Rituximab for chronic periaortitis without evidence of IgG4-related disease: a long-term follow-up study of 20 patients

Chronic periaortitis (CP) is a rare condition characterised by a peri-aortoiliac fibro-inflammatory tissue. A total of 20%–50% of the cases are immunoglobulin G4 (IgG4)-related, based on histological evidence of IgG4+ plasma cell infiltration (on a background of dense lymphoplasmacytic infiltrates, storiform fibrosis and tissue eosinophilia) and/or increased serum IgG4.[1]

Glucocorticoids are the first-line therapy for CP.[2] However, some patients are refractory, frequently relapsing or have contraindications to glucocorticoids. The anti-CD20 monoclonal antibody rituximab proved efficacious in systemic forms of IgG4-related disease (IgG4-RD) including IgG4-related CP,[3] but data on IgG4-unrelated CP are scarce.[4–6] In this study, we tested rituximab in CP patients without evidence of IgG4-RD who had relapsing/refractory disease or contraindications to standard-dose glucocorticoids.

We included patients with active, IgG4-unrelated CP who received rituximab (October 2009 to April 2017). Online supplementary methods describe the diagnostic and follow-up procedures, the definitions of remission and refractory, and the statistical analysis.

Twenty consecutive patients were included. Two of them were previously reported.[5] Of the eight patients with available CP biopsies, none had significant IgG4$^+$-plasma cell infiltration. None had other biopsy-proven IgG4-related lesions or high serum IgG4. Four patients were newly diagnosed and had contraindications to standard-dose glucocorticoids, 13 were frequent relapsers and 3 refractory.

The patients' clinical manifestations are reported in supplementary table S1. Rituximab (1000 mg 2 weeks apart or 375 mg/m^2/week×4 weeks) was given alone to 4 patients and with prednisone (median initial dose 25 mg/day, IQR 25–50 mg/day) to 16; six received rituximab maintenance (single 1000 mg doses every 6–8 months).

At month 6, all patients were symptom-free; erythrocyte sedimentation rate (ESR) (figure 1) and C-reactive protein (CRP) dropped (respectively, p<0.0001 and p=0.01, vs baseline). The proportion of patients with ureteral involvement decreased from 65% to 40% (supplementary table S2). A significant reduction was observed in periaortic (p=0.001) and peri-iliac (p=0.006) CP thickness, maximum standardised uptake value (p=0.0001) and prednisone dose (p<0.0001) (figure 1). Supplementary figure S1 shows representative CT/positron emission tomography (PET) responses, and supplementary figure S2 shows PET uptake grades after treatment. At month 12, two patients were lost to follow-up. The remaining 18 were asymptomatic, 11 (61%) being glucocorticoid-free. Ureteral involvement rate, ESR, CRP and CP thickness further decreased (supplementary table S2, figure 1). At month 18, all the 16 assessable patients were asymptomatic; two (12.5%) had ureteral involvement. Fluorodeoxyglucose (FDG) uptake further declined (p<0.0001 vs baseline).

During the follow-up (median 38 months, IQR 17–61 onths), 15 patients (75%) achieved remission; of them, three relapsed (months 4, 47 and 59) (supplementary figures S3 and S4). Two were successfully retreated with rituximab and one received methotrexate +prednisone. The main outcomes did not significantly differ between the rituximab monotherapy and the rituximab +prednisone treatment regimens, and between those who received protocolised rituximab retreatment and those who did not (data not shown), although these subgroups were small for reliable comparisons.

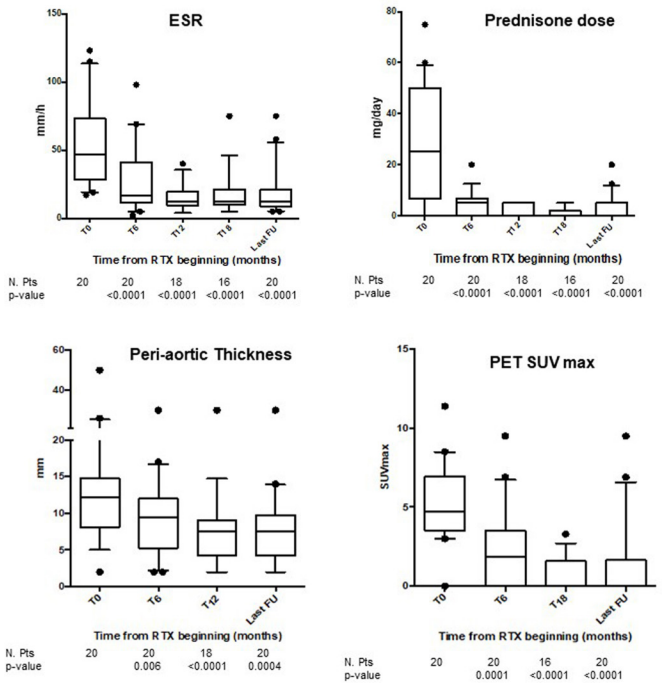

Figure 1 Variation in erythrocyte sedimentation rate (ESR), prednisone dose, periaortic thickness of chronic periaortitis (CP) and SUVmax at different time points. Significant reductions in ESR, prednisone dose, periaortic CP thickness and SUVmax were observed after rituximab (RTX) therapy. These variations were analysed using Wilcoxon signed-rank test. The reported p values refer to the comparisons between each time point and baseline. Significant reductions were also observed between T12 and T6 for ESR (p=0.02), prednisone dose (p=0.007) and CP thickness (p=0.001). Data are shown as box plots. Each box represents 25th–75th percentiles. Lines inside the boxes indicate the median. The whiskers represent 10th–90th percentiles. Circles indicate outliers. T0, T6, T12, T18 and Last FU denote, respectively, the time of RTX therapy, month 6, month 12, month 18 and last follow-up. PET, positron emission tomography; SUVmax, maximum standardised uptake value.

One patient died for stroke (month 12) and another developed chronic lymphocytic leukaemia (month 33). The remaining adverse events were graded 1–3 (supplementary table S3).

Our results show that rituximab achieves objective and metabolic responses and a high remission rate in CP patients without IgG4-RD who had relapsing/refractory disease or contraindications to standard-dose glucocorticoids. Although responses early after rituximab could also result from concomitant glucocorticoid therapy, further improvement on CT/MRI and PET was also seen after month 12, when most patients had discontinued glucocorticoids. Rituximab was well-tolerated.

Our study was retrospective and had a small sample size, which also limited subgroup comparisons (eg, rituximab alone vs rituximab plus glucocorticoids, and protocolised vs on-demand re-retreatment). Another limitation relates to the lack of biopsies in 60% of the patients, which makes their IgG4-unrelatedness uncertain. However, biopsies are routinely performed in only 10%–30% of CP patients.[2 4] These drawbacks withstanding, our

findings encourage rituximab use for difficult-to-treat CP and advocate larger confirmatory studies.

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Contributors MLU, FM and AV designed the study, analysed the data and drafted the manuscript. MLU, FM, AP, PF, F Peyronel, GT, SF, CDB, PCG, GE and AV followed the patients and collected the data. F Pegoraro and MLU generated the figures. PCG, DP, PR and GE critically reviewed the manuscript.

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