

Title: CHARACTERIZATION OF THE TIME-VARYING CLEARANCE OF RITUXIMAB IN NON-HODGKIN'S LYMPHOMA PATIENTS USING A POPULATION PHARMACOKINETIC ANALYSIS

Authors: *Micha Levi(2), *Jing Li(1), Nicolas Frey(3), Thian Kheoh(4), Song Ren(1), Michael Woo(2), Amita Joshi(1), Nancy Valente(1), Nelson 'Shasha' Jumbe(1), Jean-Eric Charoin(3)

*contributed equally to this work

Institutions: (1) Genentech, Inc., South San Francisco, CA; (2) Hoffman-La Roche Inc., Nutley, NJ; (3) Roche Pharma, F. Hoffmann-La Roche Ltd, Basel, Switzerland; (4) Biogen Idec, San Diego, CA

Objectives: Rituximab is a monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The elimination half-life of rituximab was originally determined on data from 14 Non-Hodgkin's Lymphoma (NHL) patients treated with a dose of 375 mg/m² weekly x 4, and was described to increase with time from 3.2 days following the first infusion to 8.6 days following the fourth infusion. The half-life increase with time was hypothesized to be due to a decrease of rituximab clearance in conjunction with the decrease in B-cell (CD19⁺) count and/or tumor burden. To further investigate this time-varying half-life and to explore the potential role of covariates, a population pharmacokinetic analysis was conducted by pooling data from six clinical studies in NHL patients.

Methods: The population PK analysis was performed using NONMEM V. A dataset consisting of 3739 rituximab serum concentration observations from 298 patients who received rituximab as a single agent or in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy was constructed. The following covariates were tested: body surface area (BSA), gender, age, race, WHO status, baseline CD19⁺ counts, sum of the perpendicular diameters (SPD) of tumor and CHOP therapy. The effects of covariates was assessed using a stepwise regression approach with model evaluation via non-parametric bootstrap and visual predictive check.

Results: A two compartment model with time-varying clearance described the data reasonably well. Rituximab clearance was characterized by a combination of two pathways. The first pathway (CL1) did not change during treatment. The second clearance pathway (CL2) decreased with time during treatment at a first order decay rate (Kdes) from an initial value (CL20) at the start of treatment. Typical population estimates of CL1, CL20, V1, V2, Q, and Kdes were 0.14 L/day, 0.59 L/day, 2.7 L, 1.5 L, and 0.46 days⁻¹ (or t1/2 of 15 days), respectively. BSA was found to be an important covariate for V1 explaining 27.3% of the inter-individual variability (IIV). SPD and CD19⁺ were the most significant covariates affecting CL20 explaining 26.7% of the IIV. SPD was also a significant covariate for Kdes, however, it explained only 6% of its IIV. Patients with high SPD/CD19⁺ counts were more likely to have higher CL20 and lower Kdes. Gender, age, race, WHO status, and CHOP therapy did not significantly affect rituximab PK.

Conclusions: A two compartment model with time-varying clearance described rituximab PK data pooled from six clinical studies. This model offered for the first time a quantitative estimation of the decrease in rituximab clearance by using an empirical first order time-dependent decline in rituximab clearance. Covariates associated with tumor burden (SPD and CD19⁺) appeared to add to the time-varying clearance effect, thus, offering support to the hypothesis that rituximab PK in NHL patients was affected by the disease. Following multiple infusions, the median of individual estimates of rituximab terminal half-life was 22 days (range, 6.1 to 52 days), typical for IgG antibodies.