Matuzumab - A Population Pharmacokinetic Model and its Evaluation

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Background and Objectives

Matuzumab is a humanised recombinant monoclonal antibody (mAb) of the immunoglobulin subclass IgG1 which targets the epidermal growth factor receptor (EGFR) and competitively blocks the binding of its natural ligands such as EGF and TGF-α. EGFR is expressed in a variety of tumour entities (e.g. colon, mamma and bronchial carcinoma) and is often accompanied by poor prognosis [1]. Matuzumab has shown favourable activity against different EGFR-expressing tumours in several phase I and II studies [2]. The overall aim of this population analysis was to develop a pharmacokinetic (PK) model including the identification of covariates which could explain the variability of the pharmacokinetic parameters and to evaluate the performance of the model by various techniques.

Subjects and Methods

Study characteristics

The development dataset (DD) included 90 and the evaluation dataset (ED) 81 patients from three open-label, non-randomized, uncontrolled, multi-centre phase I studies each (Tab. 1). A total number of 1256 serum mAb concentrations was available for model development and 1124 for model evaluation, respectively. In all studies the patients had different types of advanced carcinoma, mainly colon, rectum and pancreatic cancer. They received matuzumab as multiple 1 h iv infusions in a wide range of dosing regimens (DD: from 400 mg every three weeks to 2000 mg in the first week followed by 1600 mg weekly; ED: from 100 mg weekly to 800 mg weekly).

Tab. 1: Demographic statistics of the DD (study 1-3) and the ED (study 4-6)

		Study 1	Study 2	Study 3	Total	Missings (**) (Study 1-3)	Study 4	Study 5	Study 6	Total	Missings (Study 4-6)
number		17	51	22	**90**	-	35	21	25	**81**	-
	(male/female)	(9/8)	(33/18)	(11/11)	(53/37)		(23/12)	(16/5)	(17/8)	(56/25)	
age (years)	median	65	57	58	**60**	0	61	59	59	**60**	0
	(min.-max.)	(40-82)	(29-78)	(30-71)	(29-82)		(47-79)	(51-77)	(29-71)	(29-79)	
height (cm)	median	168	169	170	**169**	3	172	173	176	**173**	0
	(min.-max.)	(156-183)	(143-198)	(150-184)	(143-198)		(159-184)	(158-184)	(159-193)	(158-193)	
weight (kg)	median	68	71	72	**71**	3	67	69	80	**69**	0
	(min.-max.)	(48-81)	(46.5-125)	(44-98)	(44-125)		(43-101)	(48-101)	(55-120)	(43-120)	
body mass index (kg/m²)	median	24.7	25.8	24.3	**24.9**	4	24.7	23.1	24.4	**23.8**	0
	(min.-max.)	(17-30.7)	(20.1-37)	(15.9-33.9)	(15.9-37)		(16.2-32.6)	(19.2-30.9)	(19-32.2)	(16.2-32.6)	
body surface area (m²)	median	1.77	1.82	1.85	**1.82**	4	1.79	1.85	1.95	**1.85**	0
	(min.-max.)	(1.51-2.01)	(1.34-2.59)	(1.44-2.16)	(1.34-2.59)		(1.43-2.17)	(1.46-2.21)	(1.56-2.5)	(1.43-2.5)	
fat-free mass (kg*)	median	51.5	53.2	49.7	**52.7**	4	52.1	55.8	58.9	**54.5**	0
	(min.-max.)	(34.4-62.5)	(30.1-85.4)	(31.7-68.4)	(30.1-85.4)		(31.6-68.2)	(33.0-70.2)	(36.4-81.6)	(31.6-81.6)	

(*) calculated as: male: (9.27 x 10^3 x weight)/(6.68 x 10^3 + 216 x body mass index); female: (9.27 x 10^3 x weight)/(8.78 x 10^3 + 244 x body mass index)
(**) Missing values in the individual dataset were replaced by the median value of the population.

Pharmacokinetic data analysis

The structural model was developed in a stepwise manner. Covariates were investigated by forward inclusion (p=0.05) and backward deletion (p=0.001) techniques. All analyses were performed using the software NONMEM, version V, level 1.1; ADVAN6 TRANS1 TOL5 subroutine with FOCE INTERACTION.

Model development

Serum concentration-time profiles were best described by a two compartment model. Within this model in addition to the linear clearance (CLL) a non-linear process (Michaelis-Menten kinetics, CLNL) from the central compartment was included with the additional parameters Vmax and km [Fig. 1].

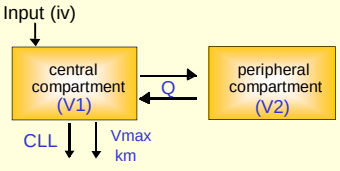


Fig. 1: Schematic structural model

Interindividual variability (IIV) was estimated for CLL, both distribution volumes (V1, V2) and Vmax using an exponential random-effects model. Residual variability was modelled using a combined error model. Additionally, interoccasion variability as random variation of CLL between different administrations within one subject could be implemented.

Covariate analysis and parameter estimates for DD and ED

The following covariates showed a significant influence and were after investigating the relevance included into the model:
- Influence of weight on V1
- Influence of weight on CLL

All estimates (DD and ED) with their relative standard errors (RSE) are shown in Tab. 3. The estimates for the ED revealed no support for the covariate weight on V1 and a high impressision for IIV on V2. In Fig. 2 goodness of fit plots are presented. The population model for the ED showed an underprediction of high observed concentrations while the individual model described them adequately.

