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Pharmacodynamics of rituximab on B cells in paediatric post-HSCT patients with EBV

Soumya Perinparajah[1], Juliana Silva[2], Austen Worth[1,2], S.Y. Amy Cheung[3], James W.T. Yates[4], Nigel Klein[1], Judith Breuer[1,5], Paul Veys[1,2], Persis J. Amrolia[1,2], Joseph F. Standing[1,6]

1) UCL Great Ormond Street Institute of Child Health, London, UK; (2) Department of Bone Marrow Transplantation, Great Ormond Street Hospital for Children, London, UK; (3) Certara, Amsterdam, Netherlands; (4) AstraZeneca, Cambridge, UK; (5) Infection and Immunity, UCL, London, UK; (6) Department of Pharmacy, Great Ormond Street Hospital for Children, London, UK

Background

Rituximab is a chimeric IgG-1 monoclonal antibody that interacts with the CD20 protein on the surface of **B cells**, targeting them for cell lysis. It is licensed for adults only, given on an **off-label** basis to **children**, for a range of conditions including B cell lymphomas and leukaemias.

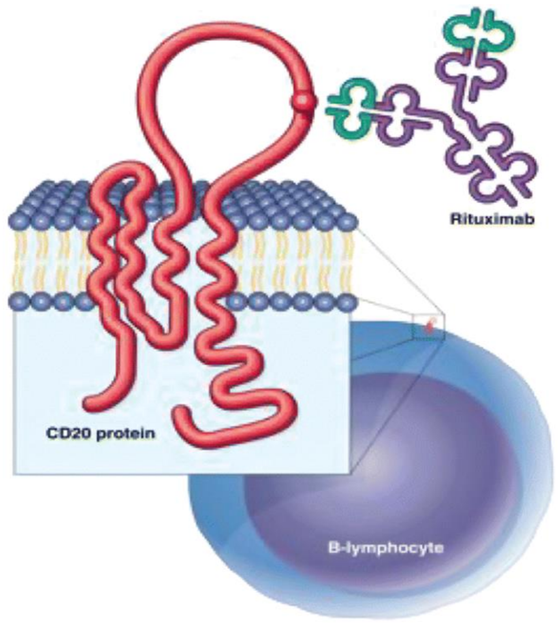

Figure 1*: Interaction of rituximab with CD20 protein (red) on surface of B cell (blue). Green variable region of rituximab is murine-derived and purple constant region is human-derived [1].*

Rituximab is also given for Epstein Barr virus (**EBV**), which is commonly reactivated after haematopoietic stem cell transplantation (**HSCT**) and is the leading cause of post-transplant lymphoproliferative disease (**PTLD**). In healthy hosts, EBV is controlled by cytotoxic T cells but in **immunocompromised** post-HSCT patients, there can be an outgrowth of EBV-transformed cells.

Aim

To identify the **pharmacodynamics** of rituximab in children with EBV post-HSCT to **optimise** the dose.

Methods

Retrospective electronic data were collected from children who underwent HSCT at Great Ormond Street Hospital between 2005 and 2017, and were prescribed rituximab for EBV post-HSCT. Intravenous infusions of rituximab were administered at a dose of 375 mg/m^2 weekly for either **one week or four weeks** on a pre-emptive regimen. **CD19$^+$ B cell counts** were available before and after treatment with rituximab.

A **two-compartment** kinetic-pharmacodynamic (**K-PD**) turnover model was applied in **NONMEM®** (version 7.4.3) [2]. Rituximab was assumed to be eliminated by first-order kinetics.

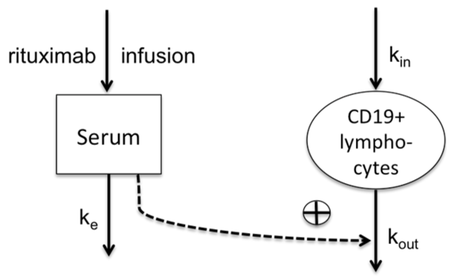

Figure 2: *Schematic of the two-compartment model where rituximab increases the death rate of CD19$^+$ B cells. See Table 1 for further parameter details.*

Results

683 measurements of CD19$^+$ B cell counts were available from **55 children**. Observations (n=317) with a CD19$^+$ B cell count below the lower limit of quantification (LLOQ) were assigned a count of 5x10^6/L (LLOQ/2). The median age at HSCT was **2.96** years.

