Population Pharmacokinetic Analysis for Matuzumab (EMD 72000) – A Humanised EGFR-Targeted Monoclonal Antibody

Kuester, K.[1], Kovar, A .[2], Brockhaus, B.[2], Kloft, C .[1,3]

[1]Dept. Clinical Pharmacy, Institute of Pharmacy, Freie Universitaet Berlin (kkuester@zedat.fu-berlin.de)
[2]Dept. Clinical Pharmacokinetics&Pharmacology, Merck KGaA, Darmstadt
[3]Dept. Clinical Pharmacy, Faculty of Pharmacy, Martin-Luther-Universitaet Halle-Wittenberg, Wolfgang-Langenbeck-Str. 4, D-06120 Halle

Background and Objectives

Matuzumab, a humanised recombinant monoclonal antibody (mAb) of the immunoglobulin subclass IgG1 (κ-chain), targets the epidermal growth factor receptor (EGFR). It specifically binds to the receptor and competitively inhibits 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 efficacy in several phase I and II studies within treatment of different EGFR-expressing tumours [2]. Regarding the pharmacokinetics of matuzumab a non-linear behaviour could be assumed from previous investigations. The overall aim of this population analysis was to develop a pharmacokinetic (PK) model comprehensively characterising the pharmacokinetics of this mAb and to identify covariates which could explain the variability of the pharmacokinetic parameters.

Subjects and Methods

Study characteristics

Serum concentration-time profiles of 90 patients from three phase I studies with 11 different dose regimens where chosen consisting of 1256 concentrations [Tab.1].

Table 1: Study characteristics. Matuzumab was given as multiple 1 h iv infusions ranging from 400 to 2000 mg, q1w-q3w

Study	Tumour Entity	Dose Regimen	No. of Subjects
1	advanced pancreatic cancer	400 mg q1w, 800 mg q2w, 800 mg q1w	17
2	various advanced cancer (mainly colon/ rectum cancer)	1200 mg q1w, q2w and q3w, 400 mg q3w, 800 mg q3w, 1600 mg q3w	51
3	various advanced cancer (mainly colon/ rectum cancer)	400 mg q1w, 800 mg q1w, 1200 mg q1w, 1600 mg q1w, 2000 mg q1w (from week2: 1600 mg)	22

Demographics

Demographic data of the three investigated studies are shown in Tab. 2. Additionally, the number of missing values are reported.

Table 2: Demographic data of the population with number or median and range

		Study 1	Study 2	Study 3	**Total**	Missings
number	(male/female)	17 (9/8)	51 (33/18)	22 (11/11)	**90** (53/37)	-
age (years)	median (min.-max.)	65 (40-82)	57 (29-78)	58 (30-71)	**60** (29-82)	0
height (cm)	median (min.-max.)	168 (156-183)	169 (143-198)	170 (150-184)	**169** (143-198)	3
weight (kg)	median (min.-max.)	68 (48-81)	71 (46.5-125)	72 (44-98)	**71** (44-125)	3
body mass index (kg/m^2)	median (min.-max.)	24.7 (17-30.7)	25.8 (20.1-37)	24.3 (15.9-33.9)	**24.9** (15.9-37)	4
body surface area (m^2)	median (min.-max.)	1.77 (1.51-2.01)	1.82 (1.34-2.59)	1.85 (1.44-2.16)	**1.82** (1.34-2.59)	4

Results

Pharmacokinetic data analysis

The structural model was developed in a stepwise manner, starting with a one-compartment model. All analyses were performed using the software NONMEM, version V, level 1.1; ADVAN6 TRANS1 TOL5 subroutine and the FOCE INTERACTION estimation method was applied.

Base Model

Serum concentration-time profiles were best described by a two compartment model. Within this model in addition to the linear clearance (CLL) a second elimination pathway as a non-linear process (Michaelis-Menten kinetics, CLNL) from the central compartment was included with the additional parameters Vmax and km [Fig. 1]. During the model finding process implementation of CLNL from only the peripheral compartment or from both compartments (Fig. 1 Vmax and km green coloured) did not result in an improvement of the model. Total clearance as the sum of CLL and CLNL [Tab. 3] was in the expected range for mAbs. The dependence of total CL on the concentration of the mAb is presented in Fig. 2. Due to the non-linearity the half-lives ranged between 1.35 d and 10.5 d at concentrations of 0.02 and 1000 µg/mL, respectively.

