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Recent Advances in Monoclonal Antibody Therapies for Multiple Sclerosis

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Abstract

Introduction—Multiple sclerosis (MS) is the most common chronic inflammatory, demyelinating disease of the CNS and results in neurological disability. Existing

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Declaration of interest

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immunomodulatory and immunosuppressive approaches lower the number of relapses but do not cure or reverse existing deficits nor improve long-term disability in MS patients.

Areas Covered—Monogenic antibodies were described as treatment options for MS, however the immunogenicity of mouse antibodies hampered the efficacy of potential therapeutics in humans. Availability of improved antibody production technologies resulted in a paradigm shift in MS treatment strategies. In this review, an overview of immunotherapies for MS that use conventional monoclonal antibodies reactive to immune system and their properties and mechanisms of action will be discussed, including recent advances in MS therapeutics and highlight natural autoantibodies (NAbs) that directly target CNS cells.

Expert Opinion—Recent challenges for MS therapy are the identification of relevant molecular and cellular targets, time frame of treatment, and antibody toxicity profiles to identify safe treatment options for MS patients. The application of monoclonal antibody therapies with better biological efficacy associated with minimum side effects possesses huge clinical potential. Advances in monoclonal antibody technologies that directly target cells of nervous system may promote the CNS regeneration field from bench to bedside.

Keywords

multiple sclerosis; immunogenicity; monoclonal antibodies; mAbs; clinical studies; safety

1. Introduction

More than a hundred years ago, Paul Ehrlich, founder of chemotherapy, conceptualized the magic bullet paradigm in cancer research with drugs that specifically target the molecular defect without harming the organism¹. Ehrlich's vision was not realized until the development of the hybridoma technology (mAbs) by *Köhler* and *Milstein* in 1975². This technology led to the production of monoclonal antibodies (mAbs) in unlimited quantity combined with desired specificity. Recent advances in technology allowed the transition from originally murine to chimeric, humanized antibodies to finally fully human mAbs^{3, 4}. The therapeutic potential of mAbs was first shown in a patient with B-cell lymphoma. The patient was first treated with an anti-idiotypic antibody followed by an anti-CD3 mAb (OKT3, Muromonab-CD3). Muromonab-CD3 was the first mAb approved by the US Food and Drug Administration (FDA) for clinical use in humans⁵.

In this review, we will present an overview of MS, followed by an overview of monoclonal antibodies for the treatment of MS. We will summarize immunotherapies that use conventional monoclonal antibodies and discuss properties and mechanisms of action for monoclonal antibodies currently used for MS patients and in clinical trials. We will also discuss recent advances in MS therapeutics and highlight natural autoantibodies (NAbs) that directly target CNS cells.

1.1. Multiple Sclerosis, an inflammatory CNS disease

MS is a demyelinating disease of the CNS that is most often relapsing, and progresses in the white (and grey) matter of the CNS with unclear pathogenesis. So far, there is no treatment available to stop disease progression or reverse existing disabilities in MS patients. Statistics

from the MS Foundation estimated more than 400,000 people in the United States and about 2.5 million people worldwide with MS (for the year 2015; http://j.mp/MS_Statistics). The most common MS subtype, relapsing–remitting MS (RRMS) is present in 80–85 percent of patients and typically begins in the second or third decade of life with a female predominance of 2:1 and most recently 3:1. Patients typically improve spontaneously or respond to corticosteroids administered intravenously; a treatment paradigm using 1 gram methylprednisolone intravenously for each of 3 consecutive days without oral corticosteroid taper was initiated by Moses Rodriguez at the Mayo Clinic in 1983 (known at the Mayo Clinic as the “Rodriguez protocol”). This treatment protocol has gone on to become the standard approach for handling acute exacerbations of MS throughout the world. Unfortunately, the patient's responsiveness to corticosteroids typically fades over time. A certain level of CNS dysfunction may persist between relapses or progresses over time (secondary progressive MS). Some of these deficits that persist after methylprednisolone therapy may respond to plasma exchange⁶. This was proven to be the case in a double blind placebo controlled trial where 40% of patients improved with true exchange⁷. Approximately 15–20 percent of MS patients are diagnosed with primary progressive MS, which progresses gradually in the absence of obvious relapses and remissions. Primary progressive MS has a similar incidence among men and women⁸ and does not respond to currently approved therapies for MS. A definitive cause (or causes) for MS are yet unknown, and a cure is beyond our grasp. However, several disease management strategies for MS were developed, starting in 1993 with the approval of interferon- β 1b (Betaseron[®]) followed by other Food and Drug Administration (FDA) approved treatments such as interferon (IFN)- β 1a (Avonex[®] and Rebif[®]), glatiramer acetate (Copaxone[®]), and mitoxantrone. However, none of these approved drugs fundamentally alter the progressive course of MS disease. In addition, each drug presents with its own unique profile of potential adverse side effects. The routine application of magnetic resonance imaging (MRI) of brain and spinal cord for diagnosis and follow-up of MS patients has significantly expanded our understanding of the pathogenesis of MS. This led to the design of different drugs that suppress inflammatory MRI readouts. However, these drugs came with a significant price, i.e., the compromise of the safety of the medication: the more powerful the medication's ability to suppress the immune system (and therefore immune-mediated attacks during early disease stages) is, the more serious and even deadly were the adverse effects. We believe a paradigm shift is necessary from immunosuppressive/immunomodulatory strategies in MS, which aim to prevent disease exacerbation, towards active regenerative strategies, which intend to repair demyelinated brain and spinal cord lesions.

2. US Food and Drug Administration (FDA)-approved monoclonal antibodies for the treatment of MS

So far, Natalizumab and Alemtuzumab are the only US Food and Drug Administration (FDA)-approved monoclonal antibodies for the treatment of MS.

2.1 Natalizumab (Tysabri)

Natalizumab is a humanized monoclonal antibody that targets the focal adhesion molecule integrin α -4 present on T lymphocytes and other immune cells. Integrin α -4 is essential for

T lymphocytes to cross the BBB and enter the CNS lesion site. Natalizumab is effective in an immune-mediated animal model of MS where it prevents T lymphocytes from entering the CNS lesions and thereby lessening the disease⁹. When administered every four weeks in a phase III trial, natalizumab reduced the exacerbation rate by approximately 68%¹⁰. Natalizumab combined with beta-interferon resulted in an additional decrease in disease activity¹¹. However, Natalizumab poses an increased risk of CNS virus infections leading to progressive multifocal leukoencephalopathy (PML). As of 31st August 2015 there were 588 cases of natalizumab-associated PML among 142,000 patients (<http://bit.ly/natpml0815>)¹².

