In multiple sclerosis patients, B cells repopulate immature yet more activated upon anti-CD20 antibody therapy

Short title: Recurrence of B cells after anti-CD20 therapy

Nitzan Nissimov[1]*, Zivar Hajiyeva[2], Wolfgang Brück[1],

Silke Häusser-Kinzel[1#]* and Martin S. Weber[1,2#]*

[1] Institute of Neuropathology, University Medical Centre, Göttingen, Germany;

[2] Department of Neurology, University Medical Centre, Göttingen, Germany

[#] Equally contributing authors listed in alphabetical order

* Main authors

Introduction: In multiple sclerosis (MS), B cells are implicated in promoting inflammation through antigen presentation and secretion of pro-inflammatory cytokines. Thus, the therapeutic removal of B cells via anti-CD20 antibodies efficiently reduces annual relapse rates and the development of new and enlargement of existing central nervous system lesions. According to the current guidelines, most patients receive anti-CD20 antibodies every 6 months to avoid B cell repopulation. However, the therapeutic need of a permanent absence of B cells is not well substantiated, as phenotype and function of recurring B cells are not yet thoroughly examined in MS.

Objective: Hence, we characterized the phenotype of repopulating B cells in MS patients after anti-CD20 antibody infusion and investigated how their reappearance affects activation and differentiation of T cells.

Methods: Along with clinical data, we collected peripheral blood mononuclear cells of 15 relapsing-remitting MS patients prior, during, and after anti-CD20-mediated B cell removal. Using flow cytometry, we determined activation, maturation, and cytokine production of B cells as well as activation and differentiation of T cells.

Results: We detected repopulating B cells in the blood of two-thirds of all participants 6-13 months after anti-CD20 antibody infusion. In all of them, the recurring B cell pool was enriched in transitional and naïve mature B cells, yet with an enhanced expression of various activation markers and co-stimulatory molecules. Upon B cell recurrence, we further observed an increase in the frequency of naïve, central memory, and effector memory T cells.

Conclusion: Our findings implicate that after their anti-CD20 mediated removal, B cells recur less mature, yet more activated in the blood of patients with MS. Their absence and subsequent reappearance is associated with changes in the phenotype of T cells. Whether these immunological changes have functional and clinical implications remain to be investigated though.