



Comparison of Individually Tailored Vs Systematic Rituximab Regimens to Maintain ANCA-Associated Vasculitis Remissions: Results of a Prospective, Randomized-Controlled, Phase 3 Trial

Pierre Charles, Benjamin Terrier, Elodie Perrodeau, Pascal Cohen, Stanislas Faguer, Antoine Huart, Mohamed Hamidou, Christian Agard, Bernard Bonnotte, Maxime Samson, et al.

► To cite this version:

Pierre Charles, Benjamin Terrier, Elodie Perrodeau, Pascal Cohen, Stanislas Faguer, et al.. Comparison of Individually Tailored Vs Systematic Rituximab Regimens to Maintain ANCA-Associated Vasculitis Remissions: Results of a Prospective, Randomized-Controlled, Phase 3 Trial. 2017 ACR.ARHP ANNUAL MEETING, Nov 2017, SAN DIEGO, United States. hal-01787131

HAL Id: hal-01787131

<https://amu.hal.science/hal-01787131>

Submitted on 25 May 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Comparison of Individually Tailored Vs Systematic Rituximab Regimens to Maintain ANCA-Associated Vasculitis Remissions: Results of a Prospective, Randomized–Controlled, Phase 3 Trial

Pierre Charles¹, Benjamin Terrier², Elodie Perrodeau³, Pascal Cohen², Stanislas Faguer⁴, Antoine Huart⁵, Mohamed Hamidou⁶, Christian Agard⁷, Bernard Bonnotte⁸, Maxime Samson⁸, Alexandre Karras⁹, Noémie Jourde-Chiche¹⁰, François Lifermann¹¹, Pierre Gobert¹², Catherine Hanrotel-Saliou¹³, Pascal Godmer¹⁴, Nicolas Martin Silva¹⁵, Grégory Pugnet¹⁶, Marie Matignon¹⁷, Olivier Aumaître¹⁸, Estibaliz Lazaro¹⁹, Xavier Puéchal²⁰, Philippe Ravaud²¹, Luc Mouthon²² and Loïc Guillevin²⁰, ¹Service de Médecine Interne, Hôpital Cochin, Paris, France, ²Service de Médecine Interne, Hôpital Cochin, Centre de référence national pour les maladies systémiques autoimmunes rares d'Ile de France, DHU Authors, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France, Paris, France, ³Epidemiology, Hopital Hotel Dieu, Paris Descartes University, Paris, France, ⁴Service de Néphrologie et Immunologie Clinique, Centre Hospitalier Universitaire (CHU) de Toulouse, Toulouse, France, ⁵CHU, Toulouse, France, ⁶Internal Medicine Department, Internal Medicine Department, Nantes University Hospital, Nantes, France, ⁷Internal Medicine Department, Nantes University Hospital, Nantes, France, ⁸Department of Internal Medicine and Clinical Immunology, Hôpital François Mitterrand, CHU de Dijon, Dijon, France, ⁹Nephrology, HEGP, Paris, France, ¹⁰Vascular Research Center of Marseille, Aix-Marseille Univ., Vascular Research Center of Marseille, Marseille, France, ¹¹Dax, Dax, France, ¹²Nephrology, Centre Hospitalier d'Avignon, Avignon, France, ¹³Brest, Brest, France, ¹⁴Medecine Interne, CH Vannes, Vannes, France, ¹⁵Department of Internal Medicine, Caen University Hospital, Caen, France, ¹⁶Department of Internal Medicine, Toulouse University Hospital, University of Toulouse, INSERM UMR 1027, Toulouse, France, ¹⁷Service de Néphrologie, Hôpital Henri-Mondor, Créteil, Créteil, France, ¹⁸CHU Pitié-Salpêtrière - Department of Internal Medicine 2. Referral center for SLE/APS, Paris, France, ¹⁹service de médecine interne et maladies infectieuses, CHU de Bordeaux, Pessac, France, ²⁰National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP-HP, Université Paris Descartes, Paris, France, ²¹Hôpital Hôtel Dieu, Paris, France, ²²Service de Médecine Interne, Hôpital Cochin, Centre de référence national pour les maladies systémiques autoimmunes rares d'Ile de France, DHU Authors, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France ;Université Paris Descartes Sorbonne Paris, Paris, France

Keywords: ANCA, B cells, rituximab and vasculitis

Background/Purpose:

Once ANCA-associated vasculitis (AAV) remission was obtained, rituximab (RTX) superiority to azathioprine (AZA) to maintain remission was shown.¹ In that study, at month 28, only 5% of RTX recipients vs 29% taking AZA suffered major relapses. However, at present, neither ANCA-positivity and/or titers (status) nor peripheral blood CD19 B-cell–detection are considered reliable AAV-relapse predictors. The MAINRITSAN2 trial (ClinicalTrials.gov, no. NCT01731561) was designed to evaluate RTX infusions individually tailored to ANCA status and/or circulating CD19 B-cell reappearance to maintain AAV remission.

Methods:

Patients with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) in complete remission after induction therapy (glucocorticoids and cyclophosphamide, rituximab or methotrexate) were included in an open-label, multicenter, randomized-controlled trial to compare RTX regimens: given according to ANCA status and/or circulating CD19 B-cell reconstitution vs systematically infused (controls). The experimental arm received fixed, 500-mg RTX infusions on day-0 postrandomization, then every 3 months until month 18, when CD19 lymphocytes exceeded $0/\text{mm}^3$ or ANCA status (reappearance)/titer (higher) differed from the previous determination. Controls received 500 mg of RTX on days 0 and 14 postrandomization, then 6, 12 and 18 months after the first infusion. The primary endpoint was the number of relapses (new or reappearing symptom or worsening disease with BVAS>0) at month 28, as assessed by an independent Adjudication Committee blinded to treatment arms.

Results: The 162 patients included [117 (72.2%) GPA and 45 (27.8%) MPA] were equally allocated to the experimental (n=81; 50%) and control (n=81; 50%) groups. Prerandomization induction therapy was cyclophosphamide for 100 (61.7%) patients, RTX for 61 (37.7%) or methotrexate for 1 (0.6%). Median RTX-infusion numbers were: 3 (interquartile range (IQR) 2–4) for the experimental arm and 5 (IQR 5–5) for controls. Twenty-one (13%) patients suffered 22 relapses: 14 (17.3%) in 13 experimental arm patients and 8 (9.9%) in 8 controls (P=0.22). The relapse-free-survival rate was 83.8% (95% confidence interval [CI], 76.1–92.3%) for the experimental arm and 86.4% (95% CI, 79.2–94.2) for controls (P=0.58). Twenty-six (32.1%) experimental arm patients experienced at least 1 severe adverse event vs 31 (38.3%) controls (P=0.51). Four patients died, 1 of an infectious complication. No association between ANCA status and/or circulating CD19 B cells and relapses was observed.

Conclusion: AAV-relapse rates for patients given individually tailored or systematic RTX-infusion schedules did not differ significantly. However, ANCA and circulating CD19 B cells could be considered useful tools to decide to reinfuse because they achieved lower RTX total doses (i.e., 3 vs 5 infusions) to prevent relapses in the experimental arm.