Population Pharmacokinetic Analysis of Trastuzumab (Herceptin) Following Long-Term Administration Using Different Regimens

Jean-Eric Charoin[1], Philippe Jacqmin[2], Ludger Banken[3], Sian Lennon[4] and Karin Jorga[1]

(1) Clin. Pharm., F. Hoffmann-La Roche Ltd., Basel; (2) Exprimo Consulting LLP ; (3) Biostatistics, F. Hoffmann-La Roche Ltd., Basel;
(4) Clin. Pharm., F. Hoffmann-La Roche Ltd, Welwyn

Objective

Trastuzumab (Herceptin) is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein.

The objectives of this population pharmacokinetic analysis were as follows :

- To build a basic (structural) population pharmacokinetic model for Trastuzumab and to estimate typical PK parameters in the target population.
- To assess the effect of covariates on the pharmacokinetics of Trastuzumab
- To assess the potential influence of regimen (once weekly vs. every three weeks) on the pharmacokinetics of Trastuzumab.

Material and Methods

- Four Phase II/III studies, median of observation duration was 116.7 days.
- Two regimens (IV infusion of 30 or 90 minutes):
  - Once weekly administration with loading dose of 4 mg/kg, maintenance dose of 2 mg/kg.
  - Every three weeks administration with loading dose of 8 mg/kg, maintenance dose of 6 mg/kg.
- Blood samples were taken at trough and peak with some full profiles. The median number of samples per patient was 10.
- Analytical method: Elisa with 0.15 µg/L as LOQ.
- 2508 exploitable concentrations from 194 patients.
- Non-linear mixed effects model approach using NONMEM (Version V).
- Age, body weight, Karnofsky performance score, number of metastatic sites, SGOT, SGPT, total bilirubin, alkaline phosphatase, creatinine clearance, HER2 overexpression and shed antigen (HER2 ECD) were investigated on CL and V1.
- Continuous covariates were modeled using the "multiplicative power model" centered around their median values, thus THETAs represent the PK estimate for the typical patient with median covariates.
- Categorical covariates were coded 0 or 1.
- A nominal p value of 0.005 (change in objective function, δ=7.9 for 1 degree of freedom) was used as statistically significant criteria in the covariates analysis.
- The magnitude of the effect of continuous covariates was estimated by computing the percent difference between expected parameters for extreme covariate values (i.e., the 5th and 95th percentiles) from the median value as follows:

$$\%\text{Change} = \left[\left(\frac{X_{5th\%}}{\text{med}(X)}\right)^{\theta} - 1\right] \cdot 100$$

where $X_{5th\%}$ is the 5th percentile of covariate X. A change of 20% was used as clinically significant criteria in the covariates analysis.

- Simulations were performed with Pharsight Trial Simulator (version 2.1.2).
- A bootstrap resampling technique (dataset replicated 800 times) was used to estimate confidence intervals for the parameters [1].

Results

- A two compartment linear PK model best described the data, ADVAN3 TRANS1, first-order method were used.
- Log-normal Inter-Patient Variability: $CL_j = TVCL * \exp(\eta_j CL)$.
- Residual Variability, modeled as exponential assuming a constant CV over the range of measured concentrations.
- Covariates analysis: after forward selection and backward deletion, covariates statistically significant were:

$$CL = 240 \cdot \left(\frac{SHED}{16.9}\right)^{-0.0538} \cdot \left(\frac{WT}{67}\right)^{0.526} \cdot \left(\frac{TBIL}{7.3}\right)^{0.0874} \cdot \left(\frac{ALKP}{118}\right)^{0.118}$$

$$V = 3150 \cdot \left(\frac{WT}{67}\right)^{0.394}$$

- Only the body weight effect on CL was considered as statistically significant and clinically relevant and therefore kept in the final population pharmacokinetic model (Table 1).
- The effect of regimen was tested on the final model. No regimen effect was found.

Table 1: Parameter Estimates of the Final Population Pharmacokinetic Model

PK Parameter	Point Estimate	CV (%)
CL (L/day)	0.226	3.8
V_1 (L)	3.17	2.6
K_{12} (day-1)	0.0828	18
K_{21} (day-1)	0.0486	19
WT on CL	0.562	25
ω_{CL} (%)	34	15
ω_{V1} (%)	24	28
ω_{K12} (%)	46	57
ω_{K21} (%)	84	28
σ (%)	20	8.5

Table 2: Bootstrap Results (800 datasets replicated)

