Slow drug-target complex kinetics and first dose overestimation of free target suppression in target-mediated drug disposition (TMDD) approximation models: An evaluation for an NGF inhibitor tanezumab for treatment of pain

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Introduction

Tanezumab is an NGF inhibitor (mAb) that is currently being developed in Phase 3 studies to treat moderate-to-severe osteoarthritis, chronic low back pain, and pain from bone metastases. To predict unobserved free NGF suppression following tanezumab administration, a TMDD approximation (QSS) model was developed [1].

TMDD model approximations are useful in allowing estimation of alternative hybrid parameters when the full TMDD modelling is over parameterized [2-5]. However, it is known that TMDD approximation models would not accurately predict the initial fast phase or terminal phase. Although the developed QSS model well described tanezumab and total NGF concentration-time data, the free NGF simulation suggested overestimation of the free NGF suppression in the initial fast phase.

Objectives of this study were to characterize the overestimation and to quantify the impact when varying the target binding parameter values.

Methods

Figure 1 shows a schematic view of TMDD models. Quasi-steady-state (QSS), Michaelis-Menten (MM), and indirect response (IR) approximation models were evaluated to confirm whether early overestimation existed (**Table 1**). Parameters available from the previous model [1] and in-vitro data [6] were used for sensitivity analyses on molar basis.

Impact of the overestimation was evaluated with sensitivity analyses focusing on k_{on}, k_{off}, and k_{int} over the first 28 days following the first subcutaneous (SC) tanezumab dosing at 10 mg. Metrics for the overestimation are shown in **Figure 2**.

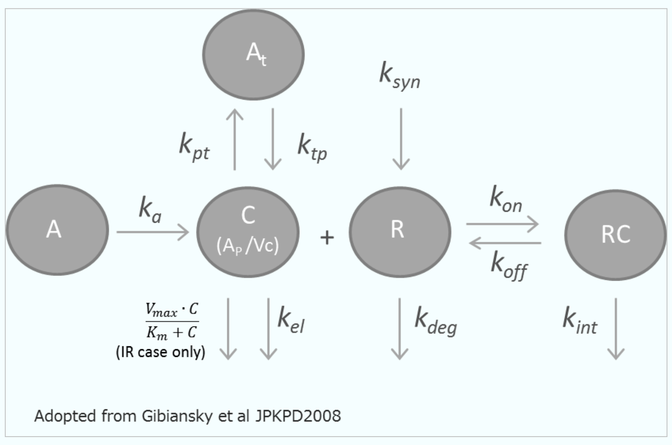


Figure 1. Schematic representation of TMDD models

A	Drug amount to be dosed
A_p	Free drug amount in plasma
A_t	Free drug amount in tissue
C	Free drug concentration
R	Free target concentration
RC	Drug-target complex
k_a	Absorption rate constant
k_{el}	Elimination rate constant
k_{pt}	Distribution rate constant
k_{tp}	Distribution rate constant
Vc	Central volume of distribution
V_{max}	Maximum elimination rate
K_m	Michaelis-Menten rate constant
k_{syn}	Target synthesis rate constant
k_{deg}	Target degradation rate constant
k_{on}	Binding rate constant
k_{off}	Dissociation rate constant
k_{int}	Degradation rate constant

Table 1. TMDD approximation models used for sensitivity analysis

Abbreviation	Model	Note
FULL_TMDD	Full TMDD	Reference model for sensitivity analysis
QSS_Apx	QSS approximation	C, R, RC assumed to be in a quasi steady state [2]
QE_Apx	QE approximation	Particular case of QSS (k_{int} << k_{off}) [2]
MM_Apx	Michaelis Menten approximation	Applicable when R << C (small RC and *dRC/dt*) [2] Useful in high kint
Ind_Rsp	Indirect response model with linear + nonlinear PK	V_{max} and K_m estimated using PK data alone. And K_{ss} estimated independent of PK [3].

Root mean squared error (RMSE)

$$\sqrt{\frac{1}{N}\sum\left(y_i - y_i^*\right)^2} \cdot 1000 \quad [\text{pM}]$$

%Root mean squared error (%RMSE)

$$\sqrt{\frac{1}{N}\sum\frac{\left(y_i - y_i^*\right)^2}{\left(y_i^*\right)^2}} \cdot 100 \quad [\%]$$

AUC %difference (%AUC)

$$\frac{AUC - AUC^*}{AUC^*} \cdot 100\,[\%]$$

Figure 2. Metrics for sensitivity analysis over the first 28 days

Note: Each metric was calculated over the first 28 days following the first subcutaneous tanezumab dosing.
y_i = *i*th free target concentration predicted from an approximation model y_i^* = *i*th free target concentration predicted from full TMDD model
AUC = free target AUC predicted from an approximation model AUC^* = free target AUC predicted from full TMDD model

Results

The previously developed QSS model well described tanezumab and total NGF concentration-time data following the SC administration as shown in **Figure 3 a-b**.

The free NGF simulated from the model suggested the approximation would overestimate the free NGF suppression in the initial fast phase, when comparing with the simulation from a tentative full TMDD model as shown in **Figure 3 c-d**.

