

Can Systemic Anti-CD20 B Cell-Depleting Antibodies Eliminate Meningeal Follicles in Multiple Sclerosis?

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The dramatic success of systemic anti-CD20 monoclonal antibody (mAb) B cell depleting therapy in the relapsing form of multiple sclerosis (MS) has highlighted the importance of B cells in MS immunopathogenesis.¹⁻³ This is believed to be due to B cells role as antigen-presenting cells² and their ability to produce proinflammatory cytokines.³ However, the impact of anti-CD20 mAb therapy on preventing long-term disability in progressive forms of MS is modest.⁴ It has been postulated that this relative lack of efficacy is because of the inadequate penetration by anti-CD20 mAb across the blood–brain barrier (BBB)⁵ into the CNS, where there is evidence of ongoing CNS B cell activation.⁶ Those CNS B cells reside in meningeal ectopic lymphoid follicles (mELT) and are associated with subpial inflammation in patients with MS, particularly in secondary progressive MS (SPMS), where they may contribute to progression and neurodegeneration.^{6,7} The effect of anti-CD20 mAb therapy on mELT remains unknown, and there continues to be several unanswered questions regarding its efficacy against the B cells within them.

Recently, 2 articles have been published in *Neurology: Neuroimmunology & Neuroinflammation* addressing these questions. In this issue, Brand et al.⁸ examined whether anti-CD20 mAb therapy could deplete B cells within mELT in a murine model of MS that develops spontaneous chronic experimental autoimmune encephalomyelitis (EAE) with mELT found around the spinal cord. In this study, the mice were treated with 2 different protocols: (1) prevention (administration from weaning) and (2) treatment after onset of paralysis (clinical score ≥ 3). In both protocols, anti-CD20 mAb therapy did not affect the clinical outcome or demyelination. Anti-CD20 mAb therapy depleted systemic B cells and central B cells within mELT. Although the cellular composition was reduced, mELT remained intact.

In the May 2021 issue, Roodselaar et al.⁹ evaluated the difference between 2 anti-CD20 mAb therapies in a novel murine model of MS. They tested a traditional anti-CD20 mAb therapy (rituximab), which they referred to as “type I” anti-CD20 mAb. In comparison, they tested an Fc-engineered mAb that conferred greater antibody-dependent cellular cytotoxicity¹⁰ that they referred to as “type II” anti-CD20 mAb. In their model, called delayed type hypersensitivity—tertiary lymphoid-like structures (DTH-TLS), mice were immunized with myelin oligodendrocyte glycoprotein (MOG) p35-55 and complete Freund’s adjuvant (CFA), which contains *Mycobacterium tuberculosis* (TB). Twelve days after immunization, heat-killed TB bacteria was injected stereotactically into the piriform cortex. This paradigm resulted in the development of clinically silent mELT that was associated with the presence of microglia followed by activated astrocytes, along with lymphocyte infiltration in mELT. Demyelination was observed within the lateral olfactory tract, adjacent to the site of injection. This model therefore shares histopathologic features of SPMS. Forty days postinduction, mice were treated with either type I or II anti-CD20 mAb therapy. Both therapies resulted in peripheral B cell depletion, reduction in B and T cells within mELT, and reduced size of mELT. Both were also associated with decreased microglial

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activation. Moreover, type II anti-CD20 mAb reduced astrocyte activation to a greater extent than type I anti-CD20 mAb and was associated with less neuronal death. Of interest, MRI with gadolinium (Gd) after anti-CD20 mAb therapy did not show enhancement, implying a lack of BBB breakdown at the time.

Although both research articles demonstrated depletion of B cells within mELT with systemic anti-CD20 mAb therapy, surprisingly they differed in the preservation of mELT. Differences between these 2 articles may be attributed to the mouse models that were used. Although the DTH-TLS model described by Roodseelaar et al. recapitulates the histopathology observed in SPMS, it is artificial because it requires direct CNS injury that results in CNS inflammation and mELT formation. In the earlier relapsing phase of MS, there are areas of focal CNS inflammation with BBB breakdown that corresponds to enhancing lesions on MRI. In SPMS, when the BBB is re-established, there are fewer or no MRI CNS enhancing lesions. Although Roodseelaar et al. demonstrated that there was no MRI enhancement, the MRI was conducted 60 days after anti-CD20 mAb administration. As the MRI was not performed at the time of anti-CD20 mAb administration, it is unclear whether the anti-CD20 mAb penetrated the CNS from residual BBB disruption that resulted from the previous stereotactic injection. It is difficult to compare results from the DTH-TLS model to the spontaneous EAE model used by Brand et al., which was created by crossing MOG-specific T cell receptor transgenic mice with MOG-specific B cell receptor knock-in mice. Systemic anti-CD20 mAb treatment of spontaneous EAE did not result in clinical benefit or decrease in size of mELT, despite reduction of B cells within mELT. The reduction of meningeal B cells with systemic anti-CD20 mAb therapy is consistent with previous data in spontaneous EAE indicating some degree of anti-CD20 mAb penetration through an intact BBB.¹¹ Overall, data from these 2 research articles do not convincingly support systemic administration of anti-CD20 for treatment of CNS B cells within mELT.

One question is whether other approaches could be used to selectively target CNS B cells in progressive MS. Two phase 1b clinical trials that tested intrathecal administration of rituximab for progressive MS showed tolerability, but no clear clinical benefit.^{5,12} Just as Roodseelaar et al. tested type II anti-CD20 mAb, it is possible that CNS targeting with more potent B cell depleting antibodies may result in greater B cell depletion and improved clinical outcomes. In the future, one can also envisage targeting molecules expressed at the BBB (e.g., selective adhesion molecules) or employing the transferrin receptor 1 to serve as a molecular shuttle to enhance

CNS penetration of B cell targeting therapies including anti-CD20 mAb or Bruton tyrosine kinase inhibitors. Cell-based therapies that target B cells may also have a role in the treatment of progressive MS. In summary, the models used by Roodseelaar et al. and Brand et al. recapitulate certain features of SPMS and also highlight the need to use multiple progressive MS models when evaluating CNS B cell targeting approaches.

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