T3213

NON-COMPARTMENTAL ANALYSIS VS. TARGET MEDIATED DRUG DISPOSITION MODELING: PREDICTIVE ACCURACY IN INTERSPECIES SCALING OF INTERFERON BETA-1A

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Background & Purpose

Predicting the pharmacokinetics (PK) of drugs in humans based on animal species is a mainstay of drug development. For therapeutic macromolecules (biologics), scaling of PK via the subcutaneous (SC) route is of particular interest due to the utility of SC dosing in the ambulatory setting. By and large, publications relating the prediction accuracy of interspecies scaling techniques for biologics focus on the intravenous route. However with a trend towards SC dosing, there is utility in techniques allowing for accurate prediction of human PK based on SC administration in the animal species.

Employing non-compartmental (NCA) methods, even when a relevant single-species is used, can result in poor prediction of PK parameters, particularly for volume of distribution (V). Employing population PK/PD approaches for estimating key parameters such as V (or V/F) and clearance (CL or CL/F) may improve the prediction accuracy when combined with single-species scaling (SSS) methods.

The purpose of this research was to test the hypothesis that PK/PD modeling of a single nonhuman primate species will improve the prediction accuracy of V/F and CL/F from a SC administered biologic (interferon beta-1a, IFNβ) compared to parameters derived by NCA. Fold-error (FE) within the range of 0.7-1.3 was considered as a reasonable prediction.

Methods

PK parameters were initially estimated by NCA for 4 rhesus monkeys administered a single SC of IFN 35 mg/kg. Scaling to human values was performed using SSS methods outlined in Table 1. FE was calculated by comparing the mean scaled values to mean observed NCA-derived PK following administration of a single 88 mcg SC dose to 128 healthy males and female participants.

Concentration data for both species were also fitted to an integrated target-mediated drug disposition (TMDD) PK/PD model based on previous work by Mager et. al. (2002, 2003) modified to account for different absorption profiles in the datasets for the two species (Figure 1). A population of 100 monkeys was simulated from the final model and scaled according to the SSS methods employed for the NCA approach. Prediction accuracy was calculated by taking the ratio of the mean scaled values from the simulated data and the mean of the empiric Bayes estimated values for the human model. CL/F was assumed to be the product of the V/F and the internalization rate constant (kint).

Figure 1: PK/PD Model Of IFNβ-1a and Neopterin Production Following a Single-dose Subcutaneous Injection in Humans and Rhesus Monkeys

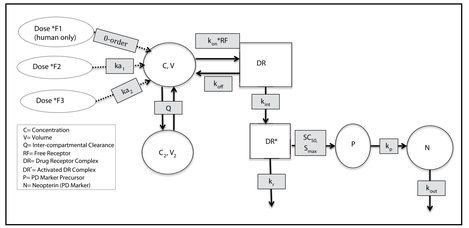


Table 1: Single Species Simplified Allometric Scaling Methods

Method	Formula	Notes
Simplified Allometry; Fixed Exponent	$\theta_{human}=\theta_{animal}*(Weight_{human}/Weight_{animal})^{b}$	b, allometric exponent; 0.75 to 1.10 with 0.05 increments
Kallynochron/Elementary Dedrick Plot	y-axis: concentration/(Dose/$Weight_{species}$) x-axis: Time/$Weight_{species}^{1-b}$	b, allometric exponent for CL
Liver Blood Flow (LBF)	$CL_{human}=CL_{animal}*(LBF_{human}/LBF_{animal})$	LBF_{human} = 20.7 mL/min/kg; LB_{rhesus} = 43.6 mL/min/kg;
Organ Blood Flow (OBF)	$CL_{human}=CL_{animal}*(OBF_{human}/OBF_{animal})$	Flow rates obtained from Davies 1993

Figure 2a: IFNβ-1a (Cobs) and Neopterin (Eobs) vs. IPRED Derived from the PK/PD Model in Rhesus Monkeys

