The Role of Monoclonal Antibodies in Neurological Disorders
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Monoclonal antibody treatment is standard therapy for multiple sclerosis and is under investigation for neuromyelitis optica, peripheral neuropathies, and inflammatory myopathies. This review will highlight the uses of monoclonal antibodies in these diseases.

Multiple Sclerosis
In multiple sclerosis, autoreactive T cells cross the blood-brain barrier under the influence of proinflammatory cytokines and cellular adhesion molecules, resulting in an attack on myelin, with resulting inflammation, degeneration and demyelination. Given the multitude of interactions involved in the immunopathogenesis of multiple sclerosis, several immunological pathways may be targeted with highly specific and selective antibodies.

Natalizumab
At present time, the only FDA approved monoclonal antibody for the treatment of multiple sclerosis is natalizumab, a humanized monoclonal antibody directed against the α4 subunit of the α4β1 integrin, also known as very late antigen-4 (VLA4), which is expressed on the surface of activated lymphocytes. Vascular cell adhesion molecule (VCAM), expressed on the luminal surface of vascular endothelium, acts as the receptor for VLA4. Their interaction ultimately results in lymphocyte adhesion to vascular endothelium and lymphocyte translocation across the endothelium. By its action on VLA4, natalizumab blocks this interaction, in effect inhibiting lymphocyte migration across the blood brain barrier.

Early studies on natalizumab had shown positive results, which led to two phase III multicenter randomized control studies. The first study, AFFIRM, randomized 942 patients to receive either natalizumab or placebo by intravenous infusion every four weeks. Natalizumab was found to reduce the risk of sustained progression of disability by 42% over two years, reduce the accumulation of new or enlarging hyperintense T2 MRI lesions by 83% over two years, and reduce the rate of clinical relapse by 68% at one year. The second study, SENTINEL, randomized 1171 patients having at least one relapse in 12 months while on beta-1a therapy, to receive either beta-1a plus natalizumab, or beta-1a plus placebo by intravenous infusion every four weeks. Combination therapy with natalizumab was found to reduce the risk of sustained disability progression by 24%, reduce the rate of clinical relapse by 54% at one year and by 55% at two years, and reduce the number of new or enlarging hyperintense T2 lesions by 83% at two years.

Based on promising data at one year outcome measures, and a generally tolerable side effect profile, natalizumab was approved in November 2004, prior to completion of the phase three studies. Three months later, in February 2005, two patients were found to have developed progressive multifocal leukoencephalopathy (PML), both of whom had received combination therapy with beta-1a in the SENTINEL trial. Natalizumab was voluntarily withdrawn from the market. In June 2006, it was placed back on the market, with the caveat that it be used as monotherapy in patients with relapsing forms of MS.

Natalizumab is currently being used as a second line agent in the treatment of relapsing and remitting (RRMS) or secondary progressive (SPMS) with relapses with excellent tolerability and encouraging results. The risk of PML remains and seems to increase with duration of therapy. At the time of writing this manuscript more than 90 cases of PML have been reported, with a mortality of about 20%, out of a total of approximately 83,000 patients exposed to natalizumab (press release). There are ongoing studies of the safety of natalizumab continues, through both the Tysabri Outreach Unified Commitment to Health (TOUCH) program, requiring enrollment before receiving the drug in the United States, and through the Tysabri Global Observational Program in Safety for Rest of World (TYGRISROW), a safety observational cohort program designed to obtain long-term safety data in MS patients treated outside of the US.

