Supplemental material

Appendix e-1. Pathophysiologic mechanisms of MS

The egg or chicken dilemma in MS: What came first – B or T-lymphocytes?

The key question of what can cause the dysfunction of B lymphocytes might be answered when looking at T regulatory cells (Tregs). Two main checkpoints are responsible for the elimination of autoreactive B lymphocytes: one 'central' in the bone marrow and another 'peripheral', mainly associated with Treg function[e1] (see more details in figure 1). Patients with MS appear to have an impairment of the peripheral checkpoint generating autoreactive B lymphocytes.[19] This is exactly the target of anti-CD20 therapy in MS, which preserves pre-B lymphocyte precursors in the bone marrow but deletes autoreactive B lymphocytes that have bypassed Treg control. Anti-CD20 therapy may therefore lead to sustained remission of disease.

In fact, it is likely that both T and B lymphocytes, particularly their dysfunctional interactions, are relevant for MS.[11] For example, recent genome-wide association studies have found that polymorphisms associated with MS are related to the interaction of T-helper cells and antigen-presenting cells (APCs).[e74] As B lymphocytes have an efficient APC function[10], this brings us back again to the initial interactions between B and T-lymphocytes.

Notably, the dysfunctional interaction of B and T-lymphocytes in MS likely generates an overly proinflammatory rather than an anti-inflammatory response. So, it is important to identify exactly which factors are promoting "bad inflammation" and which are actually protecting the individuals from further damage. We can then intervene more precisely, by enhancing protective mechanisms and diminishing the harmful ones.

Appendix e-2. Mechanisms of action of apheresis and IV immunoglobulin (IVIg)

Therapeutic apheresis exerts its beneficial effects by rapidly removing or neutralizing circulating autoantibodies and other proinflammatory molecules.[59] It also reduces the proliferation of B lymphocytes that may enhance the effect of immunosuppressants and chemotherapeutic agents.[59] A substantial reduction in antibody levels in the CSF has also been reported in AE after immunoadsorption; [e66] it is unclear whether the same happens with plasma exchange.

IV human immunoglobulins act through mechanisms of autoantibody neutralization, blockade of activating FcγR and upregulation of inhibitory FcRIIB.[e73] Moreover, it is believed that IVIg might enhance the IgG catabolism. IVIg saturates the neonatal receptor FcRn that is responsible for rescuing IgG from degradation. [e71,e72]This increase the degradation of abnormal autoantibodies.

e-References

e1. Abbas A. Imunologia Celular e Molecular 8ª Edição, 7th ed. 2015.

e2. Venkitaraman AR, Williams GT, Dariavach P, Neuberger MS. The B-cell antigen receptor of the five immunoglobulin classes. Nature 1991;352:777–781.

e3. Mackay F, Schneider P. Cracking the BAFF code. Nat Rev Immunol 2009;9:491–502.

e4. Batista FD, Harwood NE. The who, how and where of antigen presentation to B cells. Nat Rev Immunol 2009;9:15–27.

e5. Lampropoulou V, Hoehlig K, Roch T, et al. TLR-activated B cells suppress T cell-mediated autoimmunity. J Immunol 2008;180:4763–4773.

e6. Frischer JM, Bramow S, Dal-Bianco A, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain 2009;132:1175–1189.

e7. Lovato L, Willis SN, Rodig SJ, et al. Related B cell clones populate the meninges and parenchyma of patients with multiple sclerosis. Brain 2011;134:534–541.

e8. Machado-Santos J, Saji E, Tröscher AR, et al. The compartmentalized inflammatory response in the multiple sclerosis brain is composed of tissue-resident CD8+ T lymphocytes and B cells. Brain 2018;141:2066–2082.

e9. Lisak RP, Benjamins JA, Nedelkoska L, et al. Secretory products of multiple sclerosis B cells are cytotoxic to oligodendroglia in vitro. J Neuroimmunol 2012;246:85–95.

e10. Louveau A, Smirnov I, Keyes TJ, et al. Structural and functional features of central nervous system lymphatic vessels. Nature 2015;523:337–341.

e11. Bar-Or A, Grove, RA, Austin DJ et al. Subcutaneous ofatumumab in patients with relapsing-remitting multiple sclerosis: The MIRROR study. Neurology

2018;90(20):e1805-e1814.

e12. Hauser SL, Bar-Or A, Cohen J et al. Efficacy and safety of ofatumumab versus teriflunomide in relapsing multiple sclerosis: results of the phase 3 ASCLEPIOS I and II trials. Mult Scler. 2019;25(S2):890–938.