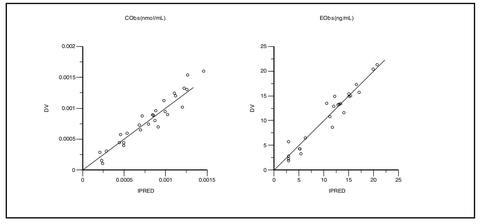


Figure 2b: IFNβ-1a (Cobs) and Neopterin (Eobs) vs. IPRED Derived from the PK/PD Model in Humans

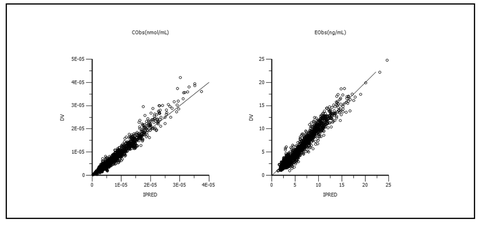


Figure 3a: Visual Predictive Check of IFNβ-1a and Neopterin Derived from the PK/PD Model in Rhesus Monkeys

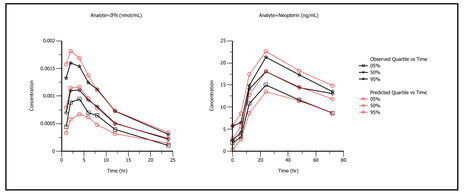


Figure 3b: Visual Predictive Check of IFNβ-1a and Neopterin Derived from the PK/PD Model in Humans

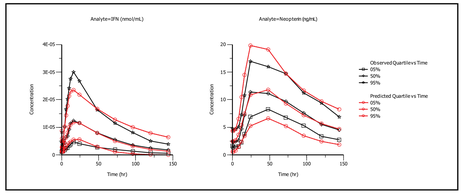


Table 2: PK/PD Model Parameter Estimates for IFNβ-1a in Rhesus Monkeys and Humans

Rhesus Monkey			
Parameter	Units	Estimate	CV%
V	mL	622.299	46.92
ka	hr-1	0.0103701	6.92
ka2	hr-1	0.670764	9.61
F		0.746212	10.83
tlag	hr	0.173572	4.39
kint	hr-1	1.26416	6.44
kon	nM-1hr-1	632.024	16.48
koff	hr-1	2.40613	9.59
Rmax	nmol	0.728996	5.91
E0	ng/mL	2.89033	12.53
kr	hr-1	0.425961	12.28
kp	hr-1	0.354536	18.00
kout	hr-1	0.0445191	12.68
Smax		22409.5	14.51
SC50	nmol	483.718	10.34

Humans				
Parameter	Units	Estimate	Bootstrap Mean	Bootstrap CV%
V	mL	11007.8	11101.68	1.841138
ka2	hr-1	0.132742	0.133728	1.170292
ka1	hr-1	0.035721	0.035606	1.257669
F1		0.104802	0.104385	0.897475
F2		0.478983	0.481287	1.06712
tlag1	hr	7.66037	7.692148	0.815569
tlag2	hr	2.9588	2.966992	0.951017
dur	hr	0.384184	0.387031	0.91941
V2	mL	115336	117209.1	2.093091
Q	mL/hr	856081	866224.2	1.921503
kon	nM-1hr-1	6462.79	6426.679	3.313204
koff	hr-1	1.35176	1.365677	1.58535
kint	hr-1	0.340042	0.341406	0.519179
Rmax	nmol	2.9817	3.055875	5.834202
E0	ng/mL	2.39087	2.392046	1.084665
kr	hr-1	0.179604	0.184455	8.885318
kp	hr-1	0.294925	0.292961	2.194236
kout	hr-1	0.28782	0.280314	7.351103
Smax		9.85576	10.48307	12.95145
SC50	nmol	0.393911	0.395951	1.438631

Results

Based on diagnostics plots (Figures 2a and 2b) including visual predictive check (Figures 3a and 3b), the model was demonstrated to fit both the PK and PD data for the respective species. Parameter estimates for the PK and PD parameters are presented in Table 2. In addition, Bootstrapped estimates and CV% are presented for the human model.

