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Rituximab PK and PD evaluation based on a study in diffuse large B-cell lymphoma: influence of tumor size on PK and assessment of PK similarity

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Objectives

- What are the PK and PKPD characteristics of rituximab?
- What is the impact of tumor size on rituximab PK?
- What are the factors influencing the PK similarity assessment between different rituximab products?

Background

Addition of rituximab to the standard-of-care chemotherapy leads to improvement in the long-term outcomes of patients suffering from diffuse large B-cell lymphoma. DRL-rituximab (DRL_RI, Dr Reddy's Laboratories SA, Switzerland) is under development as a rituximab biosimilar. Its PK equivalence to the reference medicinal product MabThera® (RMP, Roche, Germany) was shown and comparable PD, efficacy, safety, and immunogenicity profiles were observed[1,2].

Methods

Nonlinear mixed-effects models for PK, tumor size, tumor size-PK, and tumor response were developed using NONMEM version 7.3. The analyses were based on data from study RI-01-002 (CTRI/2012/11/003129)[1] in which subjects were administered 375 mg/m^2 IV infusion of rituximab in addition to standard chemotherapy.

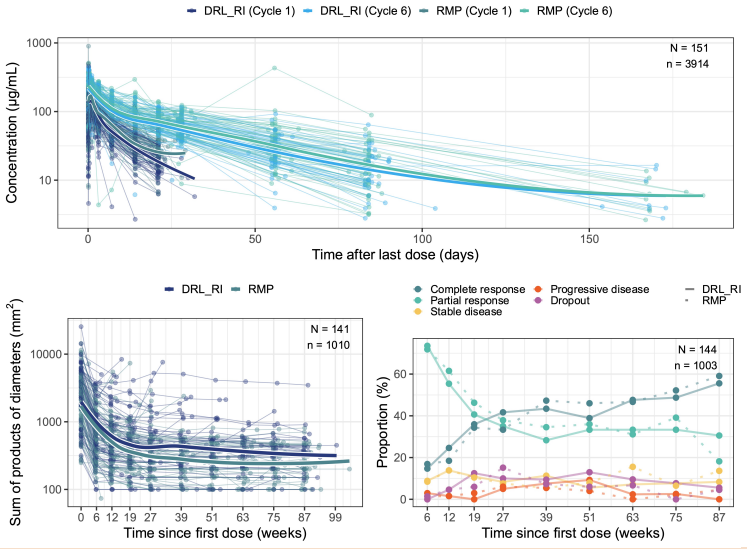

Figure 1. *Observed rituximab plasma concentrations versus time after last dose (upper panel); observed tumor size versus time since first dose (lower left panel); and observed proportion of patients in the tumor response categories or dropout versus time since first dose (lower right panel). N: number of subjects; n: number of observations*

The intermediate PK model was developed based on a previously developed model[3]; tumor size was described using the Stein 2008 model[4]; tumor response[5] was characterized using a continuous time Markov model (CTMM).

The tumor size-PK model was developed starting from the intermediate PK model, integrating the tumor size predictions from the final tumor size model.

The drug product effect was tested using SCM after testing of exploratory covariates in the preceding SCM. Finally, simulations were performed to evaluate the impact of tumor size on rituximab exposure.

Conclusions

- Higher baseline tumor size was associated with lower exposure
- No significant difference was found between drug products with respect to PK, tumor size change, or tumor response
- The apparent drug product effect on exposure was no longer significant after the difference in baseline tumor size was accounted for
- The current analysis exemplifies how PK and PKPD analyses can be applied to identify confounding factors generating apparent differences between drug products, thereby facilitating accurate similarity assessments

Results

Subjects' demographics were largely similar between treatment arms, except that baseline tumor size was slightly higher in the DRL-RI arm (median [min, max]: 2670 [273, 25500] vs 2500 [248, 14400] mm^2).

The intermediate PK model was a 2-compartment, target-mediated drug disposition model with quasi-equilibrium assumption. RMP-treated patients were predicted to have a 6.75% higher effective dose.

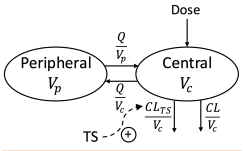

Figure 2. *Schematic of the tumor size-PK model. TS: individually predicted time-varying tumor size*

After tumor size was included as a covariate on clearance (Figure 2), the aforementioned drug product effect was no longer significant.

Further simulations showed that higher baseline tumor sizes result in lower rituximab $AUC_{0\text{-}21}$ and trough concentrations on average (not shown) but the effect on C_{max} was much less pronounced (Figure 3).

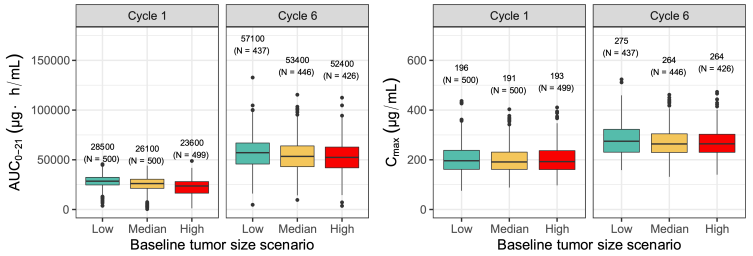

Figure 3. *Boxplot of simulated PK metrics for the low (1071 mm^2), median (2615 mm^2), and high (4681 mm^2) baseline tumor size scenarios. The number above each boxplot is the median exposure value. N: number of simulated subjects included in the evaluation*

The final tumor size model included a constant tumor kill rate and a mixture model accounting for 2 sub-populations: one with tumor regrowth (12.9%) and one without.

The final tumor response model also accounted for a sub-population with faster progression (42.4%) (Figure 4).

Drug product was not a significant covariate in either the tumor size or the tumor response models.

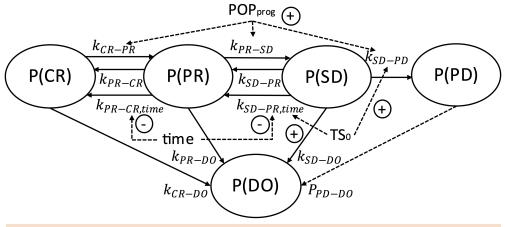

Figure 4. *Schematic of the tumor response model. CR: complete response; DO: dropout; P: probability; PD: progressive disease; POP_{prog}: sub-population with progression; PR: partial response; SD: stable disease: TS_0: baseline tumor size*

References

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