Comparison of Population PK and Exposure-Response Relationships of Intravenous Rituximab and Subcutaneous Rituximab in Patients with CLL

Ekaterina Gibiansky[1], Michael Brewster[2], Clarisse Chavanne[3], Nicolas Frey[3] and Candice Jamois[3]

[1]QuantPharm LLC, [2]Roche Innovation Center Welwyn, [3]Roche Innovation Center Basel

PAGE 2015, June 2-5, Hersonissos, Crete, Greece

BACKGROUND

- Rituximab (RTX) intravenous (IV) formulation is approved for treating many B-cell lymphomas. A subcutaneous (SC) formulation of rituximab has been developed and approved for non-Hodgkin's lymphoma. SC dosing for patients with chronic lymphocytic leukemia (CLL) was investigated in a number of studies.
- The aim of the population PK analysis was to characterize the PK properties of RTX following IV and SC administration in CLL patients and to identify covariate factors that influence its disposition in this population.
- The graphical PK-PD analysis aimed to assess and compare PK-safety and PK-efficacy relationships following IV and SC RTX in CLL patients.

PK METHODS

Data

- 255 patients from 2 studies (Phase Ib and III) contributed 4739 serum concentration values (1777 and 2962 values following SC and IV administration). Of 255 subjects, 140 subjects received at least 1 SC dose.
- RTX dosing regimens (28-day cycles):
  - IV: Cycle 1: 375 mg/m^2 IV, Cycles 2-6 500 mg/m^2 IV;
  - SC1: 5 cycles of IV regimen, Cycle 6: various SC doses up to 2200 mg
  - SC2: Cycle 1: 375 mg/m^2 IV; Cycles 2-6 1600 mg SC
- RTX dosing:
  - Study 1: IV regimen,
  - Study 2 Part 1: SC1 regimen, Study 2 Part 2: IV and SC2 regimens.

Modeling

- Nonlinear mixed-effects modeling was performed using NONMEM 7.3.0 with FOCEI method.
- The full model approach was used for covariate model development. Multiple covariates chosen based on mechanistic plausibility, exploratory analysis and scientific interest were simultaneously added to model parameters.
- Tested covariates: body weight, BSA, BMI, gender, age, and baseline values of white blood cells (WBC), tumor size (BSIZ), and serum albumin. Other covariates: normalized creatinine clearance, markers of hepatic impairment, presence of anti-drug antibodies, and B-cell count at baseline (that was confounded with WBC but had more missing values) were evaluated by diagnostic plots.

PK RESULTS & CONCLUSIONS

The final population PK model:

- 2-compartment model with first order SC absorption and time-dependent clearance:

$$CL = CL_{inf} + CL_t, \quad CL_t = CL_T \cdot \exp(-k_{des} t))$$

- Steady-state PK parameters typical for a monoclonal antibody (Table 1);
- CL_t declined with half-life of 17.4 days; simulation indicated that concentrations approached the steady-state levels after approximately six 28-day cycles;
- Clearance (both, CL_{inf} and CL_T terms), V_C, V_P, and Q increased with BSA. In subjects with extreme values of BSA, clearance and central volume were within 25% and 16% of the corresponding values for subjects with mean BSA;
- Central volume was 9% lower in females compared to males;
- SC absorption parameters k_a and F_{SC} decreased with increasing BMI;
- Consistent with target-mediated elimination, CL_T was higher in subjects with higher WBC and BSIZ;
- Anti-drug antibodies were detected in 13 subjects; they did not influence the concentration-time course;
- Conditional simulations demonstrated that, while flat SC dosing leads to larger differences in exposure (C_{trough} and AUC_τ) between subjects with low and high body sizes compared to body-weight-adjusted IV dosing, for SC2 regimen it allows to maintain C_{trough} and AUC_τ values for all body-size groups at levels not lower than levels attained by IV regimen, thus achieving at least the same target saturation as for IV regimen.