2.2 Alemtuzumab (Campath-1H)

Alemtuzumab (CAMPATH-1H) is a CD52-specific humanized monoclonal antibody that has six hypervariable loops from the rat immunoglobulin (Ig)G2b CAMPATH-1G combined to a human IgG1 (consisting of the κ light chain of the Bence-Jones protein REI and the heavy chain of a new immunoglobulin)¹³. The molecule CD52 is a cell-surface glycosylphosphatidylinositol-anchored glycoprotein that is expressed on human lymphocytes, monocytes, and eosinophils, and also on epididymis epithelial cells and mature spermatozoa. The primary indication for Alemtuzumab is the treatment of chronic lymphocytic leukemia. The treatment causes intense depletion of lymphocyte and monocyte populations in the bloodstream within minutes of initial dosing and this effect is maintained for up to one-year post-treatment. Peripheral blood monocytes returned to baseline levels within one month in MS patients treated with alemtuzumab¹⁴, and B cell populations within 3–7 months post-treatment¹⁵. A phase III trial in patients with RRMS demonstrated lower relapse rates compared to controls but without having an effect on the degree of disability¹⁶. An earlier phase II trial was terminated due to development of idiopathic thrombocytopenia in three patients¹⁶. Approximately 23% of patients under Alemtuzumab develop autoimmune thyroid disease and may be at risk to develop PML or other potentially fatal opportunistic infections. The main safety concerns include autoimmune thyroid problems and idiopathic thrombocytopenic purpura (ITP) for which patients will require monitoring.

3. The presence of immune cells and their components in CNS

3.1 Role of B cells in MS pathogenesis

An MS plaque is histologically characterized by inflammation, demyelination and gliosis. Infiltration by mononuclear cells, particularly macrophages and T cells is typical of the acute MS lesion. Previous reports indicated that autopsy material from the brains and spinal cords of MS patients had more Ig-containing cells within the plaques than outside and were more common in recent than in old plaques¹⁷. Subsequently, it was reported that B cells account for up to 25% of the CSF-infiltrating leukocytes during CNS inflammatory responses¹⁸. Other authors suggested a germinal center (GC)-like reaction takes place during the immune attack against CNS structures¹⁹. By using a rodent model with an intact blood-brain barrier, it was shown that the trafficking of activated antigen-specific B cells into the brain, retention, and antibody production was possible suggesting that the brain microenvironment supports the development of antigen-directed humoral immunity²⁰. Corcione *et al.*, confirmed this concept by showing that each B-cell subset participating in the GC reaction could be detected in the CSF of MS patients²¹. To date, the exact target antigens of

pathogenic B-cell responses in MS remain unknown. However, it is clear that not all B-cells in MS patients support detrimental autoimmunity, being able to clearly differentiate between pathologically relevant cells from normal B-cells is important. Accordingly, pro-inflammatory GM-CSF-producing B cell subset that co-expresses high levels of TNF α as well as IL-6, induces pro-inflammatory myeloid cell activation in a GM-CSF-dependent manner, and is abnormally increased in patients with MS, thus highlighting the rationale for selective targeting of distinct B cell populations in MS²².

3.2 Presence of immunoglobulins in CNS

Intrathecal production of antibodies after clonal expansion in MS patients was noted by the consistent identification of oligoclonal bands in CSF²³. Numerous publications during the last few decades supported the idea that CSF oligoclonal bands correlate to the level of B-cell involvement in MS²⁴. Further studies showed that that presence of these oligoclonal bands in MS generally correlated to a worse outcome²⁵ or disability prognosis in MS²⁶.

3.3 Role of T cells in MS pathogenesis

The most widely used mouse model of MS is experimental autoimmune encephalomyelitis (EAE). Th-1 CD4⁺ T cells determine this disease model. Due to this reason, this subset of T cells was the main area of MS research for several decades, whereas CD8⁺ T cells were neglected. The EAE model helped MS researchers understand autoimmunity, immune surveillance, CNS inflammation and immune-mediated tissue destruction and led to the development of three approved medications for treatment in MS²⁷. The report that CD8⁺ T cells outnumber the CD4⁺ T-cell subset in all samples from MS patients, regardless of the MS subtype, duration and speed of disease progression, shifted the focus towards role of CD8⁺ T cells²⁸. Clear evidence regarding the clonal expansion of CD8⁺ T cells in MS patients²⁹ and MS lesions³⁰ was also documented. The works of Tzartos et al., reported an enrichment of both IL-17⁺ CD4⁺ and CD8⁺ T cells in active MS lesions as well as an important role for IL-17 in MS pathogenesis³¹.

Finally, B cell depletion, both *ex vivo* and *in vivo*, results in significantly diminished pro-inflammatory (Th1 and Th17) responses of both CD4⁺ and CD8⁺ T cells³². Taken together, the above-listed studies provide evidence for the role of B- and T- cells in the pathogenesis of MS, and thus a therapeutic opportunity to target these immune cells to control/halt the progress of MS.

4. Non FDA-approved monoclonal antibodies for the treatment of MS: mAbs reactive to B Cells

Some of the FDA-approved drugs show some level of immunogenicity in patients (Table 1), arguing in favor of identifying other therapeutic drugs with low toxicity profiles in humans. As discussed above, recent reports advocate greater involvement of B cells and immunoglobulins in the initiation and propagation of MS lesions at different stages of their ontogeny³³. By targeting all B-cell stages including subsets of plasma cells, antibodies against CD20³⁴ or CD19³⁵ could have a better therapeutic efficacy in MS therapy.

