Comparison of Non-Linear PK Models for Filgrastim

Hung-Liang Ezra Tai and Jogarao Gobburu

University of Maryland, School of Pharmacy, Center for Translational Medicine

Baltimore, Maryland 21201 USA

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INTRODUCTION AND PURPOSE

- Filgrastim is a recombinant methionyl form of human granulocyte colony stimulating factor (G-CSF) derived from E. coli. It consists of 175 amino acids and has a molecular weight of 18,800 daltons. The biological activity of filgrastim is identical to the endogenous G-CSF, which controls neutrophil production within the bone marrow by stimulating activation, proliferation, differentiation, and survival of myeloid progenitor cells (1).
- Filgrastim is an agent used therapeutically for treatments of neutropenia associated with chemotherapy, conditions of severe chronic neutropenia, and for the mobilization of hematopoietic stem cells and progenitors for transplantation (2).
- The pharmacokinetics (PK) of G-CSF has been reported to be nonlinear (3). The receptor-mediated binding of G-CSF followed by internalization and degradation was shown to be an important mode of drug clearance (4). Glomerular filtration and subsequent renal metabolism was shown to be another elimination pathway for G-CSF besides receptor-mediated elimination (5). The non-linearity in the G-CSF clearance was previously modeled by means of the Michaelis-Menten elimination that was independent of the number of the circulating neutrophils (6).
- Recently a target-mediated drug disposition (TMDD) model was used to describe filgrastim pharmacokinetics in healthy volunteers (7). A general model for drugs exhibiting TMDD exists (8). After administration, drug can be distributed to the peripheral compartment, directly eliminated, or bind to receptors. The drug-receptor complexes can be eliminated or dissociated to free receptors. The TMDD model uses receptor binding and receptor-mediated endocytosis as the primary mechanism of nonlinear drug disposition.
- In this report, we intend to compare two non-linear PK models described above for G-CSF.

METHODS

Modeling with Michaelis-Menten Elimination

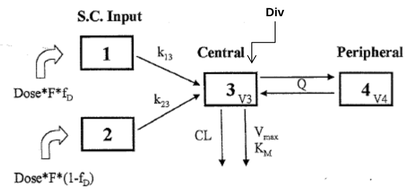
The disposition of filgrastim can be described by a two-compartment model with two parallel elimination pathways: a Michaelis-Menten type saturable pathway via receptor-mediated endocytosis and degradation of filgrastim and a first-order pathway mediated by renal elimination of filgrastim (6). A bisegmental input model was used to explicate the two-phase absorption pattern of subcutaneously administered filgrastim (6). A diagram of the model was shown (Figure 1).

TMDD Modeling

A published TMDD PK model was used for the mechanism-based modeling of G-CSF (7, Figure 2). The free G-CSF concentration C in the serum was assumed to be in an instantaneous equilibrium with the bone marrow and to bind to G-CSF receptors R present on blood and bone marrow neutrophils at a second order rate constant k_{on}, to form drug receptor complex RC. The G-CSF can also be directly eliminated by a glomerular filtration and subsequent renal metabolism represented by a first order eliminate rate k_{el}. The endogenous G-CSF was assumed to be continuously produced at a zero-order rate constant k_{GCSF}. The drug receptor complex RC can dissociate at a rate k_{off} or be internalized at a rate k_{int}. Based on the assumption of rapid equilibrium between drug and receptor that TMDD model of G-CSF was further reduced to a rapid binding form ($K_D = k_{off} / k_{on}$). Bioavailability of SC dosing is fixed to 0.6.

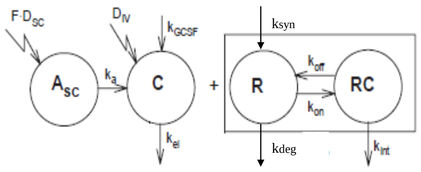
PK Modeling of digitized G-CSF concentration-time profiles (7) after IV infusion and Subcutaneous (SC) administration of filgrastim in humans was performed simultaneously with Naïve pooled method by Phoenix WinNonlin 6.3.

Figure 1. Schematic Diagram of a PK Model for G-CSF with Saturable Elimination.



Where F = Absolute bioavailability of subcutaneously administered filgrastim
f_D = Fraction of subcutaneously administered filgrastim initially in the first depot compartment
k_{13} = Absorption rate constant for subcutaneously administered filgrastim in the first depot compartment
k_{23} = Absorption rate constant for subcutaneously administered filgrastim in the second depot compartment
K_M = filgrastim concentration corresponding to half-maximum elimination rate for the saturable elimination pathway
V_{max} = Maximum rate of elimination for the saturable elimination pathway
CL = Systemic clearance for the first-order elimination pathway
V_n = Volume of distribution for compartment n, n = 3, 4
Q = Intercompartmental clearance

Figure 2. Schematic diagram of TMDD model for G-CSF



Where k_a = first order absorption rate constant
k_{el} = first order elimination rate constant from the central compartment
K_D = Dissociation constant of drug-receptor complex = k_{off} / k_{on}
k_{GCSF} = Zero order rate constant for endogenously generated G-CSF
k_{int} = First order rate constant of internalization and degradation of the drug-receptor complex
R_{tot} = Total receptor concentration being equal to R + RC
C = Free G-CSF concentration in the serum
RC = Drug-receptor complex concentration
k_{syn} = Rate constant of receptor synthesis
k_{deg} = Rate constant of receptor degradation

Variations of TMDD Models

TMDD-1 Reduced form of TMDD model based on the hypothesis of rapid binding of ligand and receptor (9)
$K_D = k_{off} / k_{on}$; k_{GCSF}; assuming constant concentration of free receptor.

