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POPULATION PHARMACOKINETICS OF RITUXIMAB IN RA PATIENTS: COMBINING TWO PHASE II STUDIES

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INTRODUCTION

- Rituximab, a B cell-specific, CD20-targeted therapeutic monoclonal antibody, is approved for the treatment of relapsed refractory, low-grade and follicular CD20+ B cell non-Hodgkin's lymphoma (NHL) using a body surface area (BSA)-adjusted dosing regimen. However, a fixed-dose regimen of rituximab, in combination with a short course of glucocorticoids (GC), is being explored as a novel approach to treating rheumatoid arthritis (RA).
- In patients with active RA despite methotrexate (MTX) treatment, a single course of two infusions of rituximab (either alone or in combination with cyclophosphamide [CTX]) or continued MTX has been shown to improve disease symptoms significantly at 24 and 48 weeks post-treatment.[1]
- The population pharmacokinetics (POP PK) of rituximab in RA have been explored in two Phase II studies (IIa and IIb). The Phase IIa[2] study included a smaller sample of patients than the Phase IIb study but this group was assessed more frequently. One dose level was explored in the Phase IIa study, whereas two dose levels were explored in the Phase IIb study.

OBJECTIVES

- To explore the POP PK of rituximab using data from two Phase II studies in patients with RA.
- To investigate if a number of variables had an effect on the pharmacokinetics of rituximab; in particular, the potential effect of rituximab dose, and concomitant use of GC on rituximab pharmacokinetics.

METHODS

Study population

- A total of 3196 serum rituximab concentrations from 423 patients were used in the POP PK analysis.
- The effects of the following covariates on the POP PK of rituximab were explored: age (AGE), gender (SEX), race (RACE), geographical region (RGO), body surface area (BSA), prior use of anti-tumour necrosis factor (TNF)-α therapy (TNF), use of GC (CORT), dose of rituximab (DOS) and duration of RA disease (DUR).
- **Phase IIa study:** A total of 1002 serum rituximab concentrations from 107 patients with RA were included in the analysis. Patients were randomised to receive one of the following three treatment regimens:
  - Rituximab monotherapy (1000 mg intravenous (IV) on Days 1 and 15)
  - Rituximab (1000 mg IV on Days 1 and 15) plus oral CTX (750 mg on Days 3 and 17)
  - Rituximab (1000 mg IV on Days 1 and 15) plus oral MTX (>10 mg/week).
- All patients in the Phase IIa study received methylprednisolone 100 mg IV (Days 1, 3, 15 and 17), oral prednisone 60 mg (Days 2 and 4–7) and oral prednisone 30 mg (Days 8–14).
- **Phase IIb study:** A total of 2194 serum rituximab concentrations from 316 patients with RA were included in the analysis. Patients were randomised to nine treatment arms as presented in Table 1.

Table 1. Patient randomisation in the Phase IIb study

	GC regimen component		
Rituximab regimen component[a]	Placebo	IV GC[b]	IV + PO GC[c]
Placebo	Group A	Group B	Group C
2 x 500 mg[c]	Group D	Group E	Group F
2 x 1000 mg[c]	Group G	Group H	Group I

[a]Rituximab infusions were administered on Days 1 and 15. [b]Methylprednisolone 100 mg IV on Days 1 and 15. [c]Methylprednisolone 100 mg IV on Days 1 and 15 plus oral prednisone (60 mg/day on Days 2–7 and 30 mg on Days 8–14). GC = glucocorticoid; IV = intravenous; PO = per os (oral).

Data analysis

- A POP PK model was simultaneously fitted to the combined data from the two Phase II studies using the FO method of NONMEM V.[3]
- One- and two-distribution compartmental linear PK models with a zero-order IV infusion were fitted to the data.
- The interindividual variability in the PK parameters was modelled generically:

$$P_{jk} = \hat{P}_k * \exp(\eta_{jk})$$

where j is to identify individuals, P_{jk} is the PK parameter value ($k = CL, V1$) for the jth subject, $\hat{P}_k$ is the (population) expected value of the parameter, and η_{jk} is an individual random effect parameter. The random individual vectors $\eta j = (\eta_{jCL}, \eta_{jV1})$ are assumed independent, with a normal distribution, a mean of zero and a variance ω^2.

