The pharmacodynamic effects of rituximab at very low doses in healthy volunteers

Christian Schörgenhofer, Christa Firbas, Ulla Derhaschnig, Robert M. Mader, Raute Sunder-Plaimann, Petra Jilma-Stohlawetz, Kalpana Desai, Priya Misra, Ulrich Jäger and Bernd Jilma

Department of Clinical Pharmacology, Medical University of Vienna, Austria; Department of Emergency Medicine, Medical University of Vienna, Austria; Department of Medicine I, Medical University of Vienna, Austria; Department of Laboratory Medicine, Medical University of Vienna, Austria; Apotex Inc., Toronto, Ontario, Canada

Background: No dose-finding trials are available for rituximab that could guide dosing in non-malignant diseases. We hypothesized that currently used doses (≥375 mg/m²) exceed several hundred-fold the half-maximal effective dose, which is most sensitive for detecting putative differences between biosimilars and important for dose-finding.

Methods: In an exploratory, dose-finding trial, healthy volunteers received single infusions of 0.1 (n = 4), 0.3 (n = 4) and 1.0 mg/m² (n = 8) rituximab. Subsequently, in a randomized, double-blind trial, healthy volunteers received single infusions of 0.1 (n = 24) or 0.3 mg/m² (n = 12) of two rituximab products. CD19/20⁺ cell counts were measured, and pharmacokinetics and immunogenicity were assessed.

Results: Single infusions of 0.1, 0.3 and 1 mg/m² rituximab transiently depleted CD20⁺ cells by 68% (95% CI: 24 – 100%), 74% (59 – 84%) and 97% (95 – 99%), respectively. In the randomized trial, infusion of 0.1 mg/m² or 0.3 mg/m² proposed biosimilar or reference rituximab decreased CD20⁺ cells by 45% (32 – 58%) – 55% (45 – 66%), and 81% (73 – 87%) – 87% (74 – 100%), respectively. In the randomized trial, 26 of 36 patients developed human anti-chimeric antibodies, and 9 of 36 patients developed neutralizing anti-drug antibodies. Pharmacokinetic analyses were limited by the assay sensitivity and the very low rituximab doses. However, there was a clear pharmacokinetic signal during the first 24 hours in the 1 mg/m² group.

Discussion: It is important to understand that <1% of the authorized rituximab doses depletes all circulating B lymphocytes in healthy volunteers. This will particularly help countries struggling to meet the financial burden of therapy with biologics.

Acknowledgements: This trial was funded by Apotex Inc., Toronto, Ontario, Canada.