	NONMEM		Bootstrap Simulation			
	Estimate	SE	Median	SE	5^{th} – 95^{th} Percentile	
CL (L/day)	0.226	0.008	0.227	0.008	0.212	0.242
V_1 (L)	3.17	0.08	3.17	0.08	3.05	3.32
K_{12} (day-1)	0.0828	0.0149	0.0847	0.0143	0.062	0.11
K_{21} (day-1)	0.0486	0.00938	0.0501	0.00933	0.0338	0.0646
WT on CL	0.562	0.14	0.567	0.148	0.313	0.805

Figure 1 : Goodness of Fit Plots

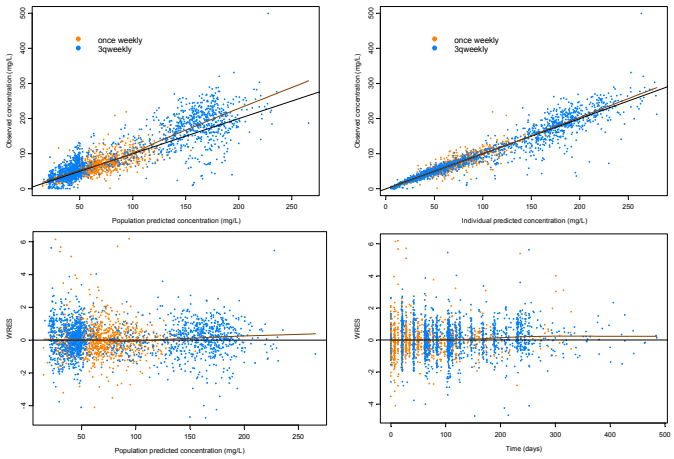

Figure 2: Examples of Individual Fitting

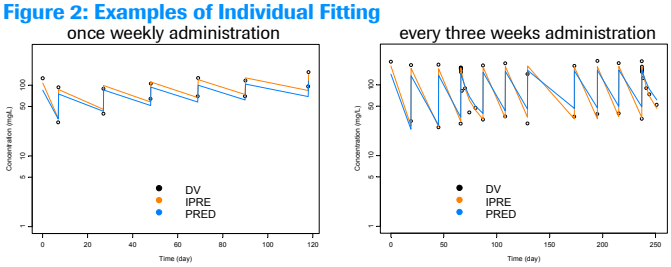

Figure 3: Body Weight Effect on CL

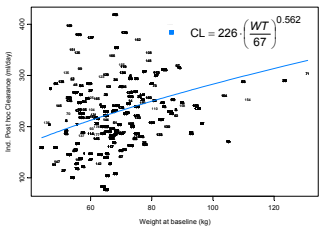

Figure 4: Simulated Trastuzumab Conc.

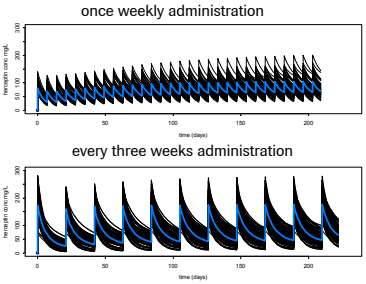

Table 3: Summary Statistics on Individual $AUC_{0\text{-}3wks}$, C_{max} and C_{min} Estimates

	Once Weekly Regimen		3qWeekly Regimen	
Steady-State Parameter	Median	5^{th}–95^{th} Percentiles	Median	5^{th}–95^{th} Percentiles
$AUC_{0\text{-}3wks}$ (mg·day/L)	1677	1225-2666	1793	959-2896
C_{max} (mg/L)	104	78.8-158	189	128-253
C_{min} (mg/L)	64.9	44.2-107	47.3	19.6-51.2

Discussion and Conclusion

- Trastuzumab concentrations can be predicted by a linear two-compartment pharmacokinetic model with a long half-life, typical of that of IgG immunoglobulins.
- The central volume of distribution (3.17L) corresponded to the typical human plasma volume which is characteristic of that of IgG immunoglobulin.
- PK parameter estimates were similar to the ones obtained in a previous population PK analysis performed by Genentech [2].
- The model performed well and the results of the bootstrap compare well with those from the model parameters and SEs.
- There was no effect of dosing regimen on the primary trastuzumab PK parameters such as CL and V.
- Based on the equilibrium half-life of 26.3 days, a three weekly regimen could be considered for this drug.
- Trastuzumab CL depended on body weight, which is consistent with the medical practice for this compound to adjust the dose on body weight.

References

[1] Ette EI.
Stability and performance of a population pharmacokinetic model.
J Clin Pharmacol 1997;37:486–95.

[2] Washington C.B., Lieberman G., Liu P., Fox J.A., Bruno R.
A population pharmacokinetic model for trastuzumab following weekly dosing.
Clin. Pharmacol. Ther., 71(2), P12 (abstract MPI-30), 2002.

Acknowledgement

The help of Per Olson (Exprimo Consulting LLP) with the Bootstrap technique is much appreciated.