

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

Sasha Gupta, MD,* and Scott S. Zamvil, MD, PhD*

Neurol Neuroimmunol Neuroinflamm 0;8:e1000. doi:10.1212/NXI.0000000000001000

Correspondence

Dr. Gupta
sasha.gupta@ucsf.edu
or Dr. Zamvil
zamvil@ucsf.neuroimmunol.org

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

RELATED ARTICLE

Anti-CD20 Depletes Meningeal B Cells but Does Not Halt the Formation of Meningeal Ectopic Lymphoid Tissue
Page e1012

*These authors contributed equally to this work.

From the Department of Neurology, Weill Institute of Neurosciences and Program in Immunology, University of California, San Francisco, CA.

Go to [Neurology.org/NN](https://www.neurology.org/NN) for full disclosures. Funding information is provided at the end of the article.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

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.

Study Funding

The authors report no targeted funding.

Disclosure

S. Gupta—no disclosures. S.S. Zamvil—Deputy Editor of *Neurology: Neuroimmunology & Neuroinflammation* and is a member of the advisory board for the International Society of Neuroimmunology. He has served as a consultant and received honoraria from Biogen-Idec, EMD-Serono, Genzyme, Novartis, Roche/Genentech, and Teva Pharmaceuticals, Inc., and has served or serves on Data Safety Monitoring Boards for Lilly, BioMS, Teva, and Opexa Therapeutics. Currently, S.S. Zamvil receives research grant support from the NIH, the NMSS, The Maisin Foundation, Biogen, and Celgene. Go to Neurology.org/NN for full disclosures.

References

1. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med*. 2008;358:676–688.
2. Molnarfi N, Schulze-Topphoff U, Weber MS, et al. MHC class II-dependent B cell APC function is required for induction of CNS autoimmunity independent of myelin-specific antibodies. *J Exp Med*. 2013;210:2921–2937.
3. Weber MS, Prod'homme T, Patarroyo JC, et al. B-cell activation influences T-cell polarization and outcome of anti-CD20 B-cell depletion in central nervous system autoimmunity. *Ann Neurol*. 2010;68:369–383.
4. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med*. 2017;376:209–220.
5. Bergman J, Burman J, Gilthorpe JD, et al. Intrathecal treatment trial of rituximab in progressive MS: an open-label phase 1b study. *Neurology*. 2018;91:e1893–e1901.
6. Magliozzi R, Howell O, Vora A, et al. Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology. *Brain*. 2007;130:1089–1104.
7. Absinta M, Vuolo L, Rao A, et al. Gadolinium-based MRI characterization of leptomeningeal inflammation in multiple sclerosis. *Neurology*. 2015;85:18–28.
8. Brand R, Zhou Y, Leppert D, et al. Anti-CD20 depletes meningeal B cells but does not halt the formation of meningeal ectopic lymphoid tissue. *Neurol Neuroimmunol Neuroinflamm*. 2021;8:e975.
9. Roodseelaar J, Zhou Y, Leppert D, et al. Anti-CD20 depletes meningeal B cells but does not halt the formation of meningeal ectopic lymphoid tissue. *Neurol Neuroimmunol Neuroinflamm*. 2021;8:e975.
10. Mössner E, Brünker P, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. *Blood*. 2010;115:4393–4402.
11. Lehmann-Horn K, Kinzel S, Feldmann L, et al. Intrathecal anti-CD20 efficiently depletes meningeal B cells in CNS autoimmunity. *Ann Clin Transl Neurol*. 2014;1:490–496.
12. Bhargava P, Wicken C, Smith MD, et al. Trial of intrathecal rituximab in progressive multiple sclerosis patients with evidence of leptomeningeal contrast enhancement. *Mult Scler Relat Disord*. 2019;30:136–140.