Rituximab in Anti-Neutrophil Cytoplasmic Antibodies (ANCA)-associated vasculitis: population pharmacokinetic modeling and simulations of alternative doses in under-exposed patients

Blaise Pasquiers[1,2], Xavier Declèves[2,3], Benjamin Terrier[4,5], Pascal Cohen[4], Mathieu Felices[1], Marion Casadevall[4], Xavier Puéchal[4,5], Benoit Blanchet[3], Alicja Puszkiel[2,3]

1) PhinC Development, Massy, France
2) UMR-S 1144 – Université Paris Cité, Paris, France
3) Biologie du Médicament et Toxicologie, Hôpital Cochin, Assistance Publique Hôpitaux de Paris, Paris, France
4) Department of Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, Paris, France
5) Université Paris Cité, Paris, France

Background and objectives:

Rituximab is a monoclonal antibody directed against transmembrane antigen CD20 expressed by B cells. It is approved for the treatment of patients with Anti-Neutrophil Cytoplasmic Antibodies (ANCA)-associated vasculitis. The treatment consists in an induction phase (375 mg/m^2 once a week) for 4 weeks followed by a maintenance phase (500 mg every 6 months) for 18 to 36 months. In a previous study, we showed that a rituximab plasma concentration < 4 mg/L at 3 months after initiation of maintenance phase ($C_{3months}$) was significantly associated with higher risk of major relapse [1]. The objective of this study was to develop a population pharmacokinetic (popPK) model for rituximab based on real-world data from patients with ANCA-associated vasculitis. The model was used to identify significant covariates on rituximab PK and to simulate alternative doses in under-exposed patients ($C_{3months}$ < 4 mg/L).

Methods:

This retrospective analysis included patients with ANCA-associated vasculitis treated with rituximab in the Cochin University Hospital (Paris, France). Plasma concentrations of rituximab were measured using a validated liquid chromatography method coupled with tandem mass spectrometry detection (LC-MS/MS) using mAbXmise kit (Promise, France) [2]. Concentration-time data were analysed using Monolix 2022R1. A two-compartment structural model with linear clearance (CL) from the central compartment was tested. Time-dependency on rituximab CL was tested using a hyperbolic and sigmoidal function as previously described [3]. Alternatively, inter-occasion variability (IOV) on CL was tested with two occasions defined according to the treatment phase (induction or maintenance). The

following covariates were tested on CL and central volume of distribution (V1): age, sex, body weight (BW), C-reactive protein (CRP), serum albumin, immunoglobulins G (IgG), estimated glomerular filtration rate (eGFR). Covariate analysis was performed using a full model estimation followed by a backward selection method with a Wald test (p-value < 5%). Model evaluation and validation were based on goodness of fit plots, pcVPC and likelihood-ratio test using BICc. The final model was used to simulate 1000 patients with standard dosing regimen (375 mg/m^2 once a week for four weeks followed by 500 mg every six months) and their $C_{3months}$ were compared to the 4 mg/L threshold. Then, simulations of alternative doses in the maintenance phase (750 and 1000 mg every six months) were performed in under-exposed patients and the percentage of patients reaching the 4 mg/L threshold was calculated.

Results:

A total of 251 rituximab plasma concentrations (97 and 154 in the induction and maintenance phases, respectively) were collected from 99 patients. A linear two-compartment model was developed and the mean (RSE) estimates were: CL = 0.13 L/day (5%), V1 = 3.02 L (4%), V2 = 2.44 L (7%), Q = 0.31 L/day (30%). Interindividual variability (IIV) on CL was 19% (41%). IOV was estimated to 30% (17%) and 23% (11%) on CL and V1, respectively. Several covariates were found to significantly impact CL (age, BW, CRP and IgG). When the IgG, CRP or BW value increased from median to 95^{th} percentile in the studied population, CL increased by 35%, 19% and 17%, respectively, whereas CL decreased by 11% when age increased from the median value to the 95^{th} percentile. The proportional residual error was estimated at 16% (9%). The pcVPC of the final model showed that the observed and simulated data were in good accordance. At the standard dosing regimen, 18% of the simulated population was below the efficacy threshold. Simulations in under-exposed patients showed that at 750 mg and 1000 mg dose, 35% and 53% of them, respectively, reached the target residual concentration of 4 mg/L. Finally, in the total population, 88% and 92% of patients would reach target residual concentration at 750 and 1000 mg, respectively, compared to 82% at 500 mg dose.

Conclusion:

For the best of our knowledge, this is the first popPK model of rituximab in a real-world ANCA-associated vasculitis population. Our simulations justify adapting the maintenance dose for under-exposed patients in a personalized therapeutic perspective.

References

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