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Modelling of Rituximab Clearance Reduction Due to Ibrutinib Co-administration

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BACKGROUND

- Ibrutinib is an oral covalent inhibitor of Bruton's tyrosine kinase, a key enzyme in B-cell signalling. It is indicated for the treatment of patients with B-cell malignancies such as chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) [1]. In this population, single-agent ibrutinib has been shown to significantly improve overall survival in both relapsed/refractory and previously untreated patients [1].
- In a recent phase III study (HELIOS), the combination of ibrutinib with bendamustine + rituximab (BR-I) in patients with previously treated CLL or SLL resulted in significant improvements in disease outcomes, including progression-free survival, overall response, and quality of life, compared to BR + placebo (BR) [2].
- In this study, the pharmacokinetic (PK) interactions between ibrutinib, bendamustine, and rituximab were explored.

OBJECTIVE

- While bendamustine PK is not influenced by ibrutinib, the systemic exposure of rituximab (assessed only at selected sites) was observed to be higher in the BR-I arm than in the BR arm [3], by up to 3 fold in early cycles and 1.7 fold subsequently. The aim of this work was to explore this difference in rituximab exposure using a modelling approach.

METHODS

Study Design Overview

- HELIOS was a phase III, randomized, placebo-controlled, double blind study [2].
  - o Eligible patients were ≥18 years, had a diagnosis of CLL or SLL without del(17p), and had relapsed or refractory disease with ≥1 previous lines of systemic therapy.
- Patients were randomized to receive 420 mg ibrutinib or placebo in combination with 6 cycles (28 days per cycle) of bendamustine and rituximab until disease progression or unacceptable toxicity.
  - o The bendamustine intravenous (IV) dose was 70 mg/m^2 on days 2-3 of cycle 1 and days 1-2 of cycles 2-6. Infusion duration was typically 30 minutes.
  - o The rituximab IV dose was 375 mg/m^2 on day 1 of cycle 1 and 500 mg/m^2 on day 1 of cycles 2-6. Infusion duration varied based on individual tolerability (as per the approved product labeling for rituximab [4]).

Study Assessments

- In a subset of patients at selected study sites, sparse blood sampling was performed in both treatment arms for bendamustine and rituximab PK analyses.
- Rituximab serum concentrations were obtained at day 1 (predose) and 15 of cycle 1, predose on day 1 of cycles 2-6 and day 1 of cycles 7-9, in the washout phase.
  - o Rituximab concentrations were determined using an immunoassay by QPS (Newark, DE, USA).
- Tumor burden was evaluated every 12 weeks and assessed as sum of the products of the largest diameters (SPD).
- Demographics and baseline characteristics of patients included in the dataset are reported in **Table 1**.

Table 1. Characteristics of Patients With Both Rituximab PK Data and SPD Assessments (N=147).

	BR-I (n=77)	BR (n=70)
Number of rituximab PK observations	612	562
Number of lymph node SPD observations	476	381
Sex, n (%)		
Male	46 (59.7)	45 (64.3)
Female	31 (40.3)	25 (35.7)
Median age (range), y	61 (40-82)	61 (36-83)
Median body weight (range), kg	82.75 (52.5-125.4)*	78.35 (45-130)
Median CRCL (range), mL/min	91.5 (43.8-207.3)*	82.8 (47.0-197.3)
Median total bilirubin (range), µmol/L	10.6 (3.42-28.4)	10.5 (3.42-36.3)
Median ALT (range), U/L	22 (9-75)	21 (4.3-101.7)
Median AST (range), U/L	23 (5-57.1)	23.15 (10-67)

BR = bendamustine and rituximab; I=ibrutinib; SPD=sum of the products of the largest diameters; CRCL=creatinine clearance; ALT=alanine transaminase; AST=aspartate transaminase; *Data missing for 1 subject (n = 76).

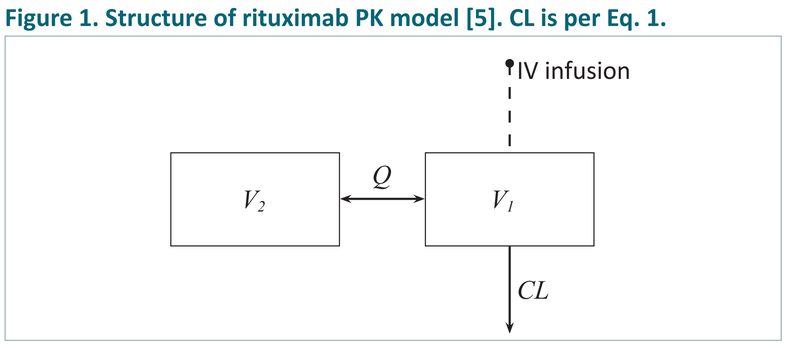
Modelling analysis

- Rituximab PK parameters were assessed using a nonlinear mixed-effects compartmental approach.
- A two-compartmental model, including a nonlinear clearance term decreasing exponentially with time, was previously reported in the literature [5] (see **Figure 1**).