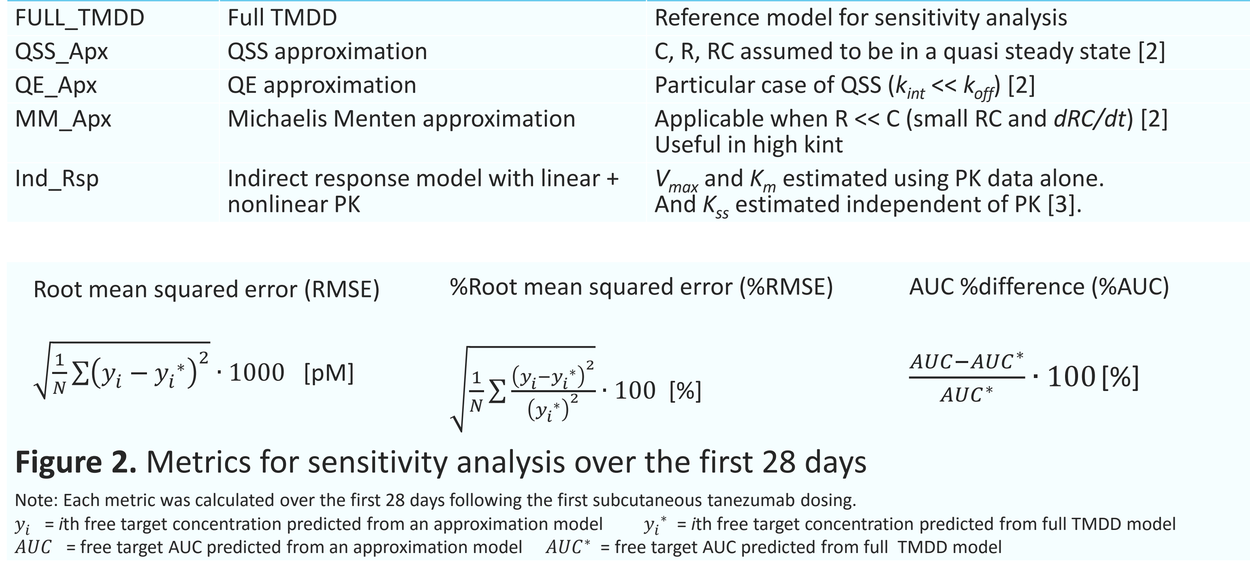


Figure 3 a-b. Visual predictive check plots of the previously developed QSS model for (a) tanezumab and (b) total NGF (SC 2.5, 5, 10 mg Q8W). **Figure 3 c-d.** Simulated free NGF suppression at 5 mg Q8W based on (c) the QSS model and (d) a tentative full TMDD model with some parameters fixed to certain values.

Note: For (a)-(b), dashed lines and shaded areas (95%CIs) show observed and predicted 10, 50, and 90 percentiles, respectively. For (c)-(d), shaded areas show predicted 95%CIs.

In the sensitivity analysis, as expected, simulations indicated overestimation existed and its extent was similar across approximation models in our simulation settings (**Figure 4-5**).

Overestimation of the free target suppression reduced or disappeared when k_{on}, k_{off}, or k_{int} was made larger (i.e. when complex kinetics was faster) as shown in **Figure 4**. The overestimation existed specifically when k_{on}, k_{off}, or k_{int} was made smaller (i.e. when complex kinetics was slower) as shown in **Figure 5**. These results indicate higher complex production and/or elimination rates relative to drug-target complex rate (*dRC/dt*) are needed to reduce the overestimation.

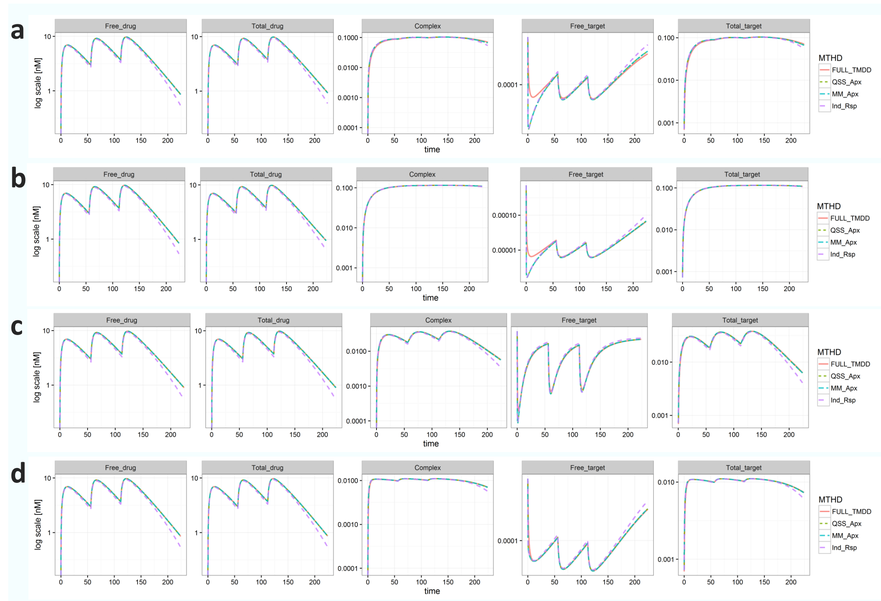


Figure 4. Examples for reduced overestimation of free target suppression when k_{on}, k_{off}, or k_{int} was larger (faster complex kinetics)

a: Original parameters
b: Original k_{on} x 10 times
c: Original k_{off} x 50 times
d: Original k_{int} x 10 times

