



Comparative analysis of Target-Mediated Drug Disposition (TMDD) models and Compartment models in biologics: Analysis of pharmacokinetic exposure parameters through case-based model simulations

Woojin Jung ², Taewook Sung ¹, Seonghwa Song ¹, Soyoung Lee ^{1*}, Hwi-yeol Yun ^{1,2,3*}, Jung-woo Chae ^{1,2,3*}

¹ College of Pharmacy, Chungnam National University, Daejeon, Republic of Korea

² Senior health Coverage Research Center, Chungnam National University, Daejeon, Republic of Korea

³ Department of Bio-AI Convergence, Chungnam National University, Republic of Korea

*Those of authors contributed equally as correspondence

BACKGROUND

What are Biologics

- Biologics, in contrast to conventional small-molecule drugs, are characterized by complex PK profiles, primarily arising from their specific interactions with targets.
- Biologics can exhibit substantial inter-individual variability, significantly influenced by patient-specific factors such as individual physiological status and the expression levels of target proteins.

Pharmacokinetic(PK) Model

- A pharmacokinetic (PK) model is a tool that quantitatively describes and predicts the entire process of a drug's absorption, distribution, metabolism, and excretion (ADME) in the body over time after administration.

1. **Classical Compartment Model:** A fundamental pharmacokinetic model that describes drug movement and elimination using first-order kinetics by dividing the body into hypothetical compartments.
2. **Michaelis-Menten(MM) Model:** A model that explains changes in drug kinetics at high doses by incorporating Michaelis-Menten kinetics to reflect non-linear processes, such as enzyme saturation in the elimination pathway of a compartmental model.
3. **Target-Mediated-Drug-Distribution(TMDD) Model:** A model centered on the binding of a drug to a specific target protein and the kinetics of the resulting complex, explaining complex non-linear drug distribution and elimination mechanisms mediated by the target.

type	Equation
Classical Compartment Model	$\frac{dc}{dt} = \left(\frac{Dose}{V}\right) - K_{el} \cdot c$
MM Model	$\frac{dc}{dt} = \left(\frac{Dose}{V}\right) - \left(\frac{V_{max} \cdot c}{K_m + c}\right)$
TMDD Model	$\begin{aligned} \frac{dc}{dt} &= -K_{el} \cdot c - K_{on} \cdot C \cdot R + K_{off} \cdot RC \\ \frac{dR}{dt} &= K_{syn} - K_{deg} \cdot R - K_{on} \cdot C \cdot R + K_{off} \cdot RC \\ \frac{dRC}{dt} &= K_{on} \cdot C \cdot R - K_{off} \cdot RC - K_{int} \cdot RC \end{aligned}$

OBJECTIVES

This study aimed to compare TMDD and classical compartment models' prediction characteristics for biologics

- Three types of model forms were compared using biologics: Classical compartment model, MM model, and TMDD model.
- Evaluation of the impact of each compartment model's predictions on decision-making compared to traditional approaches.

METHODS

Method Flow

- This study was conducted in four stages: verification of observation data for each drug, construction and evaluation of a pharmacokinetic model, simulation of the pharmacokinetic model, and Comparison of the simulation results.

1. Data inspection	2. PK model development and Evaluation	3. PK simulation	4. Simulation result and Comparison
• NCA • Data linearity	• Comp/MM/TMDD Model development • Model evaluation	• Multiple-admin simulation (Long-term)	• PK profile comparison • PK exposure parameter • Superposition NCA • Internal validation

Biologics data inspection & Model development

- Data of biologics and relevant information were collected and processed using R(4.3.3)

	Drug A	Drug B	Drug C	Drug D	Drug E
Drug	Anakinra	rhIL-7-hyFc	Human IL-9 antagonist hybrid Fc	Fully recombinant anti-PD-L1 monoclonal antibody	Tn-pyglutylated filgrastim
Average drug concentration(C ₀)	33 (6.68)	0.013 (0.011)	34.39 (29.14)	1,770 (9,000)	3773.85 (1,404.62)
Receptor concentration(R _{tot})	1.54	1.36	1.19	3.4	4.54
Co/R _{tot}	21.85	< 0.05	28.9	520.59	831.24
FcRn concentration	-	91.950	749	291	-
Co/FcRn	-	< 0.05	0.046	6.08	-
R _{tot} - K _{ss}	0.75	29.83	237	1.55	-
FcRn - K _{ss}	-	29.83	14.5	71,300	-
Unit			nmol/L		
Administration Dose	Single	Single	Single	Multiple	Single

For accurate dose prediction and optimization, classical compartment model, MM model, and TMDD models were constructed for all five biologics.

Evaluation

- Numerical diagnostics: Objective Function value (OFV), corrected Akaike Information Criterion (AICc).
- Visual diagnostics: Visual Predictive Check (VPC), Goodness of fit (GOF).

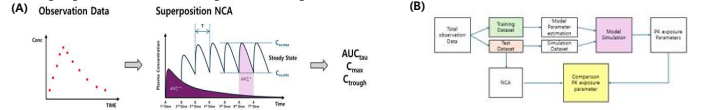
Simulation



- NONMEM(7.5.0); Model simulations were performed to evaluate the predictive performance

Performance evaluation of the model

(A) Superposition NCA/ Comparison PK parameter



- (A).Superposition NCA (R PKNCA package): PK exposure parameters at steady state were derived from observed data.
- (B).Comparison of PK parameters: Comparison of simulated PK exposure parameters through datasets with PK parameters calculated through NCA.

