Receptor Mediated PK/PD Model of Filgrastim in Healthy Adults following Intravenous and Subcutaneous Administrations

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Objectives

Granulocyte Colony Stimulating Factor (G-CSF) is an endogenous protein also administered as a drug to stimulate the proliferation of neutrophils in oncology patients after chemotherapy. Filgrastim is a human granulocyte-colony stimulating factor (r-metHuG-CSF) produced by recombinant DNA technology. The biological activity of filgrastim is identical to the endogenous G-CSF. The purpose of this study was to develop a mechanism based pharmacokinetic (PK) and pharmacodynamic (PD) model of human G-CSF, that would account for the change in the filgrastim clearance upon multiple dosing due to an increase of the G-CSF receptor mediated endocytosis.

Methods

Clinical Study Design

Healthy male (n=68) and female (n=52) volunteers were treated in three randomized crossover studies with two filgrastim products (Neupogen® and Zarzio®). About 6000 plasma concentration-time records were evaluated from rich sampling profiles. Filgrastim was administered as repeated s.c. daily administration for one week of 2.5, 5 and 10 μg/kg doses and single iv. dose (5 μg/kg). Pharmacodynamic data (blood absolute neutrophil count, ANC) were available for the same time. PK and PD parameters were obtained through non linear mixed effect regression using NONMEM version VI (Globomax Corp., Hanover, MD).

PK/PD Model

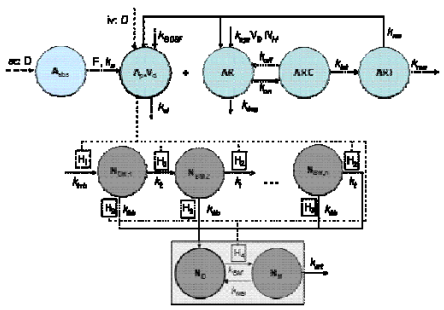

Fig. 1. The free G-CSF, A_p, in the plasma is assumed to be in an instantaneous equilibrium with the bone marrow and binds to G-CSF receptors on blood and bone marrow neutrophils at a second order rate constant, k_{on}, to form drug receptor complex, A*RC*. The G-CSF can also be directly eliminated by a first-order elimination rate, k_{el}. The endogenous G-CSF is assumed to be continuously produced at a rate, k_{GCSF}. The free receptor, A*R*, is assumed to be synthesized at a rate that is a product of a zero-order synthesis rate of individual neutrophil, k_{syn}, and a total body neutrophil pool, N_H. Free receptors are degraded by a first-order process, k_{deg}. The drug receptor complex ARC can dissociate at a rate k_{off} or be internalized at a rate k_{int} to the cell endosomes. The internalized G-CSF receptor complex, A*RI*, can be either removed, k_{rem}, or recycled back as a free receptor and drug molecule at a rate k_{rec}. The dose D of drug is absorbed from the subcutaneous site A_{SC} at the first-order rate k_a with the bioavailability F. The neutrophils dynamics was described by a series of transit compartments that represent the bone marrow pool. The input to that pool is a zero-order rate, k_{inb}, that is stimulated *via* the Hill function H_1 by the plasma G-CSF concentration C_p. Neutrophils in a maturing compartment N_{BMi} are aging (moving to the next transit compartment) at a transfer rate k_t, or directly migrate to the blood at a rate, k_{bb}. Both processes are stimulated *via* the Hill functions H_2 and H_3 by C_p that reflects the increase in maturation and migration of neutrophils to blood upon G-CSF administration. Neutrophils in the blood, N_B, marginate at a rate k_{bm} to the marginal pool N_M. The marginal neutrophils either demarginate at a rate k_{mb}, or migrate to the tissue at a first order rate k_{int} [1].

$$\frac{dA_{tot}}{dt} = Input + k_{GCSF} - k_{el}A_p - k_{int}(A_{tot} - A_p) + k_{rec}ARI$$

$$\frac{dAR_{tot}}{dt} = k_{syn}V_D N_H - k_{deg}(AR_{tot} - (A_{tot} - A_p)) - k_{int}(A_{tot} - A_p) + k_{rec}ARI$$

$$\frac{dARI}{dt} = k_{int}(A_{tot} - A_p) - k_{rem}ARI - k_{rec}ARI$$

$$A_p = 0.5((A_{tot} - AR_{tot} - K_D V_D) + \sqrt{(A_{tot} - AR_{tot} - K_D V_D)^2 + 4K_D V_D A_{tot}})$$

where A_{tot} is the sum of a unbound drug and drug receptor complex, AR_{tot} is the sum of a free receptor and a drug receptor complex and $K_D = k_{off}/k_{on}$ represent the equilibrium dissociation constant.

$$\frac{dN_{BM,1}}{dt} = k_{inb}H_1 - k_t H_2 N_{BM,1} - k_{bb}H_3 N_{BM,1}$$

$$\frac{dN_{BM,j}}{dt} = k_t H_2 N_{BM,j-1} - k_t H_2 N_{BM,j} - k_{bb}H_3 N_{BM,j} \quad i = 2, \ldots, n$$

$$\frac{N_M}{N_B} = \frac{k_{BM}}{k_{MB}} H_4 = K_M H_4$$

where K_M is a constant representing the ratio of the marginal and circulating neutrophils.

$$\frac{dN_T}{dt} = k_{bb}H_3 \sum_1^n N_{BM,j} + k_t H_2 N_{BM,n} - k_{int}\frac{K_M H_4}{1 + K_M H_4} N_T$$

$$H_j = 1 + \frac{S_{max,j} C_p}{SC_{50} + C_p} \qquad N_B = \frac{N_T}{1 + K_M H_4} \qquad N_T = N_B + N_M \qquad N_H = \sum_1^n N_{BM,j} + N_B + N_M$$