Alemtuzumab
Alemtuzumab is a humanized monoclonal antibody directed against CD52, a cell surface antigen located on T cells, B cells, monocytes, macrophages, and eosinophils. Its mechanism of action is still unknown, but its end result is profound lymphopenia. Early studies of alemtuzumab showed significantly reduced annual relapse rate in both relapsing-remitting and secondary progressive MS. Despite this, the secondary progressive group showed sustained disability, while the relapsing-remitting group showed a reduction in disability. This was followed by a phase 2 study, including 334 patients with early relapsing-remitting multiple sclerosis randomized to either subcutaneous interferon beta-1a three times per week or annual intravenous alemtuzumab at either 12mg or 24mg over 36 months. Alemtuzumab was found to significantly reduce the rate of disability, the annual relapse rate, and the lesion burden on MRI when compared to interferon beta 1a. Patients receiving alemtuzumab were found to have significantly higher rates of autoimmune disorders, most commonly hyperthyroidism and immune thrombocytopenic purpura.

There are currently two phase three trials underway, CARE-MS I, comparing alemtuzumab to interferon beta-1a in treatment naïve patients, and CARE-MS II, comparing alemtuzumab to interferon beta-1a in patients who have received an adequate trial of disease modifying therapy, but continue to have relapses. All patients receiving alemtuzumab in these studies are also followed in an extension study designed to evaluate safety and efficacy.

Daclizumab
Daclizumab is a humanized monoclonal antibody, directed against CD25

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surface antigen, which is identical to the interleukin-2 receptor, located on activated T cells. Interleukin-2 induces secretion of proinflammatory cytokines and stimulates proliferation of lymphocytes. Daclizumab acts as an antagonist at the interleukin-2 receptor. Results from preliminary open label trials showed significantly decreased numbers of contrast enhancing lesions on MRI, decreased exacerbation rates, and decreased Expanded Disability Status Scale (EDSS) scores. Decreased EDSS scores were also observed in five of 14 patients with secondary progressive multiple sclerosis, an important finding, as there is currently no therapeutic option for this group of patients. A phase II study of nine patients with multiple sclerosis on interferon therapy, with continued relapses and contrast enhancing lesions, showed significant reduction in contrast enhancing lesions, number of relapses, EDSS scores, timed ambulation scores, and neurologic rating scale. A larger, phase II study, CHOICE, included 230 patients already on interferon beta, randomized to combination therapy with placebo. There was a statistically significant decrease in the mean number of new or enhancing lesions in the high dose daclizumab group. Phase III trials are currently underway, evaluating daclizumab vs. interferon beta-1a as well as safety and efficacy studies.

**Rituximab**

Rituximab is a chimeric monoclonal antibody against CD-20 antibodies expressed on B cells. It causes B cell lysis though its effects on complement activation, antibody-dependent cellular cytotoxicity, and apoptosis. A phase II, double blind, trial involving 104 patients with relapsing remitting multiple sclerosis assigned to either rituximab or placebo showed that patients receiving rituximab had significantly fewer total and new gadolinium enhancing lesions on MRI, and fewer relapses when studied up to 48 weeks. Rituximab has also been looked at in patients with primary progressive multiple sclerosis in the OLYMPUS trial, in which 439 patients were randomized to receive placebo or rituximab every 24 weeks for a total of 96 weeks. There were no significant differences between rituximab and placebo in terms of time to confirmed disease progression, although in a subgroup analysis, there was a significant difference in a subset of patients who were younger and had an inflammatory component to their disease process. Ocrelizumab, a humanized MCA against CD20 is being studied in MS in phase III trials.

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**Neuromyelitis optica**

Neuromyelitis optica (Devic’s disease) is an inflammatory demyelinating disease that attacks the spinal cord and optic nerves. It is associated with more rapid disability than typical multiple sclerosis. A specific antibody against aquaporin-4 channels in the CNS has been found to be highly specific for this disease. There is a prominence of IgG and complement in neuromyelitis optica (NMO) lesions, suggesting B cell involvement in pathophysiology. Rituximab has therefore been considered a treatment option. One open label study of eight patients with worsening NMO treated with rituximab showed that six of the eight patients remained attack free during an average time period of 12 months, and the EDSS score improved from a pretreatment score of 7.5 to a score of 5.5 at follow-up. Another retrospective analysis looked at 25 patients, 23 of whom had previously relapsed on other therapies, found that median annualized post-treatment relapse rate went from 1.7 to zero at 19 month follow-up, and median EDSS scores decreased from seven to five after treatment.