RESULTS

1. Dose proportionality test

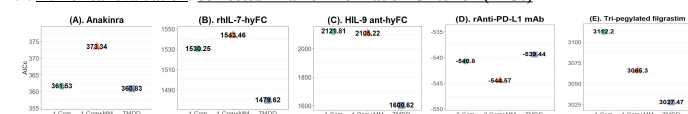
Table. Dose proportionality assessment of PK parameters based on ANOVA

	Drug A	Drug B	Drug C	Drug D	Drug E
C _{max}	—	X (0.0243)	O (0.424)	O (0.281)	X (0.00537)
AUC _{0-∞}	—	O (0.143)	O (0.0965)	X (0.369)	X (0.00652)
C _{trough}	—	O (0.291)	X (~0.05)	O (0.722)	O (0.569)

*Drug A: Dose proportionality analysis for linearity assessment was impossible due to only single-dose data.

2. Model estimation

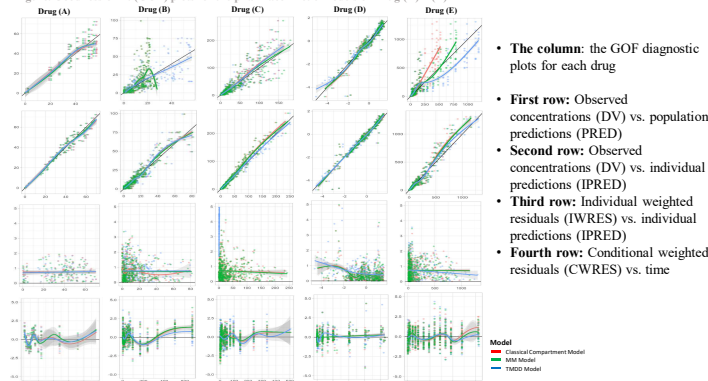
2.1. Numerical evaluation: corrected Akaike Information Criterion (AICc)



- Drug A showed similar AICc values across the compartment and TMDD models.
- Drugs (B), (C), and (E) exhibited the lowest AICc values with the TMDD model. Drug (D) demonstrated the lowest AICc value with the model incorporating Michaelis-Menten elimination.

2.2. Visual evaluation: Goodness of Fit (GOF)

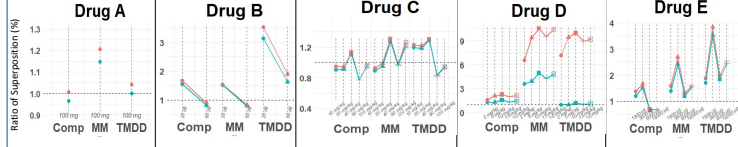
Figure. Goodness-of-fit (GOF) plots for the pharmacokinetic models of Drug (A) – (E)



- The column: the GOF diagnostic plots for each drug
- First row: Observed concentrations (DV) vs. population predictions (PRED)
- Second row: Observed concentrations (DV) vs. individual predictions (IPRED)
- Third row: Individual weighted residuals (IWRES) vs. individual predictions (IPRED)
- Fourth row: Conditional weighted residuals (CWRES) vs. time

3. Parameter simulation: Superposition NCA

Figure. Comparison of Model-Predicted PK Parameters to Superposition NCA Results



- Y-axis: Simulated-to-Superposition NCA ratio of PK parameters.
- 1(horizontal dashed line) : Superposition NCA baseline.
- In cases of Drug B, C, and E, TMDD model indicated differences from the Superposition NCA baseline.
- In cases of Drug A and D, both the classical compartment model and the TMDD model indicated comparable PK exposure parameters relative to the superposition NCA baseline. In contrast, MM model provided differences relative to the baseline.

4. Comprehensive Diagnosis

Table. Results of Model Diagnosis

Drug	AICc	OFV	VPC	GOF
Drug A	Y	Y	Y	Y
Drug B	Y	Y	Y	Y
Drug C	Y	Y	Y	Y
Drug D	Y	Y	Y	Y
Drug E	Y	Y	Y	Y

Table. Evaluation of simulation results

Drug	Superposition NCA	Comparison PK parameter
Drug A	Y	Y
Drug B	Y	Y
Drug C	Y	Y
Drug D	Y (C _{max}) / Y (AUC _{0-∞})	Y
Drug E	Y	Y

Evaluation was based on numerical (AICc, OFV) and visual (VPC, GOF) diagnostics, Superposition NCA, and Comparison PK parameter. Each evaluation result was classified by drug, and the optimal model for each drug was evaluated.

CONCLUSION & DISCUSSION

- This study compared and analyzed the results of three models through model diagnosis and simulation for five biologics
- In cases where PK linearity stands in dataset, TMDD and MM models indicated comparable predictive PK parameters, in particular for AUC_{0-∞}.
- The general properties of the TMDD model were explored through diagnostic assessments and analysis of linearity between the data and model predictions. Nonetheless, further validation is necessary to substantiate these observations.

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