e13. Hawker K, O'Connor P, Freedman MS et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. Ann Neurol. 2009;66(4):460-71.

e14. X. Montalban, S.L. Hauser, L. Kappos et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. N Engl J Med 2017;376:209-20.

e15. Alping P, Frisell T, Novakova L et al. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. Ann Neurol. 2016 Jun;79(6):950-8.

e16. Clifford DB, Ances B, Costello C et al. Rituximab-associated progressive multifocal leukoencephalophathy in rheumatoid arthritis. Arch Neurol. 2011. Sep;68(9):1156-1164.

e17. Stashenko P, Nadler LM, Hardy R, Schlossman SF. Characterization of a human B lymphocyte-specific antigen. J Immunol 1980;125:1678–1685.

e18. Bar-Or A, Calkwood MC, Chognot C et al. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: The VELOCE study. Neurology, Accepted, Apr 2020.

e19. De Flon P, Söderström L, Laurell K. Immunological profile in cerebrospinal fluid of patients with multiple sclerosis after treatment switch to rituximab and compared with healthy controls. PLOS ONE 13(2): e0192516.

e20. von Büdingen HC, Bar-Or A, Zamvil SS. B cells in multiple sclerosis: connecting the dots. Curr Opin Immunol 2011;23:713–720.

e21. Baker D, Pryce G, Amor S, Giovannoni G, Schmierer K. Learning from other

autoimmunities to understand targeting of B cells to control multiple sclerosis. Brain 2018;141:2834–2847.

e22. Derfuss T, Weber MS, Hughes R et al. Serum immunoglobulin levels and risk of serious infections in the pivotal Phase III trials of ocrelizumab in multiple sclerosis and their open-label extensions. Mult Scler 2019; 25: (S2) 20-21.

e23. Cooles FAH, Anderson AE, Drayton T, et al. Immune reconstitution 20 years after treatment with alemtuzumab in a rheumatoid arthritis cohort: implications for lymphocyte depleting therapies. Arthritis Res Ther 2016;18:302.

e24. Dall'Era M, Chakravarty E, Wallace D, et al. Reduced B lymphocyte and immunoglobulin levels after atacicept treatment in patients with systemic lupus erythematosus: results of a multicenter, phase Ib, double-blind, placebo-controlled, dose-escalating trial. Arthritis Rheum 2007;56:4142–4150.

e25. Tak PP, Thurlings RM, Rossier C, et al. Atacicept in patients with rheumatoid arthritis: results of a multicenter, phase Ib, double-blind, placebo-controlled, dose-escalating, single- and repeated-dose study. Arthritis Rheum 2008;58:61–72.

e26. Longbrake EE, Cross AH. Effect of Multiple Sclerosis Disease-Modifying Therapies on B Cells and Humoral Immunity. JAMA Neurol 2016, 73(2):219-225.

e27. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology 1999;53:1107–1114.

e28. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. J Exp Med 2005;202:473–477.

e29. Waters PJ, Pittock SJ, Bennett JL, Jarius S, Weinshenker BG, Wingerchuk DM. Evaluation of aquaporin-4 antibody assays. Clin Exp Neuroimmunol 2014;5:290–303.

e30. Barnett M, Prineas J, Buckland M, Parratt J, Pollard J. Massive astrocyte destruction in neuromyelitis optica despite natalizumab therapy. Mult Scler J 2012;18:108–112.

e31. Popescu BFG, Lennon VA, Parisi JE, et al. Neuromyelitis optica unique area postrema lesions: Nausea, vomiting, and pathogenic implications. Neurology 2011;76:1229–1237.

e32. Shimizu F, Schaller KL, Owens GP, et al. Glucose-regulated protein 78 autoantibody associates with blood-brain barrier disruption in neuromyelitis optica. Sci Transl Med 2017;9:eaai9111.

e33. Melamed E, Levy M, Waters PJ, et al. Update on biomarkers in neuromyelitis optica. Neurol Neuroimmunol Neuroinflamm 2015;2:e134.

e34. Vaknin-Dembinsky A, Brill L, Orpaz N, Abramsky O, Karussis D. Preferential increase of B-cell activating factor in the cerebrospinal fluid of neuromyelitis optica in a white population. Mult Scler 2010;16:1453–1457.

e35. Chu VT, Fröhlich A, Steinhauser G, et al. Eosinophils are required for the maintenance of plasma cells in the bone marrow. Nat Immunol 2011;12:151–159.