4.1 Rituximab

The chimeric monoclonal antibody Rituximab (Rituxan[®]) binds and destroys B cells through binding to a phosphorylated glycoprotein (CD20). Rituximab was primarily used for diseases characterized by overactive B cells. Based on antibody-mediated injury seen in an immune-mediated animal model of MS (EAE), and its assumed predictive value for relapsing and progressive MS, Rituximab was considered as an alternative treatment for MS and studied in more detail. Rituximab lowers the rate of relapses in MS patients by 50 % as determined 48 weeks after administration³⁴. However, the clinical outcome in patients with primary progressive disease was not significantly different³⁶. In addition, Rituximab may also cause PML and is associated with reactivation of dormant prior infections like hepatitis B³⁷. Neuromyelitis optica (NMO) is an inflammatory autoimmune disorder of the CNS, usually relapsing, that causes variable degrees of attack-related disability. The disease varies in responsiveness to current treatments, which mainly consist of immunosuppression. Rituximab was previously listed in consensus statements as an option for the treatment of NMO, however an increasing number of reports have recently demonstrated that this drug is not effective in all patients with NMO³⁸. In some cases, Rituximab caused a rapid exacerbation of NMO following treatment³⁹.

4.2 Ocrelizumab

The fully humanized monoclonal antibody Ocrelizumab targets the phosphorylated glycoprotein CD20 (see Rituximab) on circulating B-lymphocytes but not plasma cells. Similar to Rituximab, Ocrelizumab causes depletion of B-lymphocytes through complement- and antibody-dependent cytotoxicity plus stimulation of apoptosis. An important reason for its development was the detection of anti-chimeric neutralizing antibodies against the chimeric antibody Rituximab in 24% of patients. This disturbing outcome is likely to be reduced in patients treated with the humanized antibody Ocrelizumab. The favorable outcome in a phase II trial comparing Ocrelizumab against interferon beta-1a and placebo led to a phase III study in primary progressive MS and RRMS⁴⁰. There are, however, safety concerns using Ocrelizumab based on the phase II MS trial noted above with a 41-year old patient dying from brain edema 14 weeks into the trial. A phase III trial of Ocrelizumab in systemic lupus erythematosus was discontinued due to opportunistic infections after methotrexate exposure⁴¹. In September of 2015 (http://j.mp/ocrelizumab_1509) Genentech announced positive results from a pivotal Phase III study that evaluated Ocrelizumab in patients with primary progressive multiple sclerosis (PPMS). The study (called ORATORIO) met its primary endpoint, showing treatment with Ocrelizumab significantly reduced the progression of clinical disability sustained for at least 12 weeks compared with placebo, as measured by the Expanded Disability Status Scale (EDSS). In recently concluded OPERA studies (October of 2015), researchers randomized 1,656 patients with RRMS to a 600-mg IV infusion of Ocrelizumab every 6 months or to interferon beta-1a (Rebif) given as 44-mg subcutaneous injections three times per week. The results showed that Ocrelizumab reduced the annualized relapse rate by about 50% over 2 years compared with interferon (0.292 versus 0.156 in OPERA I and 0.290 versus 0.155 in OPERA II, $P < 0.0001$ for both studies). Overall adverse events were similar in both groups in both trials at about 83%, but as expected, infusion-related reactions were higher in the

Ocrelizumab group (34.3% versus 9.7%). There were similar rates of serious adverse events (6.9% and 8.7%), with no cases of PML reported (http://bit.ly/OPERA_Trial).

4.3 Ofatumumab

Ofatumumab (Arzerra® or HuMax-CD20) is a fully human monoclonal antibody that targets CD20. This monoclonal antibody attaches to a dissimilar region of the CD20 molecule than the other two CD20-specific monoclonal antibodies, Rituximab and Ocrelizumab. It suppresses the activation of B-lymphocytes and is presently approved by the FDA for treatment of certain cases of chronic lymphocytic leukemia, which are refractory to therapy with Alemtuzumab and Fludarabine and has been used experimentally for the treatment of RRMS. Results from phase I/II trials using Ofatumumab vs placebo for RRMS reported no major safety concerns. Ofatumumab-treatment resulted in a 90% reduction in new T1 gadolinium-enhancing lesions for all doses of Ofatumumab 30 mg ($P < .001$)⁴².

4.4 MEDI-551

MEDI-551 is humanized IgG1k mAb that targets CD19. The antibody had potent effects in deletion of several B-cell lines obtained from patients with B-cell malignancies *in vitro*⁴³. The mAb is currently investigated in a randomized, double-blind, placebo-controlled Phase I/II study in patients with RRMS (NCT01585766). MEDI-551 is also being investigated in patients with scleroderma and B-cell malignancies. Phase II clinical studies demonstrated an acceptable profile of safety. The most frequent adverse events described were neutropenia, nausea, pyrexia, cytokine release syndrome and fatigue⁴⁴.

4.5 Tabalumab

Tabalumab (LY2127399) is a high-affinity human antibody with neutralizing activity against membrane-bound and soluble B-cell activating factor (BAFF, CD257)⁴⁵. BAFF is a survival and maturation factor for B cells belonging to the tumor necrosis factor (TNF) superfamily⁴⁶. Dysregulated BAFF expression contributes to autoimmune diseases or B-cell malignancies via effects on abnormal B-lymphocyte activation, proliferation, survival, and immunoglobulin secretion. BAFF binds to three different receptors, which are mainly found on mature B cells, so playing a crucial role in B-cell activation and B-cell survival. Eli Lilly and Company performed a phase II clinical trial of multiple subcutaneous doses of Tabalumab in patients with RRMS (NCT00882999). The primary outcome of the study was to look at reduction in MRI lesions at 12, 16, 20, and 24 weeks compared to placebo. No data from this study completed in June 2012 is published yet.

