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Anti-CD20 treatment shows changes not only in B-lymphocytes but also in T-subpopulations

In renal pathology, Rituximab has been proven to be useful in the treatment of some primary glomerulopathies, vasculitis with renal involvement, severe lupus with kidney disease, and especially in renal transplantation, where it is applied during the treatment of desensitization in hyperimmunized patients, patients receiving transplantation from an ABO incompatible living donor, and patients with antibody-mediated rejection. After anti-CD20 treatment of patients with systemic lupus erythematosus (SLE), published works describe clear and significant changes in the phenotype of circulating lymphocytes, in both B- and T-cells: (a) next to the expected depletion of B-cells by Rituximab, an unexpected decrease of naïve and memory T-lymphocytes have been described, particularly between three and six months after treatment, when a gradual recovery of naïve B- and T-cells occurs. These changes extend for two years post-treatment, in relation to disease remission, while the return of memory cells correlates with relapse. (b) An increase in regulatory T-cells in patients with clinical response to treatment has also been described. (c) Finally, a reduction of co-stimulatory molecules (CD40 and CD80) suggests less T-cell activation has been also involved. In a longitudinal study it has been described that a single dose of rituximab in the induction therapy in renal transplant recipients leads (in addition to a depletion of B-cells) to a relative increase of transitional and memory-like B cells, without affecting T-cell phenotype and function. There are certain similarities between the SLE immunopathology and humoral kidney rejection, involving both humoral (IgG and hypermutated antibodies explained by T and B cooperation in both situations) and cellular immunity (Th1 and Th17 responses). Thus, as with the SLE studies, it seems feasible and potentially useful to develop evaluations of lymphocyte dynamics in pathological processes after anti-CD20 treatment. Therefore, the main objective of our study was to describe qualitatively and quantitatively the different immune lymphocyte phenotypes of patients with renal disease after treatment with anti-CD20.

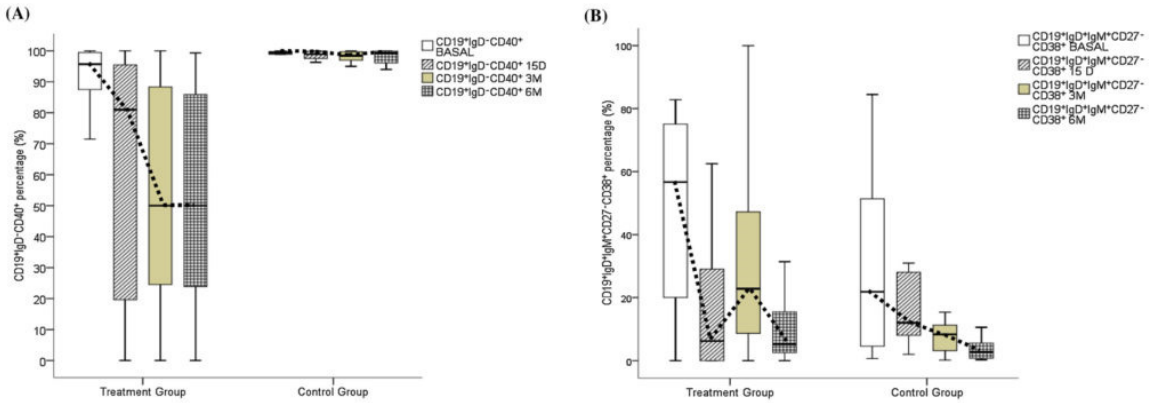

Fig. 1. Box plots representing the percentage of (A) memory B cells (CD19+IgD−CD40+ Lymphocytes) and (B) naïve B-cell (CD19+IgD+IgM+CD27−CD38+ Lymphocytes) during follow-up study on both groups, CG (Control Group) and TG (Treatment Group). Numeric data are shown in Supplementary Table 3. Each boxplot represents from the top to the bottom: the whiskers are lines that extend from the upper and lower edge of the box to the highest and lowest values which are no greater than 1.5 times the interquartile (IQ) range, 75th percentile (top box line), 50th percentile (middle box line) and 25th percentile (bottom box line). The discontinuous lines follows the median during the

different times of follow-up. U Mann-Whitney tests for comparison between Treatment Group-Control Group was used: (A) basal $p = 0.059$, 15 days $p = 0.002$, 3 months $p < 0.001$, 6 months $p < 0.001$. (B) basal $p = 0.121$, 15 days $p = 0.184$, 3 months $p = 0.051$, 6 months $p = 0.155$. Number of patients per group (N): Basal (Treatment Group = 19, Control Group = 18), 15 days (Treatment Group = 15, Control Group = 16), 3 months (Treatment Group = 16, Control Group = 14) and 6 months (Treatment Group = 19, Control Group = 14).

Two cohorts of transplanted and autoimmune kidney patients were compared: Those that began treatment with Rituximab, matched (for sex, age and general clinical parameters) with non-treated control kidney patients. Different analyses were performed: (A) B-lymphocyte subpopulations; (B) T-cell subpopulations; (C) serum levels of BAFF, APRIL, Rituximab and anti-Rituximab; (D) rs396991 polymorphism of CD16a and 4 time points post-antiCD20 for each group of parameters were analyzed (baseline, day 15, three and six months). Main results of our study were: (A) An expected depletion of all B cell subsets analyzed, although preferentially decreases of CD40+memory B-cells, switched memory cells and plasmablasts were observed. (B) A significant decreased percent-age of CD4+T-lymphocytes was defined, while consequently a significant decrease of the percentage of memory T-cells while naïve T-cells increased. (C) A significant increase for APRIL was also observed, as well as a positive correlation between these APRIL levels, and the differential of B-cell disturbance. (D) The presence of CD16a Valine-variant (that is known to improve clinical response to rituximab) induced greater changes in the variations of total T-cell and T-naïve subpopulations.

Our results highlight that the treatment of renal disease with Rituximab affects T-cells, par-ticularly naïve/memory balance, while APRIL could be also a secondary biomarker in this treatment. The sequential analysis of phenotypic alterations of B- and T-cells could help patient management, although further studies to identify periods of remission or clinical relapse are warranted.

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Publication

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