The K-PD model described the time course of CD19$^+$ B cells well following treatment with rituximab. The model **parameter estimates** are summarised in **Table 1**. These were consistent with values reported in previous literature [2,3], except ED50 which was higher in the present study.

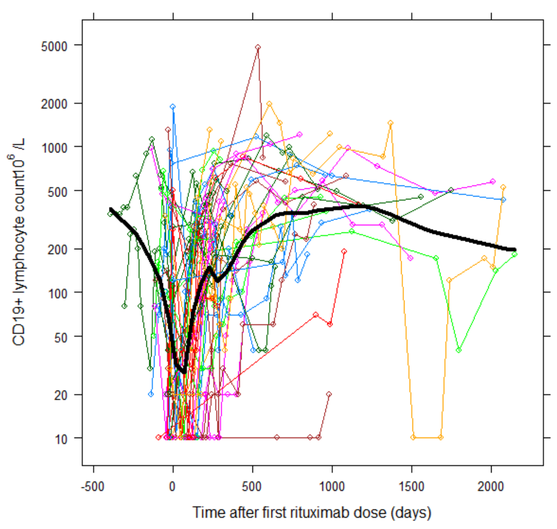

Figure 3: *Data for CD19$^+$ B cell reconstitution after paediatric HSCT (n=55). Each coloured line is data for one individual. The thick black line is the local regression curve for the data.*

Parameter	Description	Estimate	Relative Standard Error (%)
K_{in}	B cell production rate	6.95x10^6 cells/day	6.0
K_{out}	B cell death rate	0.037 cells/day	22.4
K_e	Rituximab elimination rate	0.044/day	6.1
ED50	Rituximab dose producing 50% of maximum killing rate	40 mg	38.8
E_{max}	Fold increase in B cell death rate	56.9	10.7

Table 1: *Model parameter estimates*

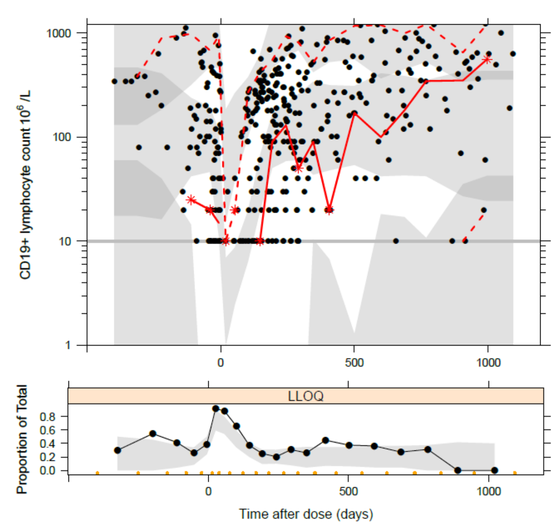

Figure 4: *Visual predictive check for model. Dots are observed data, solid red line is observed median, dashed red lines are observed 2.5th,50th and 97.5th percentiles, and grey shaded areas are 95% prediction intervals for the 2.5th,50th and 97.5th percentiles.*

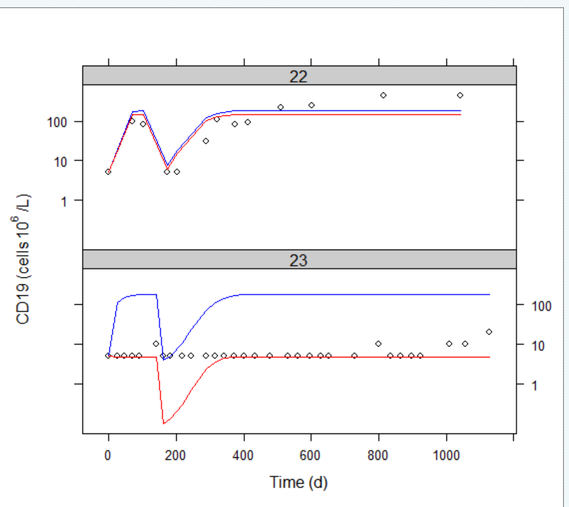

Figure 5: *Individual predictions of CD19$^+$ B cell reconstitution for two selected patients showing an example of good and poor model fit. The blue line is the population prediction and the red line is the individual prediction.*

Conclusions

The model adequately describes CD19$^+$ B cell dynamics in response to rituximab. Refinements to the model will include **age** [4] **and size scaling**, and exploration of the M3 method for LLOQ handling. **EBV viral loads** will then be included to better understand the dynamics of viral inhibition in this population, and ultimately **inform rituximab dosing**.

References

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