5. Non FDA-approved monoclonal antibodies for the treatment of MS: mAbs reactive to cytokines or chemokines or their receptors

5.1 Daclizumab

Daclizumab (Zenapax®) (anti-CD25) is a humanized monoclonal antibody of IgG1 class, which is attached to the Tac epitope on the α -chain of CD25 (interleukin-2 receptor). Daclizumab successfully ceases the generation of the high-affinity IL-2 receptor. Signaling via the high affinity IL-2 receptor, when activated, stimulates the expansion of activated T

lymphocytes⁴⁷. Daclizumab was primarily used to prevent rejection of transplanted organs. In MS, the mechanism of action is considered to be inhibition of the IL-2 receptor, which blocks the expansion and activation of T lymphocytes that ameliorates the disease. With respect to disease related processes CD25 is also expressed in neoplastic B cells, neuroblastomas and tumor infiltrating lymphocytes. Daclizumab improved the MRI outcome and clinical scores in patients with MS in combination with β -interferon or in monotherapy⁴⁷. So far, there are no reports of opportunistic infections or other life-threatening adverse effects with Daclizumab. This is in contrast to side effects seen with Natalizumab and Rituximab and may be based on its rather immune modulatory as opposed to immune suppressive effects. It was assumed that Daclizumab eradicates certain CD4⁺ and CD8⁺ T lymphocyte populations through increasing levels of CD56⁺ natural killer cells⁴⁸. A phase III trial using Daclizumab versus interferon beta-1a demonstrated a 45% reduction in annual relapses compared to interferon beta-1a in patients with RRMS⁴⁹. The safety profile of Daclizumab was consistent with that seen in the prior phase II trials. Compared to IFN, the drug caused an increased incidence of cutaneous adverse events (37% versus 19%), serious cutaneous events (eczema, drug eruption, pityriasis rubra pilaris, and urticaria) (2% versus 1%), and serious infections (4% versus 2%). Elevations in liver function tests greater than five times upper limit of normal occurred in 6% of patients on Daclizumab as opposed to 3% on IFN. There was one death in the Daclizumab-treated group that was deemed not to be attributable to the medication; there were two deaths in the phase II trials, one from autoimmune hepatitis and one from a psoas abscess whose relation to the drug could not be ruled out⁴⁹.

5.2 Secukinumab

Secukinumab (AIN457) is a fully human IgG1k mAb that targets IL-17A⁵⁰. Th17 cells produce the proinflammatory cytokine IL-17A as well as other effector cytokines, including IL-17F and IL-22. IL-17A is also expressed by multiple lineages of the innate immune system, including mast cells, neutrophils, dendritic cells, $\gamma\delta$ -T cells, macrophages and natural killer cells. Inhibition of IL-17A as a therapeutic target would exert different physiological effects than the suppression of Th17 cell activity. Rapid and sustained symptom reductions in psoriasis, rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis have been observed in Secukinumab-treated patients, with no overt safety signals⁵⁰. In several animal⁵¹ and human⁵² studies, Th17 cells and IL-17A were shown to play an important role in the pathogenesis of MS. A first proof-of-concept study (NCT01051817) enrolled 73 RRMS that were randomized 1:1 to iv. 10 mg/kg Secukinumab or placebo administered for 20 weeks. First results showed a significant reduction of combined unique active lesions during weeks 24–48 (primary outcome) in the Secukinumab-treated group. A phase II adaptive dose-ranging study (NCT01874340) to evaluate the efficacy and safety of Secukinumab in patients with RRMS terminated early. This was due to the development of a fully-human anti-IL17 monoclonal antibody with better potential for treating MS patients.

5.3 Tocilizumab

Tocilizumab (TCZ) is a humanized IgG1k mAb directed against interleukin-6 receptor (IL-6Ra). It represents a treatment strategy for patients with rheumatoid arthritis (RA) and is

currently approved in the United States for RA patients who have failed to improve with at least one anti-TNF therapy⁵³. A double-label immunohistochemistry technique showed the presence of IL-6 in acute and chronic active plaques from the brain of six MS patients⁵⁴. When a panel of Th1/Th2 cytokines and the chemokine CCL2 in serum and CSF from MS patients and healthy controls was analyzed, increased levels of IL-6 ($p<0.05$) were found in CSF from patients with RRMS. A case study in a 53-year-old Japanese woman with MS and RA reported stabilization of MS when treated with Tocilizumab for the RA⁵⁵. Clinical trials for Tocilizumab in MS are currently being planned. A very recent study reported that a 48-year-old woman developed MS while on treatment with Tocilizumab for RA⁵⁶. This case report illustrates that Tocilizumab may cause secondary auto-immunity in CNS. Therefore, anti-IL6 therapy should be considered with caution.

5.4 MOR103

MOR103 is a human IgG1 mAb against granulocyte-macrophage colony-stimulating factor (GM-CSF). The mAb works by blocking GM-CSF interaction with its receptor and thereby preventing subsequent signal transduction⁵⁷. GM-CSF can act as a pro-inflammatory cytokine mainly by inducing the activation, maturation and differentiation of macrophages and dendritic cells, which are essential for the initiation and propagation of cell-mediated immune responses. Soluble GM-CSF is a potent adjuvant for the generation of immune responses to foreign proteins as well as peptides derived from self-antigens⁵⁸. GM-CSF is required for recruitment of peripheral myeloid cells into the CNS⁵⁹. A recent Phase I/II dose-escalation trial of MOR103 evaluated the safety, tolerability and signs of efficacy in RA patients⁶⁰. There were no strong treatment-emergent adverse events reported, with the most common adverse event being nasopharyngitis. The data supported further investigation of the mAb to GM-CSF in RA patients and potentially in those with other immune-mediated inflammatory diseases. A recent report indicates that a subset of B cells that produce GM-CSF and co-express high levels of TNF α as well as IL-6 contributes to MS pathogenesis. In addition, this subset of cells abnormally increased in patients with MS²². This data implicated a pro-inflammatory B cell/myeloid cell axis in MS and provided the rationale for selective targeting of distinct B cell populations (such as the ones that produce GM-CSF) in MS. A recent clinical trial investigated in a randomized, double-blind, placebo-controlled phase Ib Study, the safety and pharmacokinetics of MOR103 in patients with MS⁶¹. The primary objective was to determine the safety and tolerability of MOR103 in patients with RRMS or SPMS. MOR103 administered at 3 different doses at 2-week intervals was well tolerated in patients with MS.