e36. Mahmood NA, Silver K, Onel K, Ko M, Javed A. Efficacy and safety of rituximab in pediatric neuromyelitis optica. J Child Neurol 2011;26:244–247.

e37. McKeon A, Lennon VA, Lotze T, et al. CNS aquaporin-4 autoimmunity in children. Neurology 2008;71:93–100.

e38. Golay J, Semenzato G, Rambaldi A, et al. Lessons for the clinic from rituximab

pharmacokinetics and pharmacodynamics. MAbs 2013;5:826–837.

e39. Batchelor TT, Grossman SA, Mikkelsen T, Ye X, Desideri S, Lesser GJ. Rituximab monotherapy for patients with recurrent primary CNS lymphoma. Neurology 2011;76:929–930.

e40. Schubert RD, Hu Y, Kumar G, et al. IFN-β treatment requires B cells for efficacy in neuroautoimmunity. J Immunol 2015;194:2110–2116.

e41. Longoni G, Banwell B, Filippi M, Yeh EA. Rituximab as a first-line preventive treatment in pediatric NMOSDs: Preliminary results in 5 children. Neurol Neuroimmunol Neuroinflamm 2014;1:e46.

e42. Valentino P, Marnetto F, Granieri L, Capobianco M, Bertolotto A. Aquaporin-4 antibody titration in NMO patients treated with rituximab: A retrospective study. Neurol Neuroimmunol Neuroinflammation. 2017;4:e317.

e43. Perumal JS, Kister I, Howard J, Herbert J. Disease exacerbation after rituximab induction in neuromyelitis optica. Neurol Neuroimmunol Neuroinflamm 2015;2:e61.

e44. Cree BAC, Bennett JL, Kim HJ, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. *Lancet*. 2019;394(10206):1352-1363

e45. Cree B, Benett, Kim HJ et al. The N-MOmentum study - a randomised, placebocontrolled, double-blind trial of Inebilizumab for neuromyelitis optica spectrum disorder: randomised controlled period and open-label extension results. Mult Scler 2019; 25: (S2) 3–130.

e46. Araki M, Aranami T, Matsuoka T, Nakamura M, Miyake S, Yamamura T. Clinical improvement in a patient with neuromyelitis optica following therapy

with the anti-IL-6 receptor monoclonal antibody tocilizumab. Mod Rheumatol. 2013;23:827–831.

e47. Araki M, Matsuoka T, Miyamoto K et al. Efficacy of the anti-IL-6 receptor antibody tocilizumab in neuromyelitis optica.A pilot study Neurology 2014; 82(15): 1302–1306.

e48. Pittock SJ, Berthele A, Fujihara K et al. Eculizumab in Aquaporin-4–Positive Neuromyelitis Optica Spectrum Disorder. N Engl J Med 2019; 381:614-625

e49. Dalmau J, Tüzün E, Wu H, et al. Paraneoplastic anti- N -methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007;61:25–36.

e50. Brierley JB, Corsellis J, Hierons R, Nevin S. Subacute Encephalitis of Later Adult Life. Mainly Affecting The Limbic Areas. Brain. 1960;83:357–368.

e51. Höftberger R, Lassmann H. Immune-mediated disorders. 2018;145:285–299.

e52. Bien CG, Vincent A, Barnett MH, et al. Immunopathology of autoantibody-associated encephalitides: clues for pathogenesis. Brain 2012;135:1622-1638.

e53. Jain A, Balice-Gordon R. Cellular, synaptic, and circuit effects of antibodies in autoimmune CNS synaptopathies. 2016; 133:77-93

e54. Wright S, Hashemi K, Stasiak L, et al. Epileptogenic effects of NMDAR antibodies in a passive transfer mouse model. Brain. 2015;138:3159–3167.

e55. Martinez-Hernandez E, Horvath J, Shiloh-Malawsky Y, Sangha N, Martinez-Lage M, Dalmau J. Analysis of complement and plasma cells in the brain of patients with anti-NMDAR encephalitis. Neurology. 2011;77:589–593.

e56. Dalmau J. NMDA receptor encephalitis and other antibody-mediated disorders of the synapse: The 2016 Cotzias Lecture. Neurology. 2016;87:2471–2482.

e57. Ariño H, Armangué T, Petit-Pedrol M, et al. Anti-LGI1-associated cognitive impairment: Presentation and long-term outcome. Neurology. 2016;87:759–765.