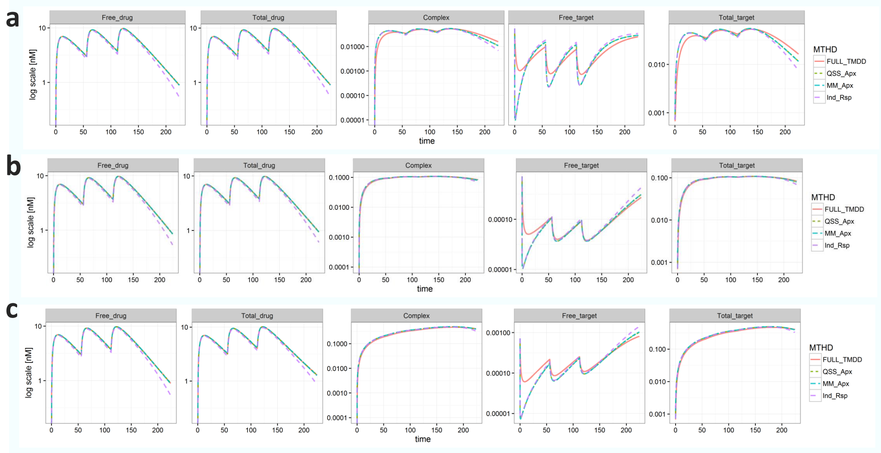


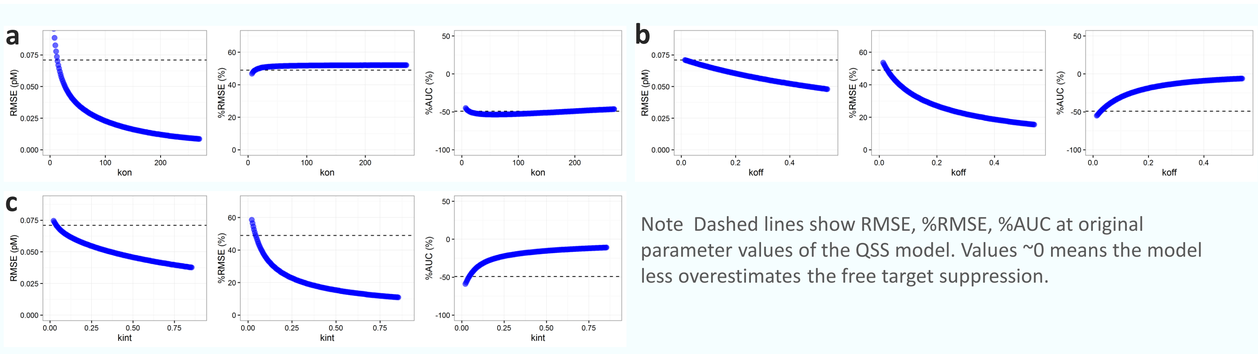
Figure 5. Examples for outstanding overestimation of free target suppression when k_{on}, k_{off}, or k_{int} was smaller (slower complex kinetics).

a: Original k_{on} x 0.1 times
b: Original k_{off} x 0.1 times
c: Original k_{int} x 0.1 times

Discrepancy between the approximation and full TMDD models at the original parameter estimates (RMSE) was 0.07 pM, which got reduced to below 0.01 (0.05 for k_{off}, k_{int}) pM when k_{on}, k_{off}, or k_{int} was increased. Meanwhile, the original discrepancy (%RMSE) was about 50%, which got reduced to below 20% when k_{off} or k_{int} was increased.

Figure 6 a shows increasing k_{on} 2- to 20-fold progressively improved RMSE in the QSS model but did not improve %RMSE or %AUC indicating that with production rate already above the drug-target complex rate for tanezumab, a greater production rate due to a higher k_{on} value would further suppress free NGF but have no impact on reducing the initial discrepancy between the full and TMDD approximation models.

Figure 6 b-c show increasing k_{off} or k_{int} ~ 6- to 7-fold or increasing both by ~4 fold relative to the tanezumab estimates reduced the overestimation to insignificant levels of %AUC ~ 20% in the QSS model.



Note Dashed lines show RMSE, %RMSE, %AUC at original parameter values of the QSS model. Values ~0 means the model less overestimates the free target suppression.

Figure 6. Sensitivity analysis when (a) k_{on}, (b) k_{off}, or (c) k_{int} was changed in the QSS model.

Conclusions

Overestimation of free target suppression during the initial "fast phase" in TMDD approximation models is already known. This work illustrates approaches to determine the extent and duration of this difference, which could be important when predicting acute effects, such as the onset of analgesia, for drugs displaying TMDD.

References

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