5.5 GNbAC1

GNbAC1 is a humanized mAb directed against Multiple Sclerosis-Associated Retrovirus (MSRV) gene that encodes an envelope protein (Env): MSRV-Env. The antibody is a recombinant DNA-derived humanized mAb of the IgG4/ κ isotype and contains human framework regions and the complementarity-determining regions (CDRs) of a parent murine antibody. GNbAC1 selectively binds with high affinity to the extracellular domain of MSRV-Env. The protein was named MSRV because the viral particles were originally isolated from the brain tissue of patients with MS^{62, 63}. Human endogenous retrovirus (HERV) genes represent about 8% of the human genome. MSRV-Env activates a pro-inflammatory and

autoimmune cascade through its interaction with Toll-like receptor 4. Due to its pro-inflammatory properties and inhibitory effects on OPC differentiation, the MSRV-Env protein plays a crucial role in MS pathogenesis. In a 10-year blind observational study the presence of MSRV in the CSF of early MS patients was found to be associated with a significantly greater rate of relapse-unrelated unremitting disability and secondary progression of the disease⁶⁴. It was also reported that brains and peripheral blood mononuclear cells of MS patients hyperexpress MSRV/HERV-W endogenous retrovirus, with the MSRV envelope protein localized to MS plaques⁶⁵. The particular therapeutic interest of the MSRV-Env target comes from the fact that this protein is highly expressed in MS patients, most specifically in brain demyelinating lesions, and it has no known role in the normal human physiology. Based on these considerations preclinical and early clinical development studies tested the efficacy of GNBAC1 in MSRV-Env induced EAE⁶⁶. The study showed an absence of safety risk⁶⁷. Additional *in vitro* analyses showed an absence of complement or antibody-dependent cytotoxicity as well as a low level of cross-reactivity to human tissues. The first-in-man clinical study in 33 healthy subjects and a long-term clinical study in 10 MS patients showed that GNBAC1 is well tolerated in humans without induction of immunogenicity and that it induces a pharmacodynamic response on MSRV biomarkers^{68, 69}. Pharmacokinetic data confirm a dose-linear pharmacokinetics with an elimination half-life of 15–17 days compatible with monthly iv. infusions⁶⁹. These data indicate that GNBAC1, a mAb antagonist of MSRV-Env, may represent a new approach to the treatment of MS without an impact on the immune system.

5.6 Ustekinumab (CNTO-1275)

Ustekinumab is a human IgG1 mAb generated via recombinant human IL-12 immunization of human Ig (hu-Ig) transgenic mice⁷⁰. The mAb binds to the p40 subunit common to IL-12 and IL-23 and prevents their interaction with the IL-12 receptor $\beta 1$ subunit of the IL-12 and IL-23 receptor complexes⁷¹. IL-12 drives Th1 cell differentiation whereas IL-23 drives the IL-17-producing Th17 CD4⁺ cells⁷². Ustekinumab is approved for treatment of moderate-to-severe plaque psoriasis⁷³ and has demonstrated efficacy in Crohn disease⁷⁴ and psoriatic arthritis⁷⁵. The basis for use of Ustekinumab for MS stems from the following studies: animal models and human disease samples established a strong link between dysregulation of the Th1/Th17 pathways and MS⁷⁶, administration of IL-12 exacerbated rodent EAE, which was prevented by administration of anti-IL-12 antibodies⁷⁷, with similar results being reported in common marmosets⁷⁸. The observation of elevated serum levels of IL-12 in patients with secondary chronic progressive course of MS⁷⁹. IL-12 and IL-23 induce differentiation of IFN γ and IL17, respectively, which drive tissue inflammation and are upregulated in active MS plaques⁸⁰. A 1,000-fold compartmentalized release of the p40 subunit of IL-12 that was associated with CSF levels of myelin basic protein (MBP) as a measure of myelin degradation was reported⁸¹. In another study that used serial MRI, Ustekinumab delayed white-matter demyelination, prevented T2 lesion accumulation, and suppressed inflammation of pre-existing brain lesions in marmosets with established EAE⁸². Finally, in a phase I clinical study, single subcutaneous doses of Ustekinumab were shown to be well tolerated in patients with RRMS that supported its investigation in large clinical trials⁸³. In a latter clinical trial, a full dose-ranging, proof-of-concept study to assess the safety, efficacy, and pharmacokinetics of repeated subcutaneous injections of Ustekinumab

in patients with RRMS was performed⁸⁴. The results showed that Ustekinumab is generally well tolerated and did not exacerbate inflammatory demyelination. However, the drug did not show any efficacy in reducing the cumulative number of gadolinium-enhancing T1-weighted lesions in MS. One of the possible failures for this drug to show any efficacy was partially due to the study's inclusion of patients with advanced disease. The authors also consider that it is unlikely that Ustekinumab consistently passed the BBB in this study. Thus, while peripheral IL-12 and IL-23 may have been neutralized, immune cells already in the CNS may not have been affected. This drug is currently discontinued for MS treatment.

6. Non FDA-approved monoclonal antibodies for the treatment of MS: mAbs reactive to CNS antigens

6.1 Anti-LINGO-1 antibody (Li81) (BIIB033)

The anti-(LINGO-1 antibody (BIIB033) is a potential treatment for MS and ON patients currently in clinical trials. LINGO-1 ("leucine-rich repeat and Ig domain containing NOGO receptor interacting protein-1") is a functional component (co-receptor) of the Nogo receptor-signaling complex and interacts with the ligand-binding Nogo-66 receptor (NogoR). Lingo-1 is almost exclusively expressed in CNS neurons and oligodendrocytes during both embryonic and postnatal stages⁸⁵⁻⁸⁹. Anti-LINGO-1 antibody demonstrated promotion of spinal cord remyelination in the EAE model. The murine monoclonal antibody mAb3B5 recognizes mouse LINGO-1 and is a surrogate antibody for the human monoclonal antibody Li81 (BIIB033). mAb3B5, improves axon function in mice after experimental spinal cord demyelination. The anti-LINGO-1 antibody Li81 blocks contact points in LINGO-1 required for protein oligomerization. Binding of the antibody's Fab region (responsible for antigen binding) to LINGO-1 results in the formation of a stable complex comprised of 2 copies of LINGO-1 and 2 copies of the Fab region. The resulting complex blocks epitopes in the LINGO-1 IgG domain that are involved in oligodendrocyte differentiation. Anti-LINGO-1 immunotherapy is intended to stimulate regrowth of the myelin sheath, which is damaged in MS CNS lesions. Serum pharmacokinetics of BIIB033 were determined in control groups and MS cohorts with similar outcomes in both groups. The antibodies serum half-life ranges from 15 to 24 days after intravenous administration. Intravenous doses >3 mg per kg in humans lead to serum concentrations that are predicted to have pharmacological activity, based on remyelination studies in rats. Cerebrospinal fluid (CSF) pharmacokinetics resulted in variable outcomes amongst tested individuals. Ratio of brain and spinal cord to plasma concentrations is likely to be about 0.1% in humans compared to 0.1 to 0.4% in rats.