Results

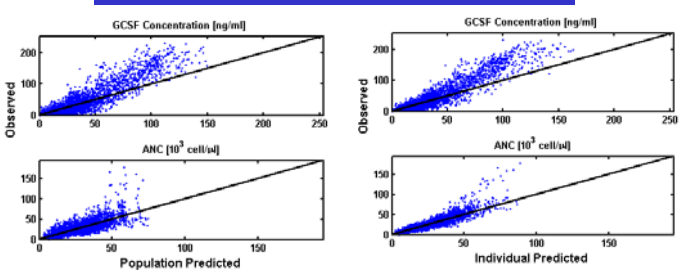

Fig. 2. Goodness of fit plots for G-CSF and ANC. The bold line is the identity line.

Parameter [units]	Estimate (%RSE)
	Fixed Effect
θ_T [-]	0.702 (5.6)
θ_{ka} [hr^{-1}]	0.293 (8.3)
θ_{el} [hr^{-1}]	0.121 (11.5)
θ_{VD} [L]	3.37 (5.1)
θ_{KD} [ng/ml]	1.63 (8.9)
θ_{inb} [hr^{-2}]	1.2 (15.3)
θ_{kdeg} [hr^{-2}]	$\theta k_{deg} = \theta k_{int}$
$\theta_{Bas0,0}$ [ng/ml]	1.65 (16.5)
$C_{p,0}$ [ng/ml]	Fixed to individual baseline
θ_{kint} [hr^{-2}]	0.198 (5.4%)
θ_{kbb} [hr^{-2}]	0.000502 (73.1)
θ_{kt} [hr^{-1}]	0.0187 (4.5)
$\theta_{N0,0}$ [10^{3}cells/μl]	3.16 Fixed[1]
θ_{SC50} [ng/ml]	3.9 (16)
$\theta_{Smax,1}$ [-]	75.7 (6.5%)

Parameter [units]	Estimate (%RSE)
	Fixed Effect
$\theta_{Smax,2}$ [-]	2.55 (62.4)
$\theta_{Smax,3}$ [-]	48.5 (64.1)
$\theta_{Smax,4}$ [-]	1.16 (13.5)
θk_{rem} [hr^{-1}]	0.099 (3.7)
$K_M \cdot H_{4,0}$	1.041 Fixed[2]
n	9 Fixed
θk_{rec} [hr^{-1}]	$\theta k_{rec} = \theta k_{rem}$
	Inter-Subject Variability
ω^2_{TD} [%]	20.5 (12.7%)
ω^2_{Nbs} [%]	32.6 (19.4%)
	Residual Variability
$\sigma_{add,Cp}$ [ng/ml]	0 Fixed
$\sigma^2_{prop,Cp}$ [%]	58.6 (7.2)
$\sigma_{add,ANC}$ [10^{3}cells/μl]	1.89 (14.2)
$\sigma^2_{prop,ANC}$ [%]	21.8 (9.5)

[1] Mean pretreatment neutrophil count calculated from subjects enrolled in this study.
[2] Based on data from 71 neutropenic patients [2].

Table 1. Summary of population PK/PD parameters, inter-subject and residual error variance estimates of filgrastim in healthy subjects following intravenous and subcutaneous administration.

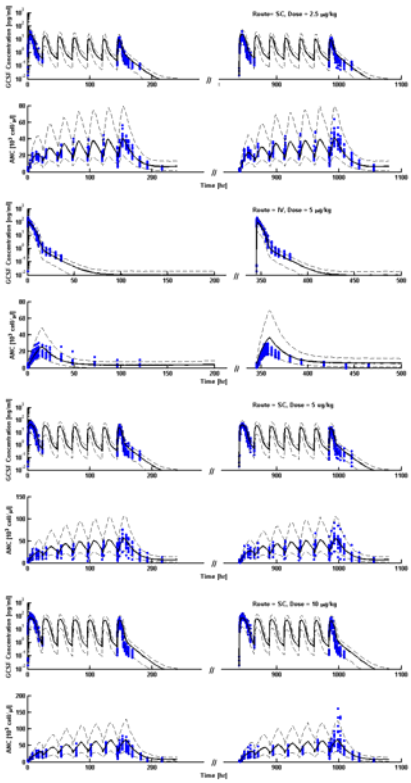

Fig. 3. The time courses of GCSF concentrations and neutrophil counts in blood. The drug was administered IV or SC at indicated doses. The visual predictive check plots were generated from Monte Carlo simulations (n = *1000*). The simulations are represented as – 50th percentile, -- 5th and 95th percentiles, ● observed responses.

Conclusions

•The presented model expanded previously published receptor mediated PK model for filgrastim [3].
•The increase in filgrastim clearance upon multiple dosing was attributed to the increase in ANC paralleled by an increase in the total G-CSF receptor density.
• Although the proposed PK/PD model accounts for receptor binding and a feedback of total neutrophils on the receptor production, systematic under predictions of G-CSF at high concentrations are present.
• Simultaneous modeling of filgrastim plasma concentrations and ANC was necessary to adequately describe PK data.

References

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[3] Wiczling P, Lowe P, Pigeolet E, Luedicke F, Balser S, Krzyzanski W, Population modeling of filgrastim pharmacokinetics in healthy adults following intravenous and subcutaneous administrations. AAPS Annual Meeting 2008.