TMDD-2 Full model with k_{off}, k_{on} for ligand binding, k_{syn}, k_{deg}, for receptor synthesis and degradation (8); with or without k_{GCSF}

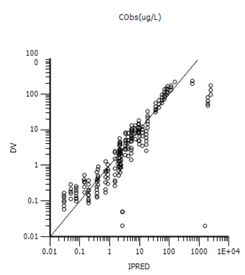
TMDD-3 Reduced model with k_{off} , k_{on} for ligand binding, Assuming constant concentration of free receptor; with or without k_{GCSF}

Zero-order input is an additional variation to these models.

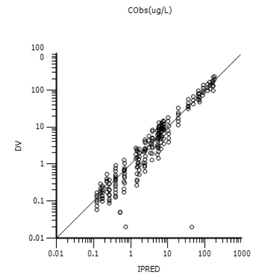
RESULTS

Goodness of Fit Between Two Models

Model with Saturable Elimination



TMDD Model



TMDD Model Comparison

TMDD Model	-2(LL)	AIC	BIC
TMDD-1	822.90846	838.90846	865.87356
TMDD-1 with zero-order input	782.0829	798.0829	825.048
TMDD-2 with k_{GCSF}	776.9553	796.9553	830.66168
TMDD-2 w/o k_{GCSF}	776.93566	794.93566	825.2714
TMDD-2 w/o k_{GCSF} with zero-order input	770.5031	788.5031	818.8389
TMDD-3 with k_{GCSF}	794.306	812.306	842.64174
TMDD-3 w/o k_{GCSF}	794.30596	810.30596	837.27106
TMDD-3 w/o k_{GCSF} with zero-order input	774.7573	790.7573	817.7224

k_{GCSF} parameter estimate was negligible, therefore models without it were selected. Models with zero-order input appears to lower the objective function.

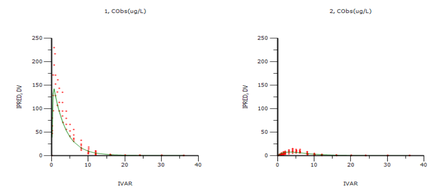
Parameter Estimates of TMDD Models

Model	TMDD-1 with First-order input		TMDD-1 with Zero-order input		TMDD-2 (w/o k_{GCSF}) with Zero-order input		TMDD-3 (w/o k_{GCSF}) with Zero-order input	
Parameter	Estimate	CV%	Estimate	CV%	Estimate	CV%	Estimate	CV%
K_a, h^{-1}	0.316	37.1	-	-	-	-	-	-
T_{abs}, h	-	-	2.46	8.32	2.51	16.7	2.40	9.44
F	0.602	fixed	0.602	fixed	0.602	fixed	0.602	fixed
V_c, L	2.17	8.74	2.01	5.95	1.81	9.24	1.69	8.25
k_{el}, h^{-1}	0.303	1.32	0.293	3.25	0.301	4.61	0.305	3.47
k_{GCSF}, µg/h	4.69E-06	173	0.075	13.0	-	-	-	-
k_{int}, h^{-1}	0.0159	63.2	0.673	801	7.93E-07	6620000	0.0228	54.1
k_D, µg/L	14.4	170	320000	2820	-	-	-	-
k_{on}, L/µg*h^{-1}	-	-	-	-	0.169	399	0.188	45.7
k_{off}, h^{-1}	-	-	-	-	0.152	228	0.120	43.2
k_{deg}, h^{-1}	-	-	-	-	0.0990	122	-	-
R_{tot0}, µg/L	7.02	44.9	43.8	2280	1.40	182	4.62	34.7
stdev0	0.503	11.4	0.476	5.82	0.466	4.82	0.469	5.79

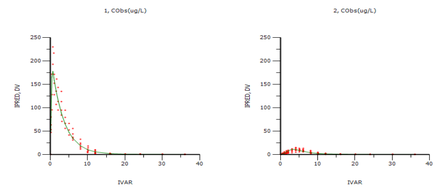
TMDD-3 with zero-order input has reasonable parameter estimates with good precision

Goodness of Fit Plots Observed (in red) vs. model-predicted (in green)

TMDD-1 (first-order with k_{GCSF})



TMDD-3 (zero-order w/o k_{GCSF})



CONCLUSIONS

- TMDD models achieved better overall goodness of fit than a non-linear PK model with Michaelis-Menten approximation, especially at low concentrations (10). Among TMDD models tested, TMDD-3 with zero-order input but without k_{GCSF} appeared to be the best model with good precision of parameter estimates.
- The choice of structural model was in line with the fact that G-CSF has been shown undergoing receptor-mediated elimination, which may be well described by TMDD models. The input parameter was also consistent with modes of filgrastim administration.

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