6.1.1 RENEW Clinical Trial—In April 2015 results from the Phase II clinical trial RENEW (Biogen) were published⁹⁰. The study tested safety and efficacy of anti-LINGO-1 in acute optic neuritis (AON). AON damages the optic nerve, causing loss of the myelin sheath and axonal injury, and may result in loss of visual function. The most common cause of AON is MS. RENEW (NCT01721161) was a randomized, double-blind, placebo-controlled, parallel-group study in subjects with first unilateral acute optic neuritis episode and was designed to study anti-LINGO-1's ability to enable repair of an optic nerve lesion via axonal remyelination. RENEW is part of the anti-LINGO-1 Phase 2 clinical

development program, which includes the SYNERGY trial (see below) in MS. 82 participants with their first episode of AON were given 6 doses of anti-LINGO-1 once every 4 weeks for 20 weeks total or a placebo. RENEW trial studied the effects on remyelination by measuring the latency of nerve conduction between the retina and the visual cortex in the brain using full field visual evoked potential (FF-VEP). The primary endpoint measured FF-VEP latency for the affected eye at week 24 compared to the unaffected eye at baseline. Results demonstrated a 34% improvement in the recovery of optic nerve latency compared to placebo in the per-protocol population, but were not statistically significant ($p=0.0504$), perhaps due to the small study population. In addition, top-line data showed no effect on change in thickness of the retinal layers (optic nerve neurons and axons), and visual function, as measured by spectral domain optical coherence tomography and low contrast letter acuity, respectively. The retinal ganglion cell layer analysis demonstrated that considerable thinning took place before treatment was administered. As a result, anti-LINGO-1 may not have had an opportunity to provide evidence of neuroprotection in this study. The authors concluded that this insight offers valuable information on the speed of axonal loss following an AON attack, and combined with the positive primary endpoint results, will help inform future studies. The analysis of the intent-to-treat (ITT) population, which includes patients in both arms who did not complete the study, showed a positive trend but did not reach statistical significance. Treatment-related anti-LINGO-1 serious adverse events (SAEs) consisted of two patients with hypersensitivity reactions occurring around the time of infusion and one patient with an asymptomatic elevation in liver transaminases, which resolved after drug discontinuation. No deaths occurred during the trial. No immunogenicity was observed.

6.1.2 SYNERGY Clinical Trial—The clinical trial SYNERGY (Biogen) tested efficacy and safety of anti-LINGO-1 in patients with RRMS or with secondary progressive multiple sclerosis (SPMS)⁹¹. The trial started in April 2013 and is due for completion in early 2016. 416 participants receive β -interferon 1a once weekly plus placebo or 3 mg, 10 mg, 30 mg or 100 mg of anti-LINGO-1 per kilogram of weight. Anti-LINGO-1 is given once monthly for 72 weeks. A major focus of this clinical trial is to investigate improvement in cognitive functions.

6.2. Non FDA-approved monoclonal antibodies for the treatment of MS: Natural antibodies reactive both to immune system and CNS myelin

High levels of CSF-IgM binding to MBP were associated with early benign course in MS⁹². When a mAb to MBP₁₀₅₋₁₂₀ recognizing the 222-228 epitope of the extracellular domain of high affinity immunoglobulin gamma Fc-receptor I (CD64) was isolated from EBV⁺ B cell clones of long-term stable RRMS patients, the mAb exerted immunosuppressive activity on MS-derived T cell lines through induction and release of high amounts of IL-10 and decreased levels of IL-12 from activated monocytes⁹³. It is remarkable that B cell clones isolated from patients with long-term stable MS can induce a monoclonal IgM to MBP with immunosuppressive activity. The demonstration that an immunosuppressive IgM mAb is part of the natural human antibody repertoire and its association mainly with stable MS suggests that it may play a role in the mechanism underlying stable course in MS. This hypothesis is further supported by the finding of the presence of significantly high levels of

circulating IgM, but not IgG, to CD64 epitope in serum of all MS patients with mAbs to CD64. These IgM antibodies showed the same *in vitro* immunosuppressive properties as the anti-CD64 222–228 mAb isolated from B cell clones. The finding that these circulating IgM bind to CD64 in its native conformation as expressed on the transfected cell surface, suggests that they bind CD64 *in vivo*, which may explain their immunosuppressive activity. The *in vitro* properties of these IgM antibodies confirm that naturally occurring antibodies (NAb)s are mainly protective, providing a potential new therapy for MS and other immune-mediated inflammatory diseases of the CNS.

6.3. Non FDA-approved monoclonal antibodies for the treatment of MS: Natural antibodies reactive to CNS cells for repair of CNS lesions

Even though the existence of NAb)s was met with initial skepticism, pioneering work by Avrameas^{94–96} and Notkins^{97, 98}, established convincing evidence that NAb)s are part of the human innate immunoglobulin repertoire⁹⁹. NAb)s utilize germline-encoded genes directed against foreign antigens, self- and altered self-structures⁹⁴ and are present in newborns without stimulation by foreign antigens¹⁰⁰. In contrast, conventional antibodies require external stimuli for their production. NAb)s are polyreactive by definition with few or no somatic mutations in the antibody's variable light and heavy chain, which are required for high affinity binding of a single antigen. NAb)s of the IgM isotype are found in invertebrates and vertebrates. High levels of IgG NAb)s and to a lower extent IgM and IgA isotypes are detected in vertebrates¹⁰¹.

In general, NAb)s bind their antigen with low affinity but high avidity¹⁰², which describes the combined synergistic strength of multiple interactions rather than the sum of interactions between antigen and antibody. In contrast, conventional antibodies, typically of the IgG isotype, undergo affinity maturation and contain somatic mutations to ensure high-affinity antigen binding, which is commonly linked to the antibody's monospecificity. Accumulating evidence categorize NAb)s as natural systemic surveillance molecules that tag damaged cells and foreign pathogens for elimination by the immune system through opsonization or antibody-dependent cellular cytotoxicity. Some NAb)s can actively signal in cancer and brain cells. The ability of identified NAb)s to detect and sometimes induce apoptosis in tumor cells may play an important function in tumor surveillance^{103, 104}. In mice and humans, another class of NAb)s, termed remyelination-promoting antibodies, actively promotes repair in demyelinated spinal cord areas^{105–107}.