$$CL = CL_1 + CL_{2_0} \exp(-k_{des}t), \qquad (1)$$

- The effect of the categorical covariate sex was explored.
- It is hypothesized that the difference in exposure between the two treatment arms of the study is due, at least in part, to a target-mediated drug disposition (TMDD) phenomenon, where B cells are targeted by rituximab. For these reasons, the model [5] was here refined through evaluation of treatment arm and tumor burden (measured as SPD) as meaningful covariates (categorical and continuous time-varying, respectively).
- Categorical covariate analysis was performed via forward inclusion and backward elimination (FI-BE), based on likelihood ratio test, with significance level α=0.05.
- The continuous covariate SPD was computed from pharmacodynamic data via linear interpolation.
- Residual error was included with an additive model, using the logarithm-both-sides approach.
- Model estimation and simulation were performed with NONMEM version 7.1.0, while model diagnostics and plots were obtained via R version 3.2.4.

Figure 1. Structure of rituximab PK model [5]. CL is per Eq. 1.



RESULTS

- The schematic of the model development process is reported in **Figure 2**.
- The inclusion of the categorical covariate sex on rituximab clearance terms did not significantly improve the adherence of the model to the PK observations.
- The covariate analysis via the inclusion of a categorical covariate for describing treatment (TRT2) led to a significant improvement when both the parameters k_{des} and V_1 of the literature model [5] were involved.
- The model was further developed by adding SPD as a continuous time-varying covariate on CL (Eq. 2) and on V_1 (Eq. 3).

$$CL = CL_1 + CL_{2_0} exp(-k_{des}t) + CL_{2_P}\left(\frac{SPD}{BASE_{median}}\right)^{\vartheta_{cov}} \qquad (2)$$

$$V_1 = V_{10}\left(\frac{SPD}{BASE_{median}}\right)^{\gamma} \qquad (3)$$

The inclusion of this covariate made negligible TRT2 effect on volume.

- The removal of the empirical exponential term on CL (model M3 II and M4 II in **Figure 2**) greatly increased OBJF. This indicates that the inclusion of SPD alone is not able to explain well the observed data.
- Final model (M4 in **Figure 2**) parameters are reported in **Table 2**. The model appears to fit well the observed PK data, as depicted by **Figure 3**.

Figure 2. Schematics of model building process. Each block represents a model (M), indicated with a number. The arrows represent the building sequence and they are coupled with increases/decreases in NONMEM objective function (OBJF).

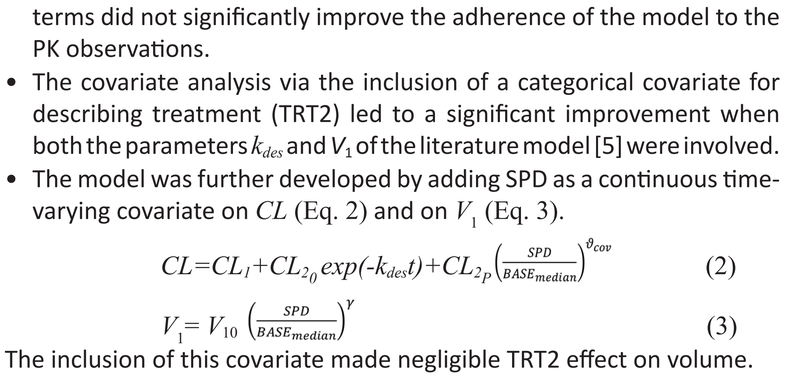
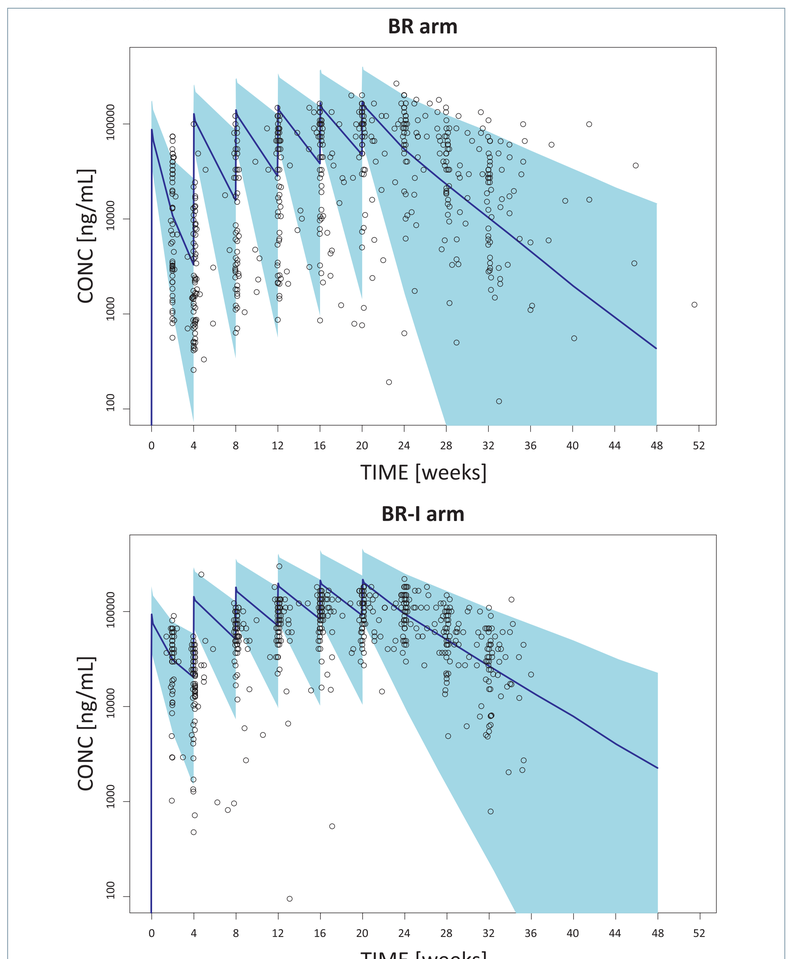


