Rituximab retreatment for relapse and maintenance therapy in IgG4-related disease

Mikael Ebbo, MD,1 Aurélie Grados, MD,1 Maxime Samson, MD, PhD,2 Anderson Loundou, PhD,3 Aude Rigolet, MD,4 Matthieu Groh, MD,5 Benjamin Terrier, MD, PhD,5 Constance Guillaud, MD,1 Clarisse Carra-Dallière, MD,7 Frédéric Renou, MD,8 Agnieszka Pozdzik, MD, PhD,9 Sylvain Palat, MD,10 Jean-Loup Pennafort, MD,11 Alain Wynckel, MD,11 Noémie Le Gouellec, MD,13 Karine Dahan, MD,14 Franck Carbonnel, MD, PhD,15 Gaëlle Leroux, MD,15 Antoinette Perlat, MD,16 Alexis Mathian, MD, PhD,17 Patrice Cacoub, MD, PhD,17 Eric Hachulla, MD, PhD,17 Nathalie Costedoat-Chalumeau, MD, PhD,17 Jean-Robert Harlé, MD,1 and Nicolas Schleinitz, MD.1

1Department of Internal Medicine, Hôpital de la Timone, AP-HM, Aix-Marseille Université, Marseille, France, 2Department of Internal Medicine and Clinical Immunology, Dijon University Hospital, Dijon, France, 3Unité d’Aide Méthodologique, Aix-Marseille Université, AP-HM, Marseille, France, 4Department of Internal Medicine and Clinical Immunology, Hôpital La Pitié-Salpêtrière, AP-HP, Université Pierre et Marie Curie Paris VI, Paris, France, 5Department of Internal Medicine, Hôpital Cochin, AP-HP, Centre National de Référence Maladies Systémiques et Auto-immunes Rares, Université René-Descartes Sorbonne Paris Santé Paris V, Paris, France, 6Department of Internal Medicine, Hôpital Henri Mondor, AP-HP, Créteil, France, 7Department of Neurology, CHRU de Montpellier, Montpellier, France, 8Department of Internal Medicine, CHU La Réunion site Félix Guyon, Saint-Denis, La Réunion, France, 9Department of Nephrology, Erasme Hospital, Cliniques Universitaires de Bruxelles, Bruxelles, Belgium, 10Department of Internal Medicine, CHU Limoges, Limoges, France, 11Department of Internal Medicine, CHU de Reims, Reims, France, 12Department of Nephrology and Internal Medicine, CH Valenciennes, Valenciennes, France, 13Department of Nephrology, Hôpital Tenon, AP-HP, Paris, France, 14Department of Gastroenterology, CHU Bicêtre, Le Kremlin Bicêtre, France, 15Department of Internal Medicine, Hôpital Sud, CHU de Rennes, Rennes, Franc, 16Fillière maladies auto-immunes et auto-inflammatoires rares (FAI²R), Hôpital Claude Huriez, CHRU Lille, Lille, France

Background: Encouraging results have been obtained with B-cell depletion by rituximab (RTX) but data reporting long-term follow-up and multiple retreatments are lacking.

Methods, materials, and analytical procedure used: This was a retrospective, multicenter study of patients treated with at least one course of RTX from a nationwide database for IgG4-RD. Response to treatment, relapse rate and tolerance were analyzed. Kaplan-Meier curves were plotted and risk factors for relapse studied with a Cox regression model. Patients retreated for relapse or systematically for maintenance therapy were specifically analyzed.

Results: Thirty-three patients with IgG4-RD were treated with RTX and clinical response was noted in 93.5% of 31 symptomatic patients. After a mean follow-up of 24.8 months, 13 patients (41.9% of responders) experienced relapse, with a mean delay of 19 months after RTX. B-cell reconstitution was observed in 57.1%, with a median delay of 12.5 months. Seventy-five percent of these experienced a relapse. A most active disease, defined by IgG4-RD Responder Index >9 before RTX, was significantly associated with relapse (HR=3.68, 95% CI: 1.1, 12.6) (P=0.04), whereas systematic RTX maintenance retreatment was associated with longer relapse-free survival (41 versus 21 months; P=0.02). Seventeen patients (51.5%) received more than 1 course of RTX, with a total number of 58 retreatment courses. Median number of retreatment per patient was 2 (range: 1–12). Retreatment was used for relapses in 9 cases, and as systematic in 12. Clinical response was obtained in all 8 evaluable patients retreated for relapse but one (non-responder to a first RTX course). For maintenance therapy, doses were variable ranging from 300 mg to 1 g, and frequency from every month to 17 months. Relapse after systematic RTX retreatment occurred in 4/12 (33%), with a median delay of 17 months after RTX (range: 14–18). Follow-up after the last maintenance RTX infusion was < 12 months in 7/8 other patients. Eight severe infections occurred in 4 patients (severe infections rate: 12.1/100 patient-years) and hypogammaglobulinemia ≤5 g/L occurred in 3.

Conclusions: RTX is effective for the treatment of IgG4-RD at diagnosis and in case of relapse. However, relapses are frequent after B-cell reconstitution. Maintenance therapy with RTX could represent a good strategy, especially in patients with initial most active disease (IgG4-RD RI>9) and with B-cell reconstitution during follow-up, but is limited by the high incidence of infectious adverse events.