- The residual variability was modelled with a proportional and additive error:

$$C_{jt} = \hat{C}_{jt} + \hat{C}_{jt}\,\varepsilon_{jt}^{prop} + \varepsilon_{jt}^{add}$$

where C_{jt} is the measured serum drug concentration at time t in individual j, $\hat{C}_{jt}$ is its prediction under the PK model, and the additive and proportional errors, ε_{jt}^{prop} and ε_{jt}^{add}, are assumed to be independent and randomly distributed with a mean of zero and variances of σ^2_{add} and σ^2_{prop}.

- Potential influence of the covariates on the clearance (CL) and the central compartment volume of distribution (Vc) was evaluated. A multiplicative covariate regression model was implemented as follows:

$$\hat{P}_k = \theta_1 \left(\frac{X_j}{med\,(X)}\right)^{\theta_X} (1 + D_j * \theta_D)\,(1 + IND_j * \theta_c)$$

where $\hat{P}_k$ is the (population) expected value of the parameter, and θ_X, θ_D and θ_C are the regression coefficients to be estimated for continuous (X_j, eg BSA), dichotomous (D_j, eg SEX) or categorical (IND_j, eg RACE) covariates. θ_1 represents the parameter estimate for a typical subject with median covariates.
  - Continuous covariates (X_j) were centred on their median ($med(X)$) values.
  - Dichotomous (D_j) covariates were coded 0 or 1 (eg SEX = 0 for female, SEX = 1 for male).
  - For categorical covariates, IND_j is an indicator variable that has a value of 1 or 0 depending on the value of the categorical covariate.
- The log likelihood test ($p<0.005$) was used as the model selection criteria.

Model validation

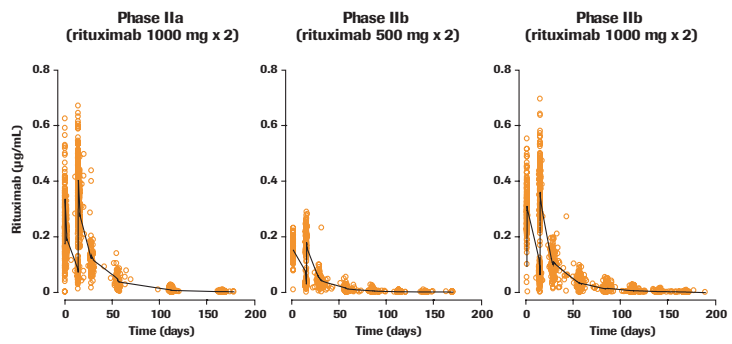
- A bootstrap re-sampling procedure was used to validate the model's stability and to estimate the 95% confidence intervals (CIs). The model was repeatedly fitted to bootstrap replicates of the data set. To avoid unbalanced bootstrap data sets, the data were stratified using the study design. Subsequently, the parameter estimates for each data set were obtained and the mean and 2.5th and 97.5th percentiles (denoting the 95% CI) of the results from 500 successful runs were reported.

RESULTS

Base model: serum PK of rituximab

- Serum concentration versus time plots of the data used in this analysis are presented in Figure 1.

Figure 1. Serum rituximab concentration versus time plots of data from all patients.



The mean serum rituximab concentrations are indicated by a black line.

- A two-compartment model could not be fitted to the data from the Phase IIb study alone.
- The fit of a two-compartment model was markedly better than that of a one-compartment model for the combined data from the two studies.
- A three-compartment model did not improve the model fit compared with a two-compartment model.
- CL and Vc estimated using the combined data set were similar to the estimates from the Phase IIa data alone (291 mL/day and 3000 mL, for CL and Vc, respectively).[2]

Final model: influence of covariates on rituximab PK

- The patient demographics in the different covariate categories for each study are given in Table 2.

Table 2. Patient demographics in each covariate category in the Phase IIa and Phase IIb studies

Parameter	Covariate score	Phase IIa	Phase IIb
Median (range) age (years)	–	55 (26–76)	52 (18–80)
Median (range) body surface area (m^2)	–	1.72 (1.41–2.35)	1.75 (1.3–2.96)
Median (range) duration of RA disease (years)	–	NA	8.7 (0.6–52)
Gender, n (%)	0=female	85 (79)	256 (81)
	1=male	22 (21)	60 (19)
Race, n (%)	0=Caucasian	107 (100)	254 (80)
	1=Hispanic	0 (0)	46 (14.5)
	2=African American	0 (0)	11 (3.5)
	3=other	0 (0)	5 (1.6)
Geographical region, n (%)	1=non-US	107 (100)	210 (66)
	2=US	0 (0)	106 (33)
Previous use of anti-TNF-α drugs, n (%)	0=no	107 (100)	221 (70)
	1=yes	0 (0)	95 (30)
GC use, n (%)	1=no GC	0 (0)	106 (33)
	2=IV GC	0 (0)	103 (32)
	3=IV GC + oral GC	107 (100)	107 (34)
Rituximab dose, n (%)	1=500 mg x 2	0 (0)	124 (40)
	2=1000 mg x 2	107 (100)	192 (60)

