Exploring Parameter Estimation When Applying Target-Mediated Drug Disposition Model with Drug Concentration Data Only

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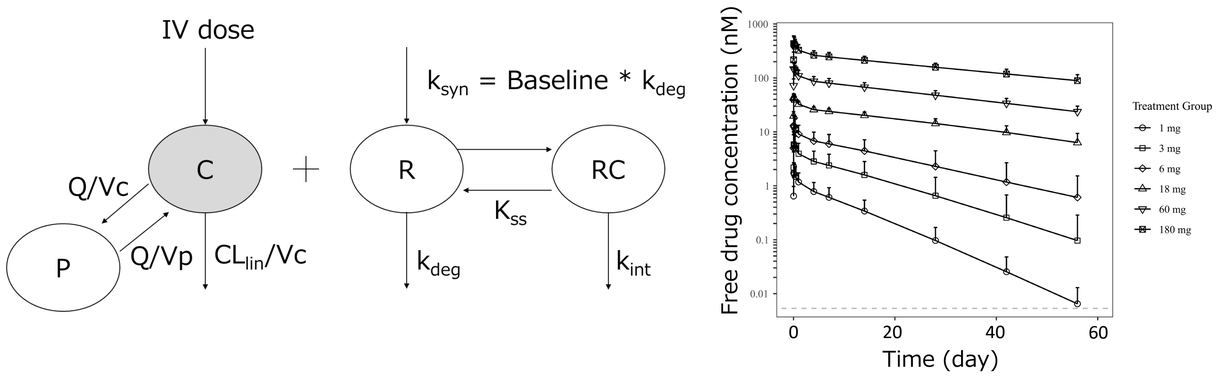
Introduction

- Monoclonal Antibody (mAb) PK exhibits non-linear elimination in the lower concentration due to target-mediated drug disposition (TMDD).
- TMDD model facilitates the prediction of appropriate dosages for future studies based on mechanisms of action from key drivers, such as target occupancy and drug-target complex concentrations.
- Establishing validated assays for both the drug and the target requires considerable time and funding.

Figure 1: Scheme of TMDD Model Structure Assuming Quasi-Steady State and Typical Mean Free Drug Concentration Time-course



Objective

We explore the identifiability of TMDD parameters through a simulation study under various scenarios using only mAb concentration data. Identifiability refers to practical identifiability based on clinical trial design.

Methods

As case examples, TMDD models with quasi-steady state approximations for denosumab (anti-RANKL mAb) and alirocumab (anti-PCSK9 mAb, ~40-folds higher of k_{deg} compared with denosumab) were used [1, 2]. Only free drug concentration data was generated using TMDD models for 200 virtual studies with rich sampling assuming a standard first-in-human study shown in Table 1 (Scenario A-1 and D-1).

Additional Scenario
- Number of dose levels (3 or 9)
- Analyte of interest (Total drug concentration)

Assessment of Practical Identifiability
- Relative estimation error (REE = (Est. - True)/True * 100)
- Relative bias (R-Bias = 1/N ∑ (Est. - True)/(True) * 100)
- Relative root mean square error (R-RMSE = √(1/N ∑ (Est. - True)^2/True^2) * 100)

- Additional assessment: Varying the initial TMDD parameter value (10 or 1/10-fold) to evaluate the impact of the initial parameter value on identifiability.

NONMEM® 7.4 with FOCE-I for parameter estimation.

Table 1: Summary of virtual study design for each scenario

Scenario	# of dose level	Root	Analyte	K_{ss} (nM)	Baseline (nM)	k_{deg} (/day)	k_{int} (1/day)
Case example 1: Alirocumab							
A-1	6	IV	Free	0.58	2.55	1.36	0.126
A-2	**3**	IV	Free	0.58	2.55	1.36	0.126
A-3	**9**	IV	Free	0.58	2.55	1.36	0.126
A-4	6	IV	**Total**	0.58	2.55	1.36	0.126
Case example 2: Denosumab							
D-1	6	IV	Free	1.1	16.9	0.0355	0.158
D-2	**3**	IV	Free	1.1	16.9	0.0355	0.158
D-3	**9**	IV	Free	1.1	16.9	0.0355	0.158
D-4	6	IV	**Total**	1.1	16.9	0.0355	0.158

Number of subjects: 6 participants per dose level, Sampling points: 12 points (0.5, 1, 2, 4, 8, 24, 96, 168, 336, 672, 1008, 1344 hours) per participant

Results

- In all scenarios (except some cases where dependency of initial TMDD parameter values were investigated), all runs were converged successfully.

