7. The role of B cells in inflammatory diseases

A134 ANTI-IL-6 RECEPTOR ANTIBODY (TOCILIZUMAB): A B CELL TARGETING THERAPY

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Background and objectives B cells function as regulatory cells by producing inhibitory cytokines such as transforming growth factor β (TGF-β) and interleukin 10 (IL-10). Human

CD25high B cells were shown to secrete higher levels of IL-10 versus CD25low B cells, suggesting this subset of cells to be immune-regulatory. Tocilizumab, a monoclonal antibody that acts as an IL-6R antagonist thus inhibiting IL-6 activity, and its autocrine growth activity on B cells is currently used for treatment of rheumatoid arthritis (RA). Following this treatment, one might expect a reduction in B cell activity status, and on the other hand increase of their regulatory properties.

Methods Freshly purified B lymphocytes were isolated from 10 active RA patients, with inadequate response to methotrexate, at baseline and 3 months following add on tocilizumab. Clinical status was assessed by DAS 28 score and erythrocyte sedimentation rate (ESR). Using flow cytometry, B cells were stained for the expression of intracellular TGF-β, IL-10, membrane CD69, and MHC-II. These markers were assessed in primary (no-stimulated) CD25high B cells and expressed in MFI, with results given in mean ± SEM.

Results Three months following initiation of tocilizumab, the expression of intracellular TGF-β in CD25high B cells was significantly increased (from 5.2 ± 2.3 at baseline to 8.1 ± 2.8; $p < 0.02$); the expression of MHC-II on B cells was significantly reduced (from 9.1 ± 2.2 at baseline to 4.2 ± 0.4; $p < 0.04$). In addition, the expression of CD69 also decreased (from 7.6 ± 2.4 at baseline to 2.7 ± 0.7; $p < 0.03$). The expression of intracellular IL-10 was too low for comparison. These phenotypic B cell changes namely, the alteration in B cell activity and antigen presenting cell (APC) properties and the shift and/or expansion of the B cell subset with regulatory properties were found to occur in association with beneficial clinical outcome, namely DAS improvement from 6.8 ± 0.3 at baseline to 3.1 ± 0.4, $p < 0.002$, and ESR decrease from 44.4 ± 8.6 at baseline to 7.4 ± 2.3, $p < 0.006$.

Conclusions Our unique finding of a shift in B cell properties following tocilizumab treatment, namely the increase in TGF-β expression and the alteration in their activation status and APC properties in CD25high B cells, suggests that the induction/expansion of B regulatory cells may be one of the mechanisms by which tocilizumab may possibly produce its beneficial clinical effects.