RA = rheumatoid arthritis; TNF = tumour necrosis factor; GC = glucocorticoid; IV = intravenous; NA = not available.

- Including the covariates BSA, gender, oral GC and rituximab dose on CL, and BSA and gender on Vc, significantly improved ($p<0.005$) the fit of the model to the data using the log likelihood test.
- The final covariate model explained approximately 28.2% of the interindividual variance for CL and 45.9% of the interindividual variance for Vc.
- Male patients had faster CL and a larger Vc compared with female patients. The coefficient explaining the effect of BSA on CL and Vc was close to 1, indicating a proportional increase in log(CL) and log(Vc) with BSA. Concomitant administration of high-dose GC (oral and IV) reduced the CL of rituximab by 12% for a typical patient compared with no GC or only IV GC.
- Rituximab dose did not have a significant effect on Vc, but did appear to affect the CL (detected by the log likelihood ratio test). However, a zero effect was observed within the bootstrap analysis 95% CIs for CL. Therefore, it was concluded that rituximab dose does not have a significant effect on the CL.
- Other covariates that were explored (age, race, prior use of anti-TNF-α drugs, duration of RA disease and the geographical region) did not show a significant effect on patients' CL or Vc.
- The effect of the covariates gender, BSA, GC use and rituximab dose on rituximab CL are presented in Figure 2.
- The equations that describe the final model of the typical values of the CL and Vc are shown below:

$$CL = \theta_{CL} \times \left(\frac{BSA}{1.72}\right)^{\theta_{BSA_CL}} \times (1 + \theta_{SEX_CL} * SEX) \times (1 + \theta_{CORT_CL} * CORT) \times (1 + \theta_{DOS_CL} * DOS)$$

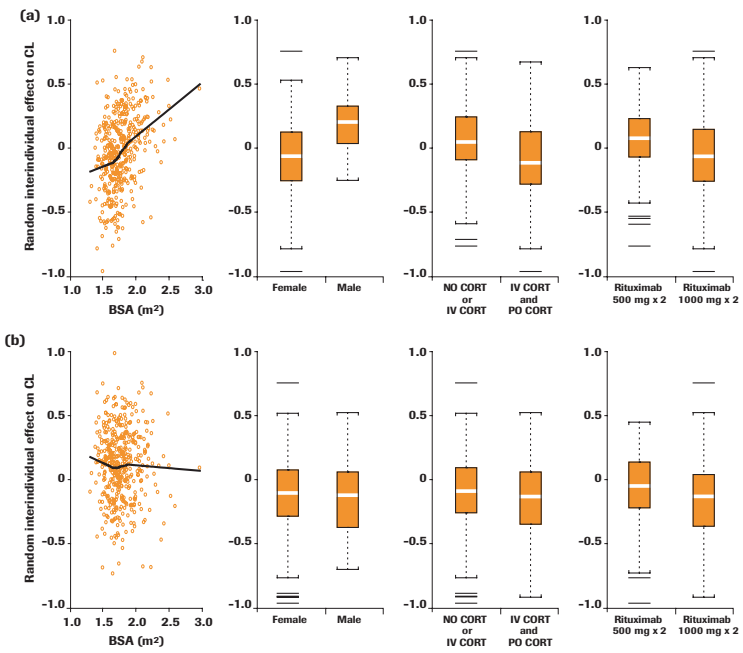
$$Vc = \theta_{Vc} \times \left(\frac{BSA}{1.72}\right)^{\theta_{BSA_Vc}} \times (1 + \theta_{SEX_Vc} * SEX)$$

- Goodness of fit plots of the final model are presented in Figure 3.
- The final parameter estimates of the model fitted to the combined data, compared with the model fitted to data from the Phase IIa study alone, and the CIs calculated from the bootstrap analyses, are presented in Table 3.