Identifiability for TMDD parameters (Figure 2)
- Base cases (A-1 and D-1) showed less than 10% of R-Biases and less than 30% of R-RMSEs for population mean value of each TMDD parameter.
- No apparent impact of # of dose levels on the R-Bias, but R-RMSE decreased with an increase in # of dose levels (A-2, 3 and D-2, 3)
- Identifiability for k_{deg} was sensitive to the analyte of interest (Total drug concentration(A-4 and D-4) vs. Free drug concentration (A-1 and D-1))

Figure 2: Relative Estimation Errors in TMDD Parameters for Each Scenario (Virtual Study = 200)

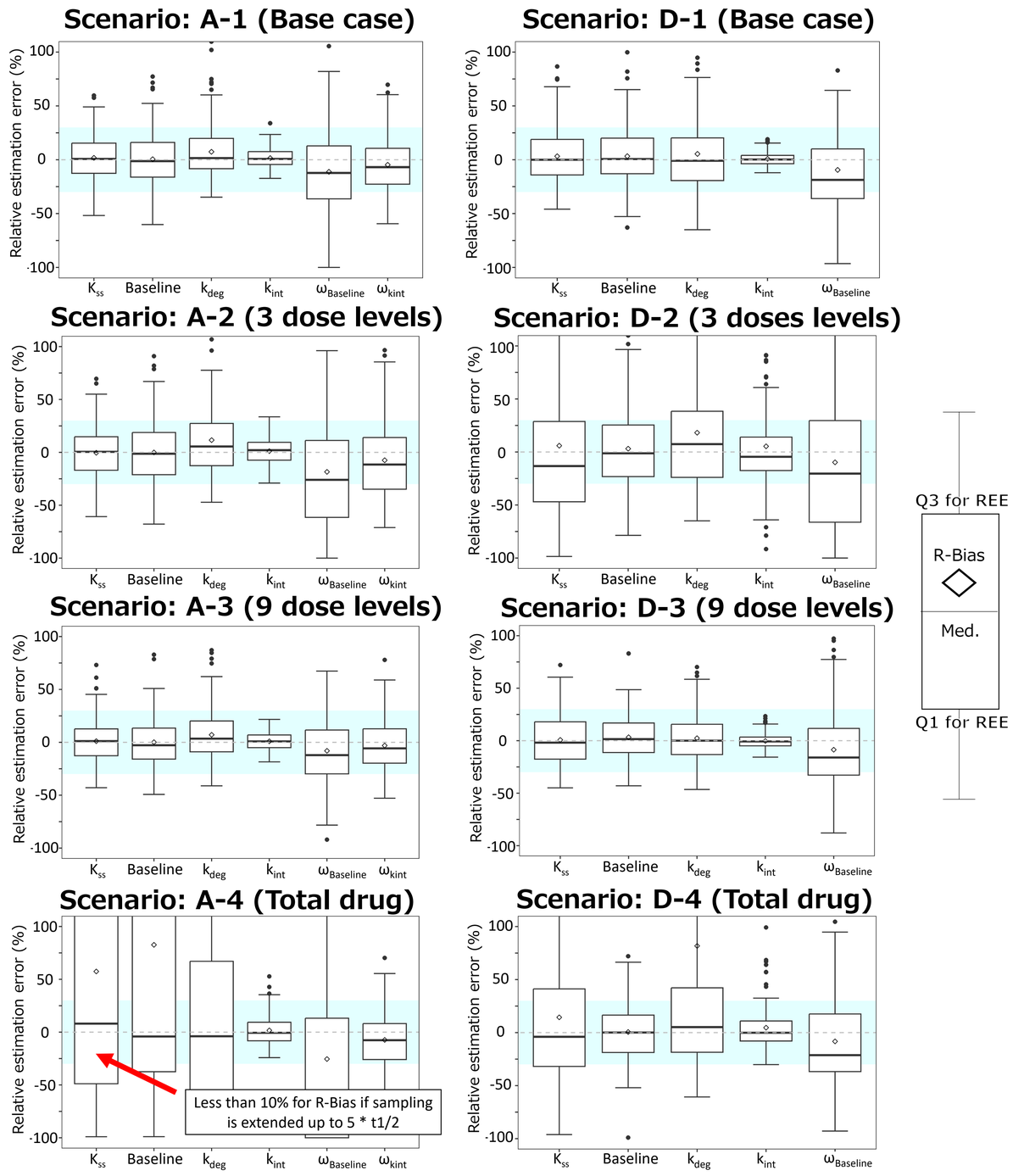
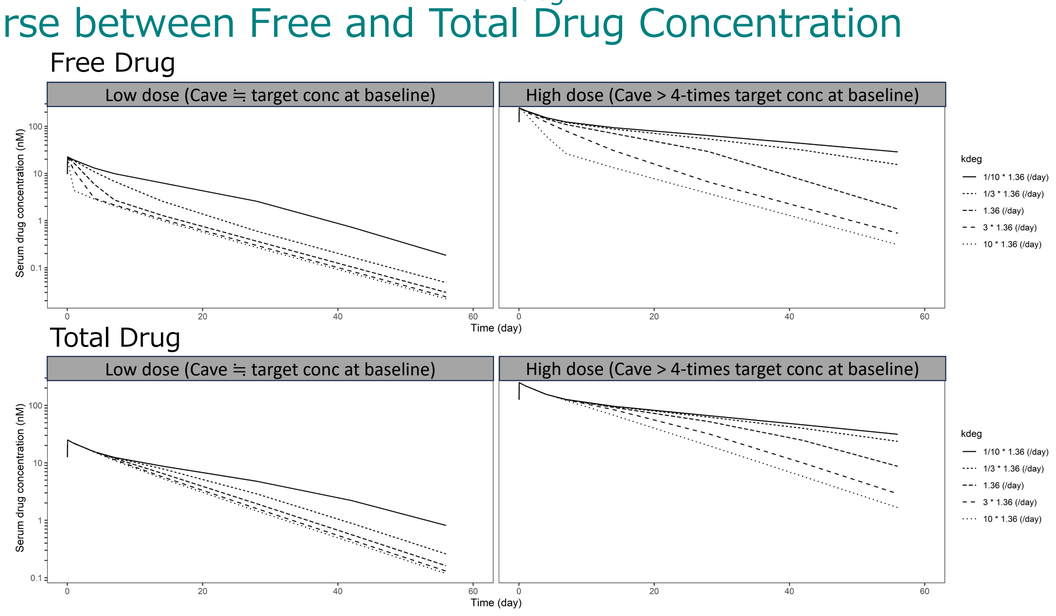


Figure 3: Impact of Value of k_{deg} on Drug Concentration Time-course between Free and Total Drug Concentration



- Altering the initial value of k_{deg} affected convergence, R-Bias, or R-RMSE. Other initial parameter values did not influence identifiability.

Conclusion

- This simulation study suggests that even with only free drug concentration data, parameter estimation for the TMDD models results in no critical issues, biases, or identifiability problems with two case examples of denosumab and alirocumab.
- Using total concentration data resulted in significant bias, particularly for estimating k_{deg}, likely due to different PK profiles compared to the scenario using free drug concentration data, especially in the alpha phase. Given that k_{int} and K_{ss} correspond to V_{max} and K_m, respectively, using the MM approximation could be viable when only total concentration data is available.

Reference
[1] Sutjandra, et al. Clin Pharmacokinet (2011) 50: 793-807.
[2] Djebli, et al. Clin Pharmacokinet (2017) 56: 1155-1171