LEPTIN ENHANCED THE EXPRESSION OF INCREASE OF CIRCULATING MEMORY B CELLS AFTER GLUCOCORTICOID-INDUCED REMISSION IDENTIFIES PATIENTS AT RISK OF IGG4-RELATED DISEASE RELAPSE

M. Lanzillotta1, E. Della Torre1, R. Milanò2, E. Bozzolo2, E. Bozzalla Cassione1, L. Roveri1, M. Falconi2, F. Cicci2, L. Dagna1.1 Internal Medicine, Allergy And Clinical Immunology, 2Unit of Hematology and Bone Marrow Transplantation, 3Unit of Pancreatic Surgery – Pancreas Translational and Clinical Research Center, 4Unit of Allergy, Clinical Immunology and Rare Disease – UniRAR, San Raffaele Scientific Institute, Milan, Italy

Background: IgG4-related disease (IgG4-RD) is relapsing-remitting systemic fibro-inflammatory condition characterised by elevated serum IgG4 concentration and by tumor-like lesions.1 Glucocorticoids represent the treatment of choice to induce IgG4-RD remission but relapses occur in almost 50% of patients at two years.2 Several evidences suggest that B cells are central to the pathogenesis of IgG4-RD, the most significant being (i) the clinical improvement induced by B-cell depletion with rituximab, and (ii) the oligoclonal expansion of circulating plasma blasts in the vast majority of patients.3 Objectives: To describe alterations of B-lymphocyte subpopulations that might predict IgG4-RD relapse in patients treated with a first course of glucocorticoids according to international guidelines.

Methods: Thirty patients with IgG4-RD were treated with glucocorticoids according to international consensus guidelines. Flow cytometry analysis of circulating CD19+ and CD20+ cells, naïve B cells, plasmablasts, and plasma cells was performed at baseline and every 6 months after the initiation of corticosteroid treatment.

Results: Patients with active untreated IgG4-RD showed reduced CD19+ B cells, CD20+ B cells, and naïve B cells compared to healthy controls (p<0.05), but expanded plasmablasts and plasma cells (p<0.01). Glucocorticoids treatment led to disease response in all patients. Clinical improvement was accompanied by a significant reduction of naïve B cells, circulating plasmablasts, and plasma cells, and by a significant increase of memory B cells compared to baseline (p<0.01). Increase of circulating memory B cells was observed only in patients experiencing disease relapse and not in patients who maintained remission at two years of follow-up (HR:14.40, 95% CI 2.96–70.1, p<0.01, figure 1 A-B). Relapse rates at 12 and 24 months were 25% and 100% with memory B cell increase at 6 months (figure 1C), respectively. No B-cell subpopulations were found to predict IgG4-RD relapse at disease onset.

Conclusions: The efficacy of glucocorticoids in IgG4-RD is associated with selective effects on different B-cell subpopulations. IgG4-RD relapse may be predicted by the increase of memory B-cells after glucocorticoid-induced remission

REFERENCES:
Background: Ligand to the inducible T cell costimulator (ICOSL) on B cells is essential for the ICOS-dependent follicular recruitment of activated T cells. In patients with rheumatoid arthritis (RA) the IGF1-IGF1R axis is altered. Inhibition of IGF1R alleviated arthritis by reducing IL-6-dependent formation of Th17 cells. Here we study the role of IGF1R on CD21+ cells in experimental arthritis.

Methods: Female B6C3F1 mice were immunised with methylated BSA or with CII. Consequences of the IGF-1R inhibition for arthritis were studied in mBSA and CII-immunised mice treated with NT157 compound promoting degradation of insulin receptor substrates or using shRNA producing construct (shIGF1R). At termination three sub-populations of CD21+ cells - were analysed: follicular dendritic cells (FDC, CD21+CD19-CXCR5-); marginal zone B cells (MZB, CD21+-CXCR5-); follicular B cells (Fbc, CD21+CD19+CXCR5+). Supernatants of LPS-stimulated splenocytes were analysed for production of cytokinones, cytokines using Cytokine Array. Serum levels of antigen specific and autoantibodies were measured in an ELISA.