Model evaluation

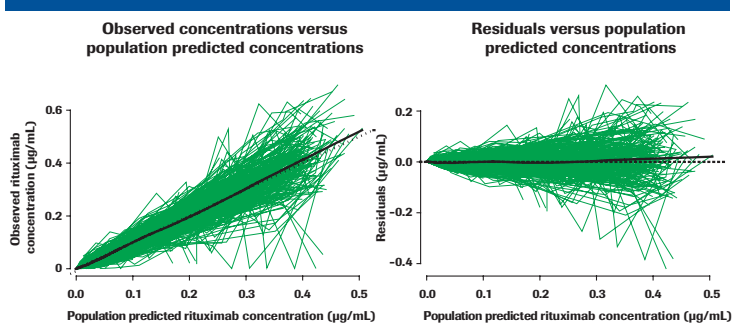
- From the original data set, 550 replicate data sets were generated and used for the evaluation of the stability of the final model. NONMEM failed to achieve successful convergences in 36 (6.5%) data sets, indicating that the model was stable.

Figure 2. The effect of the covariates BSA, gender, glucocorticoid therapy and rituximab dose on the random interindividual variability for CL of rituximab: (a) base model, (b) final model.



CORT = use of glucocorticoids.

Figure 3. Goodness of fit plots for the final model.



Green lines connect individuals. The solid black line is a non-parametric smooth of all individuals. On the left panel, the black dashed line is the line of identity. On the right panel, the black dashed line is at the ordinate of zero.

Table 3. Comparison of the model-derived parameter estimates for rituximab, determined from the Phase IIa study and the combined data set

Parameter	Phase IIa (% CV)[1]	Phase IIa + Phase IIb (% CV)	500 bootstrap replicates[a]	
			Mean	95% CI
Structural model				
CL (mL/day)	276 (3.4)	291 (4.1)	293	270 to 323
Vc (mL)	2980 (2.1)	3000 (1.1)	3000	2937 to 3073
k_{12} (day^{-1})	0.22 (6.5)	0.23 (7.0)	0.229	0.2 to 0.29
k_{21} (day^{-1})	0.18 (4.2)	0.17 (4.7)	0.17	0.15 to 0.19
Interindividual variability				
IIV CL (%)	28.2 (14.5)	30.5 (8.3)	30.4	28 to 32
IIV Vc (%)	12.3 (11.5)	14.2 (11.0)	14.1	12.6 to 15.7
Correlation between IIV CL and IIV Vc (%)	–	42 (18.8)	42	35 to 49
Covariate model				
SEX on CL (θ_{SEX_CL})	0.39 (28.2)	0.33 (16.4)	0.33	0.22 to 0.45
SEX on Vc (θ_{SEX_Vc})	0.17 (26.5)	0.15 (17.6)	0.15	0.1 to 0.19
BSA on CL (θ_{BSA_CL})	1.02 (27.2)	0.91 (15.7)	0.91	0.6 to 1.17
BSA on Vc (θ_{BSA_Vc})	0.73 (20.0)	0.96 (8.0)	0.96	0.8 to 1.1
CORT on CL (θ_{CORT_CL})	–	-0.12 (30.6)	-0.12	-0.19 to -0.04
DOS on CL (θ_{DOS_CL})	–	-0.06 (85.1)	-0.06	-0.16 to 0.03
Residual variability				
Proportional error (%)	19 (11.5)	17.8 (6.7)	17.8	0.16 to 0.19
Additive error (mg/mL)	5.4×10^{-4} (25.4)	4.3×10^{-4} (30)	4.2×10^{-4}	3.2×10^{-4} to 5.5×10^{-4}

BSA = body surface area; CI = confidence interval; CL = clearance; Vc = central compartment volume of distribution; IIV = interindividual variability; SEX = gender; CORT = use of glucocorticoids; DOS = dose of rituximab; % CV = percentage coefficient of variance; k_{12}, k_{21} = compartmental micro rate constants.

[a]The mean and 95 percentile CI ranges from 514 successful replicates (out of 550 bootstrap data sets).

CONCLUSIONS

- PK parameters for rituximab from the POP PK analysis of the combined data set did not differ from those published for the Phase IIa study alone.
- The effects of BSA and gender on the CL and Vc of rituximab were confirmed.
- Concomitant administration of high-dose GC decreased rituximab clearance by 12%; this effect will be confirmed in future analyses.
- Rituximab dose was considered not to have any significant effect on Vc or CL.

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