in recent years.
- However, target dynamics are more complex than published TMDD models currently account for. For instance, virtually all structural and functional categories of membrane proteins have been found to be shed from cells [1], and for a large percentage of marketed monoclonal antibody therapeutics (mAb), target shedding has been shown to exist and several clinical studies have also indicated a significant effect of target shedding on mAb PKPD [2].
- The objective of this study is to extend existing TMDD models to take into account the dynamic interaction between a drug and its targets in the physiological or pathophysiological condition, where the target is present as both a membrane bound and a shed, soluble form.

METHODS

Membrane bound targets can exist in the tissues or on circulating cells in blood, and they are subject to ectodomain shedding or cell breakdown, generating soluble targets, both of which may coexist in the blood, interstitial space, or both. In order to mechanistically model this more realistic target-mediated drug disposition, we have generalized the existing TMDD models to take account of the ectodomain shedding of tissue targets in the interstitial space [5]. Here we consider another scenario, both membrane-bound and soluble targets are located in blood. A typical of examples of this scenario is CD20 on B-cells, targeted by rituximab.

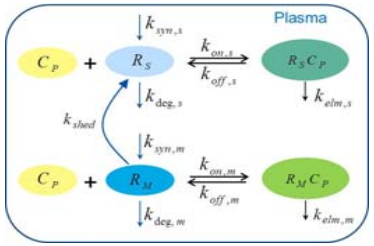
The left diagram in Figure 1 schematically shows the shedding model used in this study, where the membrane target shedding is represented by first-order rate constant (k_{shed}). The soluble target (R_S) is assumed to have its own synthesis and degradation processes to include other possible mechanism(s) of generating soluble targets. For instance, the soluble interleukin 6 receptor (sIL6R) are generated via two distinct mechanisms—limited proteolysis (shedding) and translation from differentially spliced mRNA [4]. Assuming that the system is at equilibrium before drug administration, we can derive the steady state solutions, as shown in the bottom right panel of figure 1, which serve as the initial conditions of the governing equations for drug-target dynamic interactions, as shown below. Furthermore, we allow the drug to modify the shedding rate by incorporating inhibitory or stimulatory effect into parameter k_{shed}.

Equations for both the full TMDD model and the quasi-steady-state approximation TMDD (Qss TMDD) were extended to account for shedding and the governing equations for Qss TMDD are given below. This set of equations are coupled with the equations of a minimal PBPK model for mAbs developed previously [3] (see Figure 2 for model structure and table 1 for parameter values).

$$\frac{d[R_M]_{tot}}{dt} = k_{syn,m} - \left\{\left(k_{\deg,m} + k_{shed}\right)\frac{K_{M,SS}}{K_{M,SS}+C_P} + k_{elm,m}\frac{C_P}{K_{M,SS}+C_P}\right\}[R_M]_T,\quad [R_M]_{tot}(0) = [R_M]_{SS}$$

$$\frac{d[R_S]_{tot}}{dt} = k_{syn,s} - \left\{k_{\deg,s}\frac{K_{S,SS}}{K_{S,SS}+C_P} + k_{elm,s}\frac{C_P}{K_{S,SS}+C_P}\right\}[R_S]_{tot} + k_{shed}\frac{K_{M,SS}}{K_{M,SS}+C_P}[R_M]_{tot},\quad [R_S]_{tot}(0) = [R_S]_{SS}$$

$$C_{P,tot} = C_P\left(1 + \frac{[R_M]_{tot}}{K_{M,SS}+C_P} + \frac{[R_S]_{tot}}{K_{S,SS}+C_P}\right),\quad K_{M,SS} = \frac{k_{off,m}+k_{elm,m}}{k_{on,m}},\quad K_{S,SS} = \frac{k_{off,s}+k_{elm,s}}{k_{on,s}}$$



R_M -- membrane-bound target
R_S -- soluble target
C_P -- drug in plasma
$R_M C_P$ -- complex of drug and membrane-bound target
$R_S C_P$ -- complex of drug and soluble target

$$(1)\quad [R_M]_{SS} = \frac{k_{syn,i}}{k_{shed}+k_{\deg,i}}$$

$$(2)\quad [R_S]_{SS} = \frac{k_{syn,s}+k_{shed}[R_M]_{SS}}{k_{\deg,s}}$$

Figure 1. Schematic representation of shedding model.

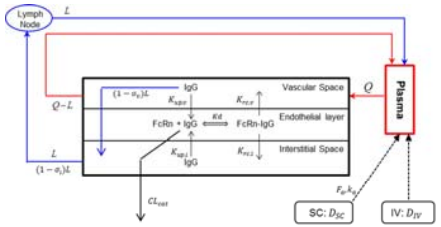


Figure 2. Minimal PBPK model structure for mAbs[3].