Results: In spleen of mBSA-immunised mice, ICOSL expression on CD21+ cells correlated to IGF1R (r=0.70, p=0.007). Inhibition of IGF1R induced a 20% reduction in ICOSL expression in all CD21+ subsets (p=0.007) followed by an increase in the number of MZB (p=0.003), while FDC and Fbc were unchanged. Inhibition of IGF1R had no effect on the expression of ICOSL on CD4 T cells or the subset of CXCR5+ follicular T cells. Reduction of the ICOSL+CD21+B cells was associated with lower production of IL-13. Inhibition of IGF1R signalling by NT157 and by shRNA, reduced production of CXCL13 and CXCL12, the chemokines essential for B cell migration towards follicles. In contrast, the production of chemokines CCL5 and CXCL12 preventing intra-follicular migration was increased, which explains the increase of MZB. Additionally, the insufficient ICOSL signalling significantly reduced the production of IL-7 and IL-4, regulating class switching of B cells in germinal centres and differentiation of B cells into plasma cells. The described disbalance in the cytokines aiding B cell development led to the reduced production anti-inflammatory IL-10 and of mBSA-specific IgM (p=0.005) and increased production of autoreactive RF-IgM levels (p=0.001).

Conclusions: The study shows that IGF1R controls B cell development through the expression of ICOSL on CD21+ cells. Insufficient ICOSL signalling disturbs a balance between antigen-specific response and autoantibody production in experimental arthritis.

REFERENCE:

Disclosure of Interest: None declared


THU0041 THE EFFECTS OF ABATACEPT ON HUMAN B CELL ACTIVITIES


1Division of Allergy, Immunology and Rheumatology, Department of Medicine, Taipei Veterans General Hospital, 2Institute of Microbiology and Immunology, 3Institute of Microbiology and Immunology, and Infection and Immunity Center, National Yang-Ming University, Taipei City, Taiwan, Province of China

Background: Abatacept is a cytotoxic T lymphocyte antigen-4 (CTLA-4) fusion protein approved for rheumatoid arthritis (RA) treatment worldwide. Abatacept mimics the natural CTLA-4 and competes with CD80 for binding the CD80/CD86 on antigen presenting cells to prevent T cell activation. However, the impacts of CTLA-4 agonist through its interaction with CD80/CD86 on B cells are not fully understood.

Objectives: The aim of this study was to test whether CTLA-4 regulates human B cell functions.

Methods: We assayed the effect of abatacept on human B cells in both in vitro and in vivo conditions. Blood was taken from 20 patients with RA before and after abatacept treatment and the expression of surface proteins on B cells was detected using immunofluorescence staining. Serum level of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA) was measured by ELISA. Purified human B cells from healthy donors were stimulated in the presence of abatacept and cell proliferation, cytokine production, plasma cell differentiation, and antibody production were measured.

Results: In RA patients, abatacept treatment transiently reduced the level of CD80/CD86 on peripheral blood memory B cells and increased the naïve to memory B cell ratio. Also, abatacept reduced IgM-RF level in 10 out of 12 patients, which correlates with patients disease activity, but it had no significant effects on serum levels of anti-citrullinated protein antibody or anti-tenasin toxoid antibodies during the 6 months of abatacept treatment. In the in vitro assays, we observed that the CD80 and CD86 induced by T-independent (TI) but not T-dependent (TD) stimulation was significantly downregulated by abatacept at both the mRNA level and protein level. Some TI-induced cytokine production by B cells from healthy donors was also reduced by abatacept. Neither TI nor TD-stimulated B cell proliferation was reduced by abatacept in “H-thymidine incorporation assay. Abatacept had no significant effect on CD38+Granzyme B and CD27+ plasma cell differentiation. Finally, abatacept inhibited Daudi-B cell induced alloimmune T cell proliferation, indicating a significant blockade of T-B interaction by abatacept.

Conclusions: In RA patients, abatacept may decrease RF level by interfering the interaction of CD28 with CD80/CD86, therefore preventing B cells from T cells'...