Interindividual variability was estimated for CLL, V1, V2 and Vmax using an exponential random effects model. Residual variability was modelled using a combined error model. Additionally, between-occasion variability (BOV) as random variation of CLL between the different administrations within one subject could be implemented. All estimates with their relative standard errors are shown in Tab. 3.

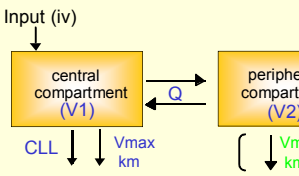

Figure 1: Schematic base model

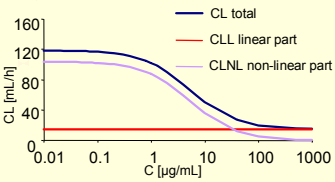

Figure 2: Dependence of total CL on concentration (C) of the mAb

Table 3: Parameter estimates of PK model based on the development dataset

Model Parameter	Unit	Estimate		Relative Standard Error, %
CLL	[mL/h]	14.6		7.1
V1	[L]	3.73		2.5
Q	[mL/h]	36.2		17.7
V2	[L]	1.8		8.6
Vmax	[mg/h]	0.552	CLNL=	17.7
km	[mg/L]	5.3	104.2 mL/h	27.0
Stochastic Submodel				
ω CLL	[%CV]	31.9		42.7 *
ω V1	[%CV]	24.4		17.9 *
ω V2	[%CV]	59.8		33.3 *
ω Vmax	[%CV]	48.3		49.4 *
π CLL	[%CV]	22.6		37.1 *
σ proportional	[%CV]	13.3		5.8
σ additive	[mg/L]	0.312 FIX		-

* based on the variance scale estimate

Model development of BOV

The inclusion of BOV was limited to 8 infusions due to insufficient data later-on and implemented by different ways of assigning the 8 infusions to a varying number of occasions:

- BOV on CLL; infusion 1 and infusions 2-7 (2 occasions)
- BOV on CLL; every 8 infusions corresponded to one occasion (8 occasions)
- BOV on CLL; infusions 1-3 and infusions 4-8 (2 occasions)
- BOV on V1 (different occasion duration for each dose regimen depending on data rich time points)

The currently best result (lowest objective function, smallest relative standard errors, Fig. 3) was achieved with BOV on CLL where every infusion corresponded to one occasion; in Fig. 4 the individual κ_i of CLL from this model are shown with their distribution around zero.

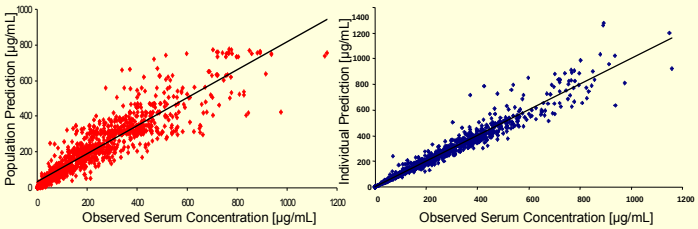

Figure 3: Goodness of fit plots; population (left panel) and individual (right panel), respectively, versus observed serum concentrations

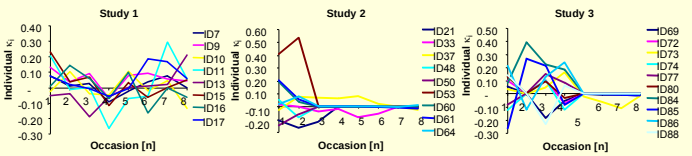

Figure 4: Individual κ_i of CLL at the 8 different occasions separated by studies

Conclusion:

A base structural population PK model including non-linear PK processes for matuzumab has successfully been developed describing the serum concentration-time profiles. Population parameters were precisely estimated and corresponded well to the known PK behaviour of mAbs.

As next steps, the influence of covariates as well as implementation of PD and *in vitro* data will be evaluated.

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.

References: [1] Dassonville O. et al., J Clin Oncol., 11, 1873-1878, 1993
[2] Vanhoefer U. et al., J Clin Oncol., 22, 175-184, 2004