e58. Malter MP, Frisch C, Schoene-Bake JC, et al. Outcome of limbic encephalitis with VGKC-complex antibodies: relation to antigenic specificity. J Neurol. 2014;261:1695–1705.

e59. van Sonderen A, Thijs RD, Coenders EC, et al. Anti-LGI1 encephalitis: Clinical syndrome and long-term follow-up. Neurology. 2016;87:1449–1456.

e60. Finke C, Prüss H, Heine J, et al. Evaluation of Cognitive Deficits and Structural Hippocampal Damage in Encephalitis With Leucine-Rich, Glioma-Inactivated 1 Antibodies. JAMA Neurol. 2017;74:50–59.

e61. Varley J, Taylor J, Irani SR. Autoantibody-mediated diseases of the CNS: Structure, dysfunction and therapy. Neuropharmacology. Epub 2017 May.

e62. Weissert R. Adaptive Immunity Is the Key to the Understanding of Autoimmune and Paraneoplastic Inflammatory Central Nervous System Disorders. Front Immunol. 2017;8:336

e63. Olnes MJ, Kotliarov Y, Biancotto A, et al. Effects of Systemically Administered Hydrocortisone on the Human Immunome. Sci Rep. 2016;6:23002.

e64. Ehrlich S, Fassbender CM, Blaes C, et al. Therapeutische Apherese bei autoimmuner Enzephalitis. Nervenarzt. 2013;84:498–507.

e65. Suppiej A, Nosadini M, Zuliani L, et al. Plasma exchange in pediatric anti-NMDAR encephalitis: A systematic review. Brain Dev. 2016;38:613–622.

e66. Köhler W, Ehrlich S, Dohmen C, et al. Tryptophan immunoadsorption for the treatment of autoimmune encephalitis. Eur J Neurol. 2015;22:203–206.

e67. Dogan Onugoren M, Golombeck KS, Bien C, et al. Immunoadsorption therapy in autoimmune encephalitides. Neurol - Neuroimmunol Neuroinflammation.

2016;3:e207.

e68. Lee W-J, Lee S-T, Byun J-I, et al. Rituximab treatment for autoimmune limbic encephalitis in an institutional cohort. Neurology. 2016;86:1683–1691.

e69. Hiepe F, Dörner T, Hauser AE, Hoyer BF, Mei H, Radbruch A. Long-lived autoreactive plasma cells drive persistent autoimmune inflammation. Nat Rev Rheumatol. 2011;7:170–178.

e70. Scheibe F, Prüss H, Mengel AM, et al. Bortezomib for treatment of therapy-refractory anti-NMDA receptor encephalitis. Neurology. 2017;88:366–370.

e71. Jacob S, Rajabally YA. Current proposed mechanisms of action of intravenous immunoglobulins in inflammatory neuropathies. Curr Neuropharmacol. 2009;7:337–342.

e72. Hansen RJ, Balthasar JP. Intravenous immunoglobulin mediates an increase in anti-platelet antibody clearance via the FcRn receptor. Thromb Haemost. 2002;88:898–899.

e73. Li N, Zhao M, Hilario-Vargas J, et al. Complete FcRn dependence for intravenous Ig therapy in autoimmune skin blistering diseases. J Clin Invest. 2005;115:3440–3450.

e74. Rieck M, Arechiga A, Onengut-Gumuscu S Greenbaum C, Concannon P, Buckner JH. Genetic variation in PTPN22 corresponds to altered function of T and B lymphocytes. J Immunol. 2007;179(7):4704-10.

e75. Whittam DH, Tallantyre EC, Jolles S, et al. Rituximab in neurological disease: Principles, evidence and practice. Pract. Neurol. 2019; 19: 5–20.

e76. Kim S, Kim W, Li XF, Jung I, Kim HJ. Repeated Treatment With Rituximab Based on the Assessment of Peripheral Circulating Memory B Cells in Patients With Relapsing Neuromyelitis Optica Over 2 Years. Arch Neurol. 2011;

68(11):1412–1420.

e77. Giovannoni G. Anti-CD20 immunosuppressive disease-modifying therapies and COVID-19. Mult. Scler. Relat. Disord. 2020; 41:102135.

e78. Salvarani C, Brown RD Jr, Muratore F, et al. Rituximab therapy for primary central nervous system vasculitis: A 6 patient experience and review of the literature. Autoimmun Rev. 2019;18(4):399-405.

e79. Patel S, Ross L, Oon S, Nikpour M. Rituximab treatment in primary angiitis of the central nervous system. Internal Medicine Journal. 2018; 48(6):724-727.