Table 2. Final Model Parameter Estimates.

Typical values	Estimate	Inter-individual and residual variabilities	Estimate
CL_1 (mL/hr)	4.15	ω_{CL_1}	0.0027
V_{1_0} (mL)	7460	ω_{V1_0}	0 FIX
Q (mL/hr)	47.9 FIX	$\omega_{k_{des}}$	1.81
V_2 (mL)	2320 FIX	$\omega_{CL_{20}}$	0.238
k_{des} for BR arm (1/hr)	0.00145	$\omega_{CL_{2P}}$	0.637
k_{des} for BR-I arm (1/hr)	0.021	$\omega_{\vartheta_{cov}}$	0 FIX
CL_{2_0} (mL/hr)	57.0	ω_{γ}	4.23
CL_{2_P} (mL/hr)	6.9	σ_{add}	0.145
ϑ_{cov}	0.266		
γ	0.0214		

Figure 3. Visual predictive check (VPC) stratified by treatment arm for the final model.



Open symbols = observations; light blue area = 5th-95th percentiles of model predictions; blue line = median of model predictions

CONCLUSIONS

- A model for describing the PK interaction between ibrutinib and rituximab in patients enrolled in the HELIOS study was developed.
  - o No apparent differences in rituximab clearance were observed between males and females.
  - o Rituximab clearance was described including an SPD-dependent term and it was influenced by the treatment arm, which affected the decreasing exponential term.
  - o The volume of distribution of the central compartment was found to be dependent on SPD.
- These data suggest that rituximab disposition is, at least in part, target mediated. This finding is in agreement with what was reported in a recent paper [6], in which rituximab clearance was related to CD20 antigen count at baseline.
- As reported in similar works on other target-mediated compounds [7], SPD does not appear able to fully explain the change in clearance during treatment. This is not unexpected, considering that SPD may not fully represent the overall tumor burden and/or B cell count.
- Final model parameters appear in agreement with those reported by Li et al [5], with the exception of the more rapid k_{des} in the BR-I arm.
- Additional data (eg, B cell measurements) and further modelling work may be needed to have a fully mechanistic representation that further elucidates rituximab disposition, for instance including a true PD model for SPD progression.

References: [1] IMBRUVICA® (ibrutinib) prescribing information. Sunnyvale, CA: Pharmacyclics LLC; 2016. [2] Khan AA, et al. Lancet Oncol. 2016;17:200-211. [3] Cramer P, et al. 58th American Society of Hematology (ASH) Annual Meeting & Exposition 2016, Abstr 4403. http://www.bloodjournal.org/content/128/22/4403. [4] RITUXAN® (rituximab) prescribing information. South San Francisco, CA: Genentech, Inc.; 2016. [5] Li J, et al. J Clin Pharmacol. 2012;52:1918-1926. [6] Tout M, et al. Clin Pharmacokinet. 2016 Oct 25 [Epub ahead of print] [7] Liu C, et al. Clin Pharmacol Ther. 2017;101:657-666.

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Registration: The HELIOS study is registered at ClinicalTrials.gov: NCT01611090

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