6.3.1 HIgM22—The human monoclonal IgM antibody 22 (HIgM22) was discovered at the Mayo Clinic (Rochester, MN, USA). The serum form of the antibody, sHIgM22, was isolated from a Waldenström macroglobulinemia patient with no incidence of any neurologic disease. A recombinant version of sHIgM22, rHIgM22, was developed by cloning the antibody variable region DNA sequence into an expression vector providing the heavy and light chain framework¹⁰⁸. GMP-grade rHIgM22 antibody was purified in gram quantities for formal toxicology studies. Both the serum and later the recombinant form of the antibody were able to induce spinal cord remyelination in the TMEV-model of demyelinating disease^{106, 107}. Compared with control-treated animals, mice that received rHIgM22 exhibited fewer lesions (34.3% [rHIgM22] vs. 41.8% [control]) and increased remyelination

(59.7% [rHlgM22] vs. 15.8% [control]). MRI studies using the same experimental animal model showed similar increases in remyelination¹⁰⁹. Moreover, the study demonstrated that the human IgM antibody was able to penetrate the BBB and enter the CNS. Further research indicates that immunomodulation plays little to no role for the rHlgM22-mediated remyelination effect¹¹⁰ but is rather associated with anti-apoptotic signaling in pre-myelinating oligodendrocytes and reduced caspase-3 activation and caspase gene expression¹¹¹. rHlgM22-promoted remyelination preserved spinal cord axons and protected functional axon integrity¹¹². Recent data identified a signaling complex in OPCs responsible for rHlgM22-mediated actions including platelet-derived growth factor (PDGF) α R, integrin α v β 3 and the Src family kinases (SFK) Lyn¹¹³ suggested an involvement of the astroglial growth factor PDGF in rHlgM22-mediated actions in OPCs. Most important, only mixed glial cultures consisting of astrocytes, OPCs and microglial cells demonstrate observable rHlgM22-mediated OPC proliferation; isolated OPCs do not respond¹¹⁴. This suggests that astrocytic or microglial co-factors or direct contact either provide a necessary microenvironment or co-stimulates the proliferative response. The fact that most glial cell-secreted PDGF derives from astrocytes further supports a role for secreted astrocytic factors in IgM-stimulated OPC proliferation and remyelination.

A recently concluded phase I clinical trial¹¹⁵ evaluated safety, tolerability, pharmacokinetics and immunogenicity of a single intravenous dose of rHlgM22 in patients with MS (NCT01803867). This was a multi-center, double-blind, randomized, placebo-controlled study designed to evaluate safety, tolerability, pharmacokinetics, and immunogenicity of a single dose of rHlgM22 in participants with any type of MS who were clinically stable for at least three months. All 72 participants remained on their existing MS treatment regimens, including disease-modifying therapies. The trial, which followed participants for up to six months after receiving a single dose of rHlgM22, found no dose-limiting toxicities at any of the five dose levels studied. Furthermore, rHlgM22 was detected in the cerebral spinal fluid (CSF) two days after intravenous injection (i.e., 0.05 ng/ml) in all 14 rHlgM22-treated patients at two dose levels. Even 29 days after treatment, rHlgM22 was measurable in the CSF of 5 out of 12 patients¹¹⁶. This human data demonstrates that IgM antibodies are able to cross the BBB and persist in the CSF (>40 % of patients) for almost a month after treatment. Recruitment for a phase Ib study (NCT02398461) started in October of 2015, in patients experiencing a clinical acute relapse (new or worsening neurological symptoms attributable to MS preceded by a stable or improving neurological state of at least 30 days) and with at least one new, active lesion (damaged area) on MRI scans. The primary outcome of the trial will be the safety and tolerability of a single dose of rHlgM22 in relapsing MS subjects. The estimated completion date for this study is November 2016.

6.3.2 HlgM12—The beneficial effects of mAbs targeting myelin/oligodendrocytes in demyelinating disease models were harnessed to identify monoclonal IgMs targeting neuronal cells. These antibodies differ from remyelination-promoting antibodies, in that they had no impact on the extent of remyelination *in vivo* or Ca²⁺ influx in glial cells *in vitro*. Two neuron-binding antibodies (sHlgM12, sHlgM42) stimulated neurite extension¹¹⁷ and a recombinant form of sHlgM12, rHlgM12, was generated¹¹⁸. Binding of HlgM12 to the neuronal surface led to membrane reorganization and stimulated neurite outgrowth¹¹⁹.

Peripheral administration of rHlgM12 as a single bolus improved motor function in chronically demyelinated mice¹²⁰. A single dose of rHlgM12 improved brainstem NAA concentrations, a biomarker for density of spinal cord axons, in a model of progressive MS¹²¹. We identified gangliosides¹²² and polysialic acid (PSA)¹²³ attached to the neural cell adhesion molecule (NCAM) as the antigens for rHlgM12. Within the CNS, NCAM is the major polysialylated molecule (> 95%) with long, negatively charged $\alpha 2'-8'$ -linked sialic acid homopolymers (n>10 sialic acid residues). PSA is abundantly present in the developing brain and its early expression is tightly linked to critical developmental events including neuronal precursor migration (neuroblasts), axonal sprouting and oligodendrocyte progenitor proliferation. PSA-NCAM, is expressed at the axonal surface and acts as a negative regulator of myelination, presumably by preventing myelin-forming cells from attaching to the axon. PSA-NCAM, normally absent from adult brain, is re-expressed on demyelinated axons in the plaques. Within shadow plaques, remyelinated axons do not express PSA-NCAM. The antibody is currently under development as a therapeutic agent for MS.

7. Expert Opinion

The outlook for MS patients continue to improve as more safe and effective therapies become available. In addition, the availability of agents with efficacies higher than the first-line agents makes it likely that the long-term outcomes in MS may be favorably affected. Figure 1 provides a schematic summary of proposed mechanisms of action of mAbs for MS therapy. Most of the antibody therapies approved target the immune system. Accordingly, monoclonal antibody therapies that target immune cells, cytokines or chemokines or their receptors are helpful in managing MS, however, these treatments do not prevent or reverse long-term disabilities. There is an immediate need to identify new treatment strategies for basically all neurologic diseases including MS and neurodegenerative diseases. In demyelinating diseases like MS, the therapeutic focus should be on strategies that actively induce brain lesion repair and stimulation of remyelination. Future prospects for remyelination therapies are encouraging. Preclinical research has identified multiple targets affecting remyelination in experimental animal models of demyelinating disease, and early stage human clinical trials have started. Potential combinatorial therapeutic approaches could include agents that target the immune system to eliminate deleterious immune system-mediated injury and perhaps anti-LINGO antibodies or rHlgM22 that stimulate remyelination. Indeed, human monoclonal IgMs that target the CNS may enhance the permissive environment for regenerating lost myelin.

