Letter to the Editors

Influence of plasma exchange on rituximab pharmacokinetics

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Rituximab, an anti CD20 monoclonal antibody is approved for the treatment of B-cell non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and rheumatoid arthritis [1]. It is also used off label for the treatment of lymphomas induced by the Epstein–Barr virus (EBV) after bone marrow or organ transplant [2], in particular forms of organ transplant rejection (acute humoral rejection) [3] and in a number of autoimmune diseases. Plasma exchange (PEX) is an extracorporeal blood purification technique allowing the removal of large molecular weight substances from the plasma and hence is used in various diseases including cryoglobulinaemia. In this last condition, its aim is to eliminate pathogenic antibodies involved in vascular and glomerular lesions. Because PEX is not selective, it also leads to the elimination of any circulating therapeutic antibody. An impact of PEX on plasma concentrations of basiliximab and rituximab [4,5] was reported but its influence of monoclonal antibody pharmacokinetics was not studied.

We report the use of compartmental pharmacokinetic modelling to quantify the impact of multiple PEX sessions on exposure to rituximab in two patients.

Two patients with non-Hodgkin's lymphoma (MALT-type lymphoma and lymphoma following liver transplantation) treated with rituximab underwent multisession PEX for cryoglobulinaemia associated with membranoproliferative glomerulonephritis. Rituximab was administered intravenously at a dose of 350 mg m⁻² weekly for 4 weeks to a 49 kg, 52-year-old woman (patient 1) and as six injections of 375 mg m⁻² over 6 months to a 80 kg, 56-year-old man (patient 2). Patient 1 underwent weekly plasmapheresis sessions. Patient 2 underwent plasmapheresis twice a month during rituximab treatment, followed by weekly sessions. In both cases, plasmapheresis sessions were performed before rituximab injections, except for one plasmapheresis session (patient 1), performed 14 h after the infusion. Blood samples were collected 2 h after rituximab injections and before, immediately and 6 h after

plasmapheresis sessions, in accordance with the policy of the local Ethics Committee. Serum rituximab concentrations were measured by enzyme-linked immunosorbent assay [6] and rituximab pharmacokinetics were described using a two compartment model with two elimination clearances, a 'physiological' clearance (CL) and a 'PEX' clearance (CL_P) taking place only during the sessions. Estimated parameters were 0.2 and 0.5 l day⁻¹ for CL, 28 and 20 l day⁻¹ for CL_P, 1.9 and 3.2 l for central compartment volume, 3.2 and 3.3 l for peripheral compartment volume and 5.2 and 4.5 l day⁻¹ for intercompartment clearance, for patients 1 and 2, respectively. The model was used to simulate cumulated rituximab areas under the concentration vs. time curves (AUC) with and without plasmapheresis (Figure 1). This simulation showed a decrease in exposure to rituximab of 38% at day 54 and 10% at day 274 for patients 1 and 2, respectively (Figure 1).

Our model is the first to describe the pharmacokinetics of rituximab when it is associated with PEX. This procedure had a marked impact on patients' exposure to rituximab. The pharmacokinetic model may also be used to predict the consequences of alterations in rituximab dose or in interval between infusion and PEX. However, the pharmacokinetic consequences of PEX can be minimized by applying PEX sessions at the end of dosing intervals. Alternatively, patients given repeated infusions of rituximab in association with PEX may benefit from an individual dose adjustment based on the monitoring of rituximab serum concentrations.

Competing Interests

The research team of Gilles Paintaud received Grants from Novartis and Pfizer, lecture fees from Chugai and Janssen, consultancy fees from Laboratoire Français du Fractionnement et des Biotechnologies (LFB) and

Figure 1

Observed (circles), model-predicted rituximab serum concentrations (black lines) and cumulated AUC (grey lines) as a function of time in the two patients. Predicted concentrations and cumulated AUC (* – dashed lines) in the absence of PEx (without CL_p) are also displayed

Pierre-Fabre Laboratories, and fees for participation to an advisory board of Roche Pharma.

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Supporting Information

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Table S1 Medical history of the patients

Table S2 Coadministred drugs