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

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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/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.