Tab. 3: Parameter estimates (development and evaluation dataset)

Model Parameter	Unit	Development dataset Parameter estimate	RSE [a], %	Evaluation dataset Parameter estimate	RSE [a], %
Fixed effects					
CLL	[mL/h]	14.5	4.1	11.6	10.3
V1	[L]	3.72	3.0	3.89	6.3
Q	[mL/h]	38,3	7.6	21.0	12.6
V2	[L]	1.84	9.0	2.72	15.0
Vmax	[mg/h]	0.456	13.7	0.584	20.9
km	[mg/L]	4.0	29.8	6.1	37.6
Covariate influence					
V1_WT [1]		0.0044	35.2	0.0001	3390.0
CLL_WT [2]		0.0087	28.2	0.0103	50.6
Random effects					
Interindividual variability					
ω CLL	[%CV]	24.0	20.5	31.6	50.5
ω V1	[%CV]	21.9	20.3	40.4	28.3
ω V2	[%CV]	61.6	27.6	31.2	96.3
ω Vmax	[%CV]	53.8	38.1	57.1	46.6
Correlation V1_V2		0.777	29.8	0.977	48.5
Correlation V2_Vmax		0.875	31.6	0.530	101.5
Correlation V1_Vmax		0.875	28.4	0.707	45.5
Inter-occasion variability					
π CLL	[%CV]	22.8	12.6	55.3	21.5
Residual error					
σ proportional	[%CV]	13.4	1.5	18.9	2.6
σ additive	[mg/L]	0.312 (fixed)	-	0.312 (fixed)	-

[a] relative standard error (standard error divided by population estimate*100; for the random effects parameters RSE is related to the corresponding variance scale)

[1] $V1_{WT\ individual} = V1 * [1 + V1\_WT * (WT\text{-}WT_{median})] * EXP(\eta V1)$ [2] $CLL\_WT_{individual} = CLL * [1 + CLL\_WT * (WT\text{-}WT_{median})] * EXP(\eta CLL + \kappa CLL)$

Results

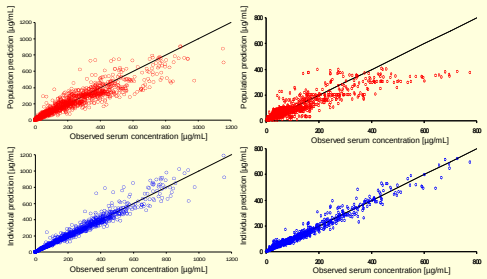
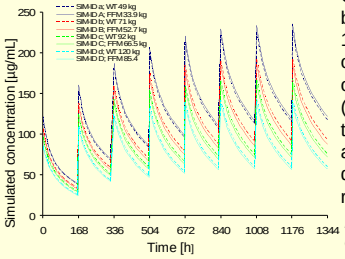


Fig. 2: Goodness of fit plots of the development (left panel) and the evaluation dataset (right panel); population (red) and indivi-dual (blue) predicted concentrations, respectively, versus observed serum concentrations

Simulation of the covariate influence

To assess the impact of the covariate "weight" on the concentration-time profile, simulations were performed (Fig. 3). Four patients representing the 5th, 50th, 95th and 100th weight percentile of the study population (49, 71, 92 and 125 kg, respectively) were simulated (SIM-ID a-d). All patients were to receive a dosing regimen of 400 mg every week.



Comparing the maximum concentrations between the 49 kg and the i) 92 kg and ii) 125 kg patient, a 26% and 38% decrease of the steady-state concentration was observed. Further analyses have to relate (steady-state) serum mAb concentrations to its pharmacodynamics (PD) in order to assess the clinical relevance and to decide if weight-adjusted dosing regimens are necessary.

Fig. 3: Simulation of the influence of mass on the concentration-time profile

For drugs with limited distribution the use of lean body weight and accordingly fat-free mass (FFM) for dose adjustment has been recommended [3]. Thus the covariate "weight" was replaced by FFM. The exchange showed similar simulated concentration-time profiles (compare Fig. 3, SIM-ID A-D and SIM-ID a-d).

Fig. 4 reflects the difference of the concentration-time profile of the lowest or the highest dosing regimens from the DD studies by simulation of one "median-weight" patient (71 kg). ID X does not reach steady state conditions while the minimal steady state concentration of ID Y is ~ 470 µg/mL.

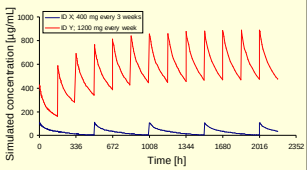


Fig. 4: Simulation of the lowest and the highest dosing regimen of DD

Visual Predictive Check

Visual Predictive Checks (VPC) after the first administration of different matuzumab doses were performed. Fig. 5 showed that the observed concentrations were well described by the DD model as the 95% confidence interval included most of the concentration data points.

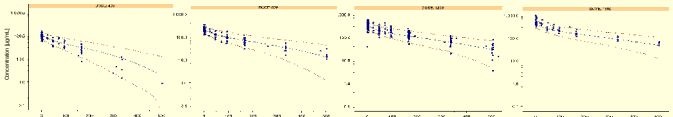


Fig. 5: VPCs after first administration of 400, 800, 1200 and 1600 mg matuzumab

Conclusion:

A population PK model for matuzumab including non-linear PK processes was successfully developed, covariates were identified and incorporated and first results of evaluation are presented. As next steps the model will further be evaluated by bootstrap and case deletion techniques and further implementation of PD and *in vitro* data will be investigated. When correlated to PD or efficacy data the final model could serve as a tool to guide selection of optimal dose regimens for matuzumab, a highly promising „targeted" cancer therapy.

Ref.: [1] Dassonville O. et al., J Clin Oncol., 11: 1873-1878, 1993; [2] Vanhoefer U. et al., J Clin Oncol., 22: 175-184, 2004; [3] Janmahasatian S. et al., Clin Pharmacokinet, 44: 1051-1065, 2005