**Peripheral Neuropathies**

Rituximab has also been tried in a number of peripheral neuropathies. In multifocal motor neuropathy (MMN), a rare, symmetric, demyelinating, purely motor neuropathy, approximately 30-50% of patients have been found to have anti-GM1 antibodies in serum, suggesting a role for humoral immunity. IVIG is first line therapy; however some patients have a decreased efficacy over time and therefore require very frequent infusions. Rituximab has been looked at in small case reports in this group of patients, with conflicting results. One case report showed yearly rituximab resulted in reduction of IVIG dosage from every seven days to every 12 days over a five year period, but another showed that in two patients with MMN, one had a decrease in total IVIG dosage while the other required an increase, and there was no significant change in any of the secondary clinical endpoints including strength or sensory improvement, or change in Rankin disability scores. In this same study, one patient with sensory ataxic neuropathy related to Sjogren’s syndrome was also treated with rituximab and showed a 63% reduction in IVIG dose at one year. Two patients with chronic inflammatory demyelinating polyneuropathy showed no reduction in dose of IVIG needed to maintain remission, however in other case reports its use has appeared more encouraging. Anti-myelin associated glycoprotein (anti-MAG) neuropathy, a chronic sensorimotor demyelinating polyneuropathy unresponsive to conventional treatments including steroids, plasma exchange, or IVIG is another entity in which rituximab has been tried. A double-blind placebo controlled trial randomizing 13 anti-MAG patients to rituximab, and 13 to placebo, showed that four of 13 patients treated with rituximab showed improvement in leg disability scores whereas zero of 13 placebo patients showed improvement. In addition, there was a significant reduction in time to ten-meter walk in the rituximab group.

**Myasthenia Gravis**

Myasthenia Gravis, an autoimmune disorder affecting neuromuscular junction transmission is associated with antibodies to nicotinic acetylcholine receptor (AchR) in about 80% of cases,
and to muscle-specific receptor tyrosine kinase (MuSK) in about 10% of cases. In patients difficult to control by conventional therapy rituximab has been tried and described in case reports. One such study looked at three AchR antibody patients and three MuSK antibody patients and showed clinical improvement as well as a significant difference in antibody titers. 

A controlled trial has yet to be performed, but a further open label pilot study looking at rituximab in refractory myasthenia gravis is currently underway.

**Inflammatory Myopathies**

The inflammatory myopathies, dermatomyositis, polymyositis, and inclusion body myositis, are also felt to have an association with autoantibodies. First-line treatment is immunosuppressive therapies, beginning with corticosteroids, with up to 70% of patients having an incomplete response. Further treatment with mycophenolate mofetil, methotrexate, cyclosporine and IVIG produces a variable response. This has led to attempts to find further treatment options. Rituximab has been looked at in several trials as well as a significant difference in strength, after six months of treatment there was a reversal of disease decline, with an average strength gain of 11.4%. On patient self report, five of the 11 patients noticed an improvement in their daily activities. An ongoing study is underway looking at etanercept, which blocks TNF-alpha, in a double-blind, randomized, placebo-controlled trial to evaluate whether it can delay disease progression.

**Conclusion**

The potential role of MCA in the treatment of neurological disorders with an inflammatory autoimmune component is become increasingly apparent. Natalizumab is currently the only MCA approved for the treatment of RRMS, but several others are in late stage trials. While the efficacy of monoclonal antibodies in the treatment of RRMS seems to be better than the standard disease modifying agents (Interferons and Glatiramer Acetate), there is a significant concern regarding long term side effects. Ongoing and future trials will further clarify the role of MCA in the treatment of MS and other neurological disorders.

**References**


**Disclosure of Financial Interest**

Valerie Gendron, MD, and/or spouse/significant other have no financial interests to disclose.

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