Competitive equilibrium binding of endogenous and exogenous IgG to FcRn with different affinities

$FcRn + IgG_m \xleftrightarrow{K_{d,m}} FcRn\text{-}IgG_m$

$FcRn + IgG_{es} \xleftrightarrow{K_{d,es}} FcRn\text{-}IgG_{es}$

RESULTS

Case study: *simulating PK of Rituximab with the presence of circulating CD20 (cCD20)*

Rituximab is a chimeric humanized IgG1 mAb, specifically targeting human CD20, a trans-membrane phosphoprotein with a molecular weight of 33-36 kDa, expressed on B cells in most lymphoid B-cell malignancies. The current recommended dose of rituximab is 375 mg/m^2 in patients with B cell non-Hodgkin's lymphomas (B-NHLs) and 500 mg/m^2 in patients with chronic lymphocytic leukemia (CLL) [6]. Clinical studies showed that rituximab had less activity in CLL when administrated with low dose and a higher dose corresponded to a higher response rate. Although CD20 is postulated to remain membrane-bound without shedding [7], very high level (up to 15 μM) of the full-length CD20 protein, known as circulating CD20 (cCD20), have been reported in patients with CLL [8] and is attributed to cell breakdown.

Here we aim to simulate the effect of cCD20 on the binding of rituximab to membrane bound CD20, using the described shedding model. Parameter values are set as follows. Assuming that B-cell density is 0.5×10^6 cells/mL and the copy number of CD20 is 65 $\times10^3$ molecules/cell [9], we can have an estimate of CD20 concentration level, 0.05 nM ($[R_M]_{SS}$). The affinity of rituximab to CD20 is K_D=8 nM [10] and thus K_{SS} is assumed to be same as this value based on quasi-equilibrium approximation. If total blood B cells are assumed to divide at an average rate of 2% per day, $k_{deg,m}$ can be set to be 0.0008 h^{-1} [11], i.e., assuming approximately 36 days of half-life of both B Cells and CD20 on B cells. $k_{syn,m}$ is calculated by equation (1) in Figure 1. Several mechanisms of cytotoxicity have been ascribed to rituximab [12], resulting in a very rapid B-cell depletion. To represent this fast elimination of B-cell as well as the associated CD20, we set $k_{elm,m}$ =0.2 h^{-1}.

First, using the parameters described above as well as K_D value (508 nM) [13] for FcRn binding in the minimal PBPK model, we simulated the case of no cCD20 present in blood. Figure 3 shows the simulated free rituximab serum concentration based on a standard dosing schedule, 375mg/m^2, once weekly for 4 weeks. The simulation is consistent with the pivotal study [14] in that peak serum concentrations doubled from the first (239 mg/L) to the fourth (461 mg/L) dose and rituximab is detectable in the serum of patients even after 3 months post-treatment (median 20.2 mg/L) and at 6 months post-treatment (1.3mg/L)[15].

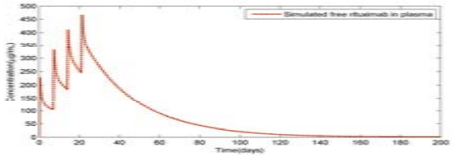


Figure 3. Simulated rituximab concentration following the standard schedule: four weekly infusion of 375 mg/m^2 with assumed body surface area of 1.73 m^2.

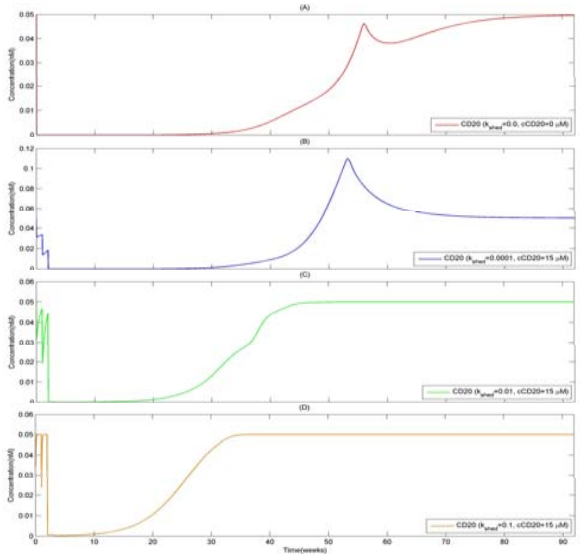


Figure 4. Simulated CD20 depletion effect by rituximab following the standard schedule: four weekly infusion of 375 mg/m^2 with assumed body surface area of 1.73 m^2. Simulations were done for different shedding rate k_{shed} with assumed initial cCD20 level of 15 μM except zero shedding rate (A).

RESULTS

Using the reported concentration of cCD20 level (15 μM; [8]) and values of $k_{syn,s}$ =0, $k_{elm,s}$ =0.2 h^{-1}, $k_{deg,s}$ can be calculated by equation (2) in figure 1 once k_{shed} is given.