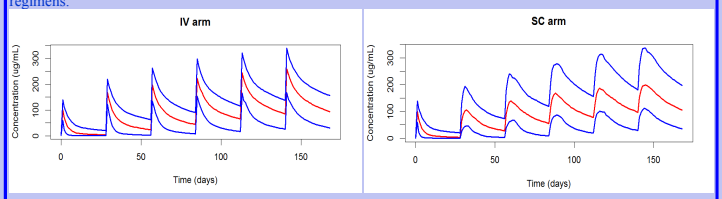
Table 1. Parameter Estimates of the Final Model

Parameter	Estimate	%RSE	Parameter	Estimate	%RSE	Shrinkage
CL_{inf} (mL/day)	207	2.62	$F_{SC,BMI}$	-0.465	35.6	
V_C (mL)	4990	1.82	$CL_{T,WBC}$	0.223	34.2	
V_P (mL)	3700	1.97	$CL_{T,BSIZ}$	0.261	21.1	
Q (mL/day)	420	3.23	ω^2_{kdes}	CV=59.7%	10.3[a]	13.2%
k_a (1/day)	0.372	3.86	ω^2_{CLT}	CV=83.1%	9.4[a]	10.5%
F_{SC}	0.633	2.52	ω^2_{CLinf}	CV=32.5%	10.5[a]	7.6%
CL_T (mL/day)	1550	8.14	$R\omega_{CLinf}\omega_{VC}$	R=0.47	15.7[a]	
k_{des} (1/day)	0.0399	5.19	ω^2_{VC}	CV=18.0%	11.3[a]	9.9%
$Cl_{inf,BSA} = Q_{BSA}$	1.37	12.3	ω^2_{ka}	CV=34.0%	17.7[a]	9.1%
$V_{C,BSA}=V_{P,BSA}$	0.80	11.4	$R\omega_{ka}\omega_{FSC}$	R=0.37	36.4[a]	
$V_{C,SEX}$	0.909	2.96	ω^2_{FSC}	CV=21.3%	19.0[a]	7.9%
$k_{a,BMI}$	-1.01	23.8	[a] RSE for variance-covariance matrix elements			

CL_{inf}, non-specific time-independent clearance; CL_T, initial value of time-dependent clearance; k_{des}, decay coefficient of time-dependent clearance. P_{COV}, effect of covariate COV on parameter P, where BSIZ is the baseline tumor size (mm^2); residual error was described by an exponential error model with CV described by an E_{max} function of concentrations (CV=13.5% at high concentrations, CV=81.0% at low concentrations, CV=47.2% at σ_{50}=6.35 µg/mL; inter-subject variability of CV was 30.5%) .

Figure 1: Model-Based Conditional Simulations

Medians (red), and 5th and 95th percentiles (blue) of the simulated concentrations following IV and SC2 regimens.



GRAPHICAL PK-PD ANALYSIS

Data

- 87 subjects from the IV (1487 concentrations) and 86 subjects from SC (1729 concentrations, SC2 regimen) arms of Study 2 Part 2.

PKPD Methods

Relationships of RTX exposure with the following safety and efficacy measures were investigated separately for IV and SC treatment arms:

- RTX concentrations over time, C_{mean} and AUC_{cum} with occurrence of SAEs grouped by each system organ class (SOC);
- RTX C_{mean} with occurrence of Grade 3+ SAEs, occurrence and grade of neutropenia, and time course of neutrophil counts;
- RTX C_{mean} and C_{trough} with time course of B-cell counts;
- RTX C_{mean} and C_{trough} with best observed response (complete response [CR], CR with incomplete bone marrow recovery [CRi], partial response [PR], and stable disease [SD]).

PKPD Results & Conclusions

- There was no apparent link between serum concentrations or exposure of RTX and occurrence of SAEs and Grade 3+ SAEs;
- There was no correlation between RTX exposure and occurrence or grade of neutropenia; there was no difference in RTX effect on neutrophil counts between IV and SC arms;
- There was a slight visual trend of stronger B-cell response in higher exposure groups for both treatments. There were no differences in nadir B-cell counts between the treatment arms, while time to nadir appeared to be slightly lower for the IV treatment arm;
- There were no differences in exposure between subjects with CR, CRi, and PR (only 2 subjects had SD) in the IV arm. In the SC arm, subjects with PR had the same exposure as subjects in the IV arm. The exposure in subjects with CR and CRi in the SC arm appeared to be higher than in the IV arm.

OVERALL CONCLUSIONS

The analysis demonstrated that the RTX SC regimen (SC2) tested in CLL patients provides exposures that are equal or higher compared to the reference RTX IV regimen across the whole range of body sizes, while there are no differences between IV and SC treatments in exposure-safety relationships. The analysis supports the conclusion that switch to the SC route of administration does not impair the anti-B-cell activity of RTX.