Is intrathecal anti-CD20 an option to target compartmentalized CNS inflammation in progressive MS?

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B cells have gained enormous attention in the treatment of multiple sclerosis (MS). While our earlier pathogenetic understanding of its cause primarily focused on B cell–derived plasma cells producing self-reactive antibodies, more recent findings support the theory that B cells themselves substantially contribute to MS pathogenesis. This conceptual change was primarily triggered by the empirical observation that anti-CD20–mediated B-cell depletion is effective in the treatment of relapsing-remitting MS (RRMS). Clearly exceeding the initial expectations, IV rituximab led to a rapid and lasting halt in the formation of new CNS lesions in patients with RRMS. Its further humanized successor ocrelizumab, as well as the human anti-CD20 antibody ofatumumab, confirmed these encouraging findings. The clinical efficacy of anti-CD20 provided greater appreciation of the fact that antigen-specific B cells are important antigen-presenting cells (APCs), most likely due to their unique capability to directly bind larger conformational antigens at very low concentrations via their B-cell receptor. Furthermore, B cells could be identified as a major source of proinflammatory cytokines, activating other APCs and fostering development of encephalitogenic T cells, jointly consolidating the concept that in RRMS, B cells exert distinctive pathogenic properties that can be targeted by systemic anti-CD20 treatment.

Emerging evidence suggests that throughout the chronic course of MS, pathogenic B-cell function gradually shifts from the periphery into the inflamed CNS. This notion is supported by the observation of B-cell follicle-like lymphatic tissue in the meninges of a proportion of patients with secondary progressive MS. Development of such ectopic structures is generally believed to indicate reproduction and differentiation of pathogenic lymphocytes within the target organ itself; this may partially explain why in later stages of MS clinical progression decreasingly correlates with MRI-detectable CNS infiltration while histopathology remains inflammatory. In this setting of compartmentalized CNS inflammation, systemically applied MS agents, in particular molecularly large monoclonal antibodies, may lose their effectiveness. Supporting this notion, only 0.1% of systemically infused anti-CD20 can be found within the CSF, raising the concern that parenchymal B cells as well as meningeal B cells and/or B-cell follicles cannot be reached and depleted by systemic anti-CD20. Accordingly, one strategy currently being explored to eradicate CNS-established B cells more efficiently is intrathecal (IT) administration of anti-CD20 in patients with progressive MS.

In this issue of Neurology® Neuroimmunology & Neuroinflammation, Svenningsson et al. report their 1-year findings from a phase 1b study in which they tested IT injection of 25 mg rituximab in 10 patients with progressive MS. Rituximab was provided via an Ommaya reservoir connected to a ventricular catheter. In the first 3 patients the dose was titrated, with daily applications of 1 mg, 2.5 mg, 5 mg, 10 mg, and finally 25 mg rituximab; lymphocyte subpopulations were monitored daily during this dose escalation period. All 10 patients thereafter received 3 weekly IT injections of 25 mg rituximab, and peripheral as well as CSF lymphocyte subpopulations were assessed every 2–3 months. As a first finding, the authors report a substantial decline of peripheral B cells, even after the initial application of 1 mg IT rituximab. Following the second dose of 2.5 mg, B lymphocytes became undetectable in the blood, and the full dose of 3 × 25 mg/week resulted in complete depletion of peripheral lymphocytes lasting for 2–3 months. In 2 patients with elevated baseline CSF lymphocyte counts, B-cell frequency rapidly declined upon IT administration of rituximab, whereas in all other patients possible changes remained undetectable due to very low initial CSF lymphocyte counts.

Although the primary outcome of this study, the safety and tolerability of IT anti-CD20 in progressive MS, will be reported upon study completion, we can draw a few important conclusions from these 1-year data. First, up to this point, IT application of rituximab seems to be well-tolerated. Second, the doses...
used systemically to date are likely substantially higher than required for rituximab’s immunologic effect. This notion is in line with ongoing clinical trials evaluating markedly lower doses of anti-CD20 systemically. Third, using this route of administration, the CNS cannot be targeted selectively, which could have been desirable to deplete pathogenic B cells while avoiding the systemic side effects of pan–B cell depletion. This key observation likely refers to the earlier finding that injected IT anti-CD20 has a very short half-life in the CSF and accumulates within the serum. Probably the most important and related limitation of this study is that it remains uncertain whether IT administration is truly capable of depleting B cells within the CNS or whether the drop in CSF B-cell counts is a consequence of a systemic effect. In an attempt to address this question, a recent experimental study compared IT anti-CD20 to its systemic application and observed that IT administration of anti-CD20 was indeed superior in depleting meningeal B cells in established CNS autoimmune disease. In conclusion and in this context, the study conducted by Svenningsson et al. is an important contribution to pioneering the use of IT anti-CD20 in the treatment of progressive MS, fueling hopes that a facilitated elimination of CNS B cells may translate into clinical benefit.

STUDY FUNDING
No targeted funding reported.

DISCLOSURE
M.S. Weber is serving as an editor for PLoS One; received travel funding and/or speaker honoraria from Biogen-Idec, Merck Serono, Novartis, Roche, and Bayer; and receives research support from the National Multiple Sclerosis Society, the Deutsche Forschungsgemeinschaft, Novartis, TEVA, Biogen-Idec, Roche, and the ProFutura Programme of the Universitätshirn Göttingen. Go to Neurology.org/nii for full disclosure forms.

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*Neurol Neuroimmunol Neuroinflamm* 2015;2;
DOI 10.1212/NXI.0000000000000084

This information is current as of March 12, 2015

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