Simulations were run for different shedding rates k_{shed}. As shown in Figure 4, with increasing shedding rate, CD20 level recovers earlier using a fixed dosing schedule of four weekly infusion of 375 mg/m^2. Mechanistically k_{shed} can be related to the cell turnover rate if the generation of cCD20 is due to cell breakdown and k_{shed} is likely to increase in treated patients.

Finally, the effect of increased dose was explored in simulations done with a fixed value for k_{shed} =0.0001 h^{-1}. As shown in Figure 5A, a 500 mg/m^2 dose is able to prevent the rebound in soluble cCD20 observed at the 375 mg/m^2 dose (Figure 4B), though there is a delay in the depletion in the beginning; whilst a dose of 1500 mg/m^2 achieves almost the same depletion effect as when cCD20 is absent (Figure 5B). Similar effects can be achieved with a mAb that has a lower affinity to cCD20 but the same potency as rituximab against CD20, (Figure 5C&5D).

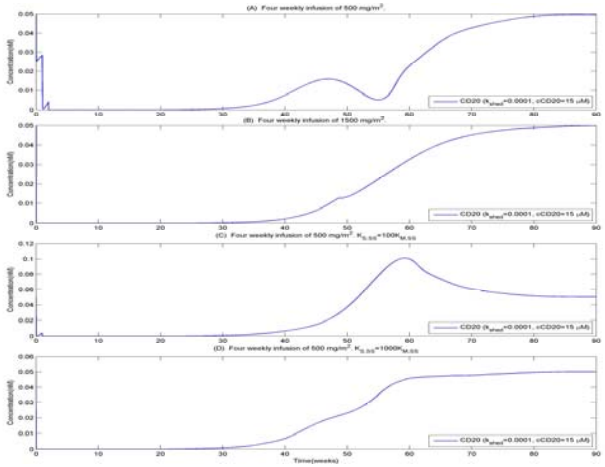


Figure 5. Simulated CD20 depletion effects by rituximab following higher doses (A&B) and assumed different affinities of rituximab to CD20 and cCD20 (C&D). k_{shed} =0.0001 h^{-1} and initial cCD20 level of 15 μM.

CONCLUSION

Published TMDD models have been extended to take into account the effect of target shedding on the behavior of a typical monoclonal antibody in a minimal PBPK model. The simulation study showed that high concentrations of shed soluble target can result in alterations in binding to membrane bound target (PD). When high levels of soluble (shed) target exist this should be factored in when determining optimal dosing regimens of therapeutics.

REFERENCES

[1] Zang et al. *Clin. Cancer Res*. 2008; 14(24), 7981-7986.
[2] Kuang et al. *Bioanalysis*. 2010; 2(6): 1125-40.
[3] Li L, Chetty M, Gardner I, Dostalek M, Grist E, Machavaram K. development of a minimal-PBPK model for simulating monoclonal antibody pharmacokinetics in human. Poster presentation at *AAPS National Biotechnology Conference* 2012 (21st—23rd May).
[4] Rose-John et al. *J of Leukocyte Biology* 2006; 80: 227-236.
[5] Li,L, Gardner, I, Rachel, R, Jamei, M. Incorporating target shedding into a minimal PBPK-TMDD model for mAbs. Poster presentation at *American Conference on Pharmacometrics* 2013 (12 – 15 May).
[6] Cartron, et al. *Critical Reviews in Oncology/Hematology* 2007.
[7] Press et al. *Blood* 1987; 69(2), 584-591.
[8] Manshouri et al. *Blood* 2003; 101(7), 2507-2513.
[9] Ginaldi et al. *J Clin Pathol* 1998; 51, 364-369.
[10] Reff et al. *Blood.* 1994; 83(2), 435-445.
[11] Macallan et al. *Blood* 2005; 105(9): 3633- 3640.
[12] Rodrguez &Gutierrez *Reviews on recent Clinical Trials* 2008; 3:22-30.
[13] Suzuki et al. *J of Immunology 2010; doi:10.4049/jimmunol.0903296* .
[14] Ginaldi et al. *J Clin Pathol* 1998; 51, 364-369.
[15] McLaughlin et al. *Semin Oncol* 1999; 26(5 Suppl 14): 79-87.
[16] Berinstein et al. *Ann Oncol* 1998;9(9): 995-1001.

Table 1. Model parameters of the minimal PBPK models

Parameters	Values	Parameters	Values
$K_{up,v}$	0.02979 (1/h)	*Lymph Flow*	120 (mL/h)
$K_{up,i}$	0.02979 (1/h)	*FcRn abundance*	40 (μM)
CL_{cat}	0.0175 (L/h)	*Plasma flow (L/h)*	190 (L/h)
$K_{rc,v}$	0.2999 (1/h)	*Binding affinity of mAb to FcRn (K_D pH 6)*	0.728 (μM)
$K_{rc,i}$	0.1196 (1/h)		

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