Reparative human monoclonal antibodies are a potential novel class of therapeutics for MS patients with the ability to actively repair CNS lesions in animal models of MS. The importance of blood brain barrier (BBB) breakdown in the context of therapeutic approaches is important. There are several anatomical features between the vascular and the nervous systems that have been recognized, with the interface between the two systems called as the neurovascular unit (NVU). The NVU is comprised of endothelial cells, astrocytes, neurons and pericytes. A major component of NVU is BBB, formed by endothelial cells and isolates CNS from blood circulation. Almost every aspect of CNS function is affected due to this interface. The term 'barrier' gives the notion of a rigid, inaccessible obstruction between the vascular and nervous systems. However, the barrier is in fact a region of dynamic molecular

transport to constantly regulate the flow of essential components such as amino acids, across endothelial walls and maintains the homeostasis of the microenvironment¹²⁴. Following CNS injury, BBB is compromised and promotes accumulation of pro-inflammatory cytokines and cell lytic products. The resulting inflammation may attenuate the efflux activity of the BBB, but also ameliorate the permeability to bring in adaptive immune cells. Under these conditions, breakdown of BBB may in fact be beneficial, as this will result in an increased influx of natural autoantibodies or drugs with reparative properties to target and protect intrinsic cells of the CNS¹²⁵. Nonetheless, the emergence of new molecules or techniques that would promote easier and safer crossing of the BBB without increasing the risk of CNS side effects is of great importance and would be crucial for the therapy of MS. The very low amount of the human antibody rHlgM22 necessary for stimulation of remyelination in mice, and an open BBB during acute phases of the human disease, are encouraging. In contrast to available immunomodulatory therapies, antibody-mediated CNS repair strategies with no- or minimal- toxicity gives hope for MS patients.

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Article Highlights

- . Both B cells and T cells play a role in the pathogenesis of MS.
- . Monoclonal antibodies (mAbs) have shown efficacy in the early phases of the disease.
- . Currently approved mAbs and few that are in clinical trials come with safety concerns and secondary side effects.
- . Naturally occurring monoclonal antibodies (NAbs) represent novel strategy to treat MS.
- . NAbs are of germline origin with little or no somatic mutations. They are often polyreactive and bind with rather low affinity to one or multiple structurally unrelated antigens.
- . NAbs that target CNS cells to promote remyelination represent a paradigm shift in MS therapeutics.
- . Most known remyelination-promoting antibodies are of the IgM isotype and bind to myelin and oligodendrocytes. Their molecular targets are cell surface SLs and, to some extent, cytoskeletal proteins.

Figure 1. Schematic of the proposed mechanisms of action of existing and emerging therapies for MS

Massive activation of the immune system is followed by the migration of activated immune cells (T and B lymphocytes as well as macrophages) across the disrupted blood-brain barrier (BBB). APC's would then present CNS antigens to the activated T lymphocytes, which leads to further differentiation of the naïve T lymphocytes to other groups such as Th1, Th2 and Th17 lymphocytes. Antibodies such as alemtuzumab, daclizumab, natalizumab, rituximab, ocrelizumab, ofatumumab, MOR103, tabalumab, secukinumab, ustekinumab, MED-551 and GNBAC1 work mostly on immune cells, cytokines or their receptors at the periphery. rHlgM22 and anti-LINGO-1 antibodies work at the level of CNS and affect OPC's and OL's to enhance the process of CNS repair (remyelination). rHlgM22 binds astrocytes in culture and induces a Ca^{2+} -influx in astrocytes. rHlgM12 is a poly-specific antibody that binds to either gangliosides or PSA_NCAM and works at the level of neurons and promotes neurite extension.

OL: oligodendrocyte, OPC: oligodendrocyte progenitor cell, MP: macrophage, APC: antigen presenting cell, Th1: Type 1 helper T cells, Th2: Type 2 helper T cells, Th17: Type 17 helper T cells (produce IL-17), T: T cell, NKT: natural killer T cell, B: B cell, M: monocyte, VCAM-1: vascular cell adhesion protein, VLA-4: very late antigen-4 (Integrin $\alpha 4\beta 1$), CD19: B-lymphocyte antigen cluster of differentiation 19, CD20: B-lymphocyte antigen cluster of differentiation 20, CD52: cluster of differentiation 52 (CAMPATH-1 antigen), TLR-4: Toll like receptor 4, MSRV-Env: Multiple Sclerosis-Associated Retrovirus-Envelope protein, BAFF: B-cell activating factor, PSA-NCAM: Polysialylated-neural cell adhesion molecule, Gangliosides: GD1a, GT1b.

Table 1

FDA approved antibody therapeutics

Antibody name	Company	Type	Target	Indication	Reported Immunogenicity
Rituximab (Rituxan)	Genentech (Roche)/Biogen Idec	Chimeric	CD20	Non-Hodgkin lymphoma	11% (2578)
Alemtuzumab (Campath)	Ilex Pharma (Genzyme)	Humanized	CD52	MS, B cell chronic lymphocytic leukemia	1.9-8.3% (133-211)
Ibritumomab (Zevalin)	Idec Pharma (Biogen Idec)	Murine	CD20	Non-Hodgkin lymphoma	1.3% (446)
Tositumomab (Bexxar)	GSK	Murine	CD20	Non-Hodgkin lymphoma	11% (230)
Natalizumab (Tysabri)	Biogen Idec	Humanized	α -4 integrin	MS, Crohn's disease	9% (627)
Ofatumumab (Arzerra)	GSK	Human	CD20	CLL	0% (79)

FDA approved (a) antibody therapeutics (adapted from <http://1.usa.gov/1Jur44k>) showing the level of reported immunogenicity observed in patients.