Results comparing prediction accuracy for CL/F and V/F for NCA vs. PK/PD modeling approaches employing the various SSS methods are presented in Tables 3 and 4. Whereas CL/F could be predicted employing NCA with a fixed exponent ranging from 0.85-1 V/F could not. In contrast, V/F was reasonably well predicted when derived from a PK/PD model and scaled employing a fixed exponent of 0.95-1. Scaling by liver blood flow did not result in predictions within 0.7-1.3 regardless of method employed for deriving the PK parameter estimates. When considering the blood flow to other organs, the results varied from 0.11-2.79 for PK/PD model derived CL/F and 0.34-1.25 for NCA derived CL/F. Scaling by kallynochrons (Figures 4a and 4b) demonstrated that normalized concentration curves do not exhibit the same profile shape.

Discussion

Scaling of biologics administered from the SC route has not been well described in literature and no single method has demonstrated reproducibility. NCA implies clearance from the central compartment which is violated with biologics cleared via TMDD. This data demonstrated that although CL/F may be scaled from NCA-derived data, V/F cannot be reasonably approximated and scaled. In contrast, fitting concentration data from monkeys administered IFNβ via the SC route could be scaled roughly according to body weight. More research is required to establish whether scaling to particular organ blood flow offers any advantages over fixed-exponent scaling. Scaling of SC administered biologics by Dedrick Plots appears of limited potentially due to sparse PK data derived from the animal species. However the shape of the profiles may be indicative of differences in the SC absorption processes between the two species.

Table 3: Single-species with Fixed Exponent Prediction Accuracy for Mean Parameters

		Fixed Exponent						
		0.75	0.80	0.85	0.90	0.95	1.00	1.05	1.10
Method	Parameter	Ratio							
PK/PD	CL/F	1.31	1.53	1.78	2.07	2.41	2.81	3.27	3.81
NCA	CL/F	0.64	0.74	0.86	1.00	1.17	1.36	1.58	1.83
PK/PD	V/F	0.50	0.58	0.67	0.78	0.91	1.06	1.24	1.44
NCA	V/F	0.09	0.11	0.12	0.14	0.17	0.19	0.23	0.26

Table 4: Single-species Scaling of CL/F by Organ Flow

	Method	
	PK/PD	NCA
Organ	Fold-Error	Fold-Error
Adipose	2.79	1.25
Brain	2.09	0.94
Cardiac Output	1.11	0.5
Gut	1.89	0.85
Heart	0.86	0.34
Hepatic Arterial	1.26	0.57
Kidneys	0.11	0.87
Liver Blood Flow	1.43	0.64
Muscle	1.79	0.81
Portal Vein	1.48	0.67
Skin	1.19	0.53
Spleen	0.79	0.36

Figure 4a: Representative Elementary Dedrick Plot with an Exponent for CL/F of 0.85 (NCA Data)

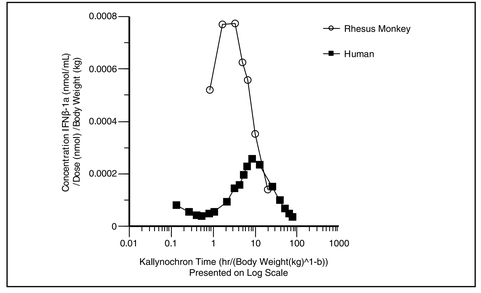
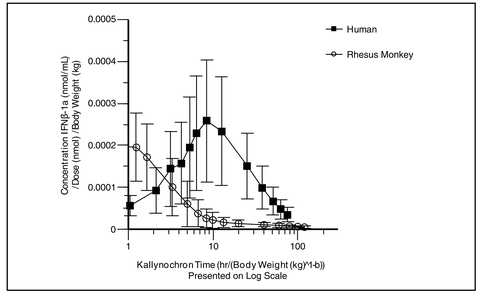


Figure 4b: Representative Elementary Dedrick Plot with an Exponent for CL/F of 0.85 (PK/PD Data)



Conclusion

PK/PD modeling of IFNβ to derive estimates of V/F in rhesus monkeys appears superior to NCA-derived values, when scaling SC administered drug to humans. No advantage for CL/F scaling was apparent. Additional investigation into the differences in SC absorption of biologics between monkeys and humans is warranted.