

Effects of glucocorticoids and methotrexate-based therapeutic regimens on B cell subpopulations in patients with IgG4-related disease.

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Objective:

IgG4-related disease (IgG4-RD) is a systemic fibro-inflammatory disorder characterized by fibrotic lesions infiltrated by IgG4 positive plasma cells. The prompt clinical responses obtained after B cell depletion with rituximab in IgG4-RD patients suggest that B lymphocytes drive the pathogenesis of this condition and sustain disease activity. This conclusion, however, requires further confirmation because IgG4-RD responds also to non-B cell depleting therapies such as glucocorticoids and methotrexate. In the present work we aim to evaluate the effects of glucocorticoids and methotrexate-based therapeutic regimens on B lymphocyte subpopulations in patients with IgG4-RD.

Methods:

Sixteen patients with active IgG4-RD were studied. FACS analysis on PBMCs was performed in order to identify the following B cell subpopulations: total B cells (CD19+CD20- and CD19+CD20+ cells), circulating plasmablasts (CD19+CD20- CD27+CD38++ cells), naïve B cells (CD19+CD20+CD27-CD38+ cells), memory B cells (CD19+CD20-CD27+CD38+ cells), circulating plasma cells (CD38+CD138+ cells). Disease activity was assessed by means of the IgG4-RD responder index (IgG4-RD RI). Flow cytometry was performed at baseline and after six months of immunosuppressive therapy with glucocorticoids (0.6-1mg/kg/day) and/or methotrexate (10-20mg/week). Ten sex and age matched healthy subjects were used as controls.

Results:

At baseline, circulating plasmablasts were expanded in IgG4-RD patients (median 3780 cell/mL; range 330-9300) compared to controls (median 280 cell/mL; range 0-1000) ($p < 0.05$); total B cells (median 133000 cell/mL; range 34000-569000) and naïve B cells (median 13080 cell/mL; range 1970-64270) were reduced in IgG4-RD patients compared to controls (median 280 cell/mL; range 194-330; and median 54020 cell/mL; range 21050-106780, respectively) ($p < 0.05$). No differences in memory B cells and circulating plasma cells were observed ($p > 0.05$). Circulating plasmablasts but not other B cell subsets positively correlated with serum IgG4 levels, number of organ involved, and IgG4-RD RI ($p < 0.05$). At six months follow-up, the median IgG4-RD RI decreased from 9 to 2. Circulating plasmablasts and naïve B cells counts decreased in all patients together with disease improvement ($p = 0.0002$ and 0.025 compared to baseline values, respectively); total B cells, circulating plasma cells, and memory B cells were unaffected by immunosuppressive therapy.

Conclusions:

Non-B cell depleting therapies based on glucocorticoids and/or methotrexate induce clinical improvement and deplete circulating plasmablasts and naïve B cells in patients with IgG4-RD; circulating plasma cells and memory B cells are not affected by glucocorticoids and methotrexate. Our study, performed with non-B cell depleting agents, provides clinical evidences that circulating plasmablasts are likely linked to IgG4-RD pathogenesis and disease activity.