Published in final edited form as:

Curr Neurol Neurosci Rep. 2013 November ; 13(11): 390. doi:10.1007/s11910-013-0390-z.

Monoclonal antibodies as disease modifying therapy in multiple sclerosis

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Abstract

Multiple sclerosis (MS), a demyelinating disease of the central nervous system, was untreatable until the mid-1990s when beta-interferons and glatiramer acetate were introduced. These agents, while effective, were relatively nonspecific in action. Over the last 10 years, research has focused towards developing more targeted therapies for the disease. Monoclonal antibodies (mAbs) have been central to these efforts and many of the mAbs studied in MS have been singularly effective. We review here the six monoclonal antibodies that have been approved for MS or are in late-stage clinical trials, focusing on the drugs' efficacy and safety. Additionally, we review several monoclonal antibodies that were studied in MS but were found to be ineffective or even deleterious in this patient population.

Keywords

monoclonal antibodies; multiple sclerosis; clinical trials; disease modifying therapy

Introduction

In the decades since Milstein and Kohler received the 1984 Nobel Prize for Physiology or Medicine for their work on generating monoclonal antibodies (mAbs) (1), the use of mAbs for therapeutics has grown exponentially. Two years after the award, the OKT3 (Muromonab-CD3) mAb became the first mAb to be approved by the U.S. Food and Drug Administration (FDA). Since these beginnings, mAbs have improved immunotherapeutics for many diseases, including rejection of organ transplants, graft versus host disease, cancer, vascular disease and numerous autoimmune disorders.

Multiple sclerosis (MS) is believed to be an autoimmune disease of the central nervous system (CNS). Its pathophysiology is not well understood, but pathologic hallmarks include demyelinating lesions in white matter and cortex along with axon destruction. The disease typically begins in young adulthood, disproportionally strikes young women, and often follows a relapsing-remitting course for years before transitioning into a progressive accumulation of neurologic disability. MS was untreatable until the development of β -interferons (β -IFNs) and glatiramer acetate (GA) in the mid-1990s. Though effective, these

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early disease modifying therapies (DMTs) were not targeted to modify specific pathogenic cells or pathways. Intense interest in more specific agents developed, and a new era of highly targeted therapies with mAbs as the prototypes began with the approval of natalizumab for relapsing MS.

Natalizumab

In 1992, Yednock et al identified the glycoprotein $\alpha 4\beta 1$ integrin, or VLA-4, as critical for leukocyte adhesion and migration into the inflamed CNS using the MS animal model experimental autoimmune encephalomyelitis (EAE) (2). Subsequent animal studies confirmed the efficacy of anti- $\alpha 4$ integrins in EAE (3, 4). An encouraging phase I trial of the humanized anti- $\alpha 4$ integrin, natalizumab, was published in 1999 (5) and phase 2 and 3 trials also showed efficacy (6–8). Natalizumab reduced clinical relapses by 68% in the first year, decreased the risk of 3 month sustained disability by 42% over two years, and decreased new or enlarging T2-weighted MRI lesions by 83% compared to placebo (7). Natalizumab acted rapidly, and its benefits persisted throughout the two year clinical trials and beyond. On the strength of these data, it was introduced into the US market for treatment of MS in 2004.

During ongoing phase 3 trials, two cases of progressive multifocal encephalopathy (PML), an opportunistic brain infection caused by reactivation of latent JC virus infection, developed in natalizumab-treated patients (8–10). Due to these serious adverse events, natalizumab was voluntarily recalled from the US market in early 2005. An intensive, global risk-management program was initiated and the drug was ultimately reintroduced in mid-2006 as a therapy for patients with inadequate response or intolerance to other MS therapies. Rare cases of PML continued to develop in natalizumab-treated patients, and it became clear that this was a drug-specific risk. As of May 6, 2013, 359 cases of confirmed PML had been reported, with over 115,000 patients receiving the drug (11). Several risk factors associated with PML development have been identified. These include seropositivity for JC virus, prior treatment with immunosuppressive agents (e.g. azathioprine, methotrexate, or mitoxantrone, but not corticosteroids, GA, or IFN β), and longer duration (>24 months) of natalizumab treatment (12–14). Current analysis suggests that patients who are seronegative for JC virus, have taken natalizumab for <24 months, and have not previously been exposed to immunosuppressants are at low risk for PML. Indeed, patients who are seronegative for JC virus (indicating that they do not harbor the virus), have an estimated PML incidence of 0.09 per 1000. In contrast, patients with all three risk factors develop PML with an incidence of 11.1 per 1000 patients (13). Twice yearly screening for JC virus antibodies in seronegative patients taking natalizumab is now common. Ongoing work aims to determine more precisely which patients are at highest risk. Early data suggest that high plasma natalizumab concentrations due to low body mass or prolonged exposure to natalizumab may also confer higher risk for PML [Foley J.: Natalizumab related PML: an evolving risk stratification paradigm [abstract S30.002]. Presented at 65th American Academy of Neurology meeting. San Diego, CA; March 16–23, 2013].

In cases of natalizumab-associated PML, survival is better compared to HIV-associated PML; however residual disability may be severe (15). Use of MRI to screen patients taking natalizumab has led to the detection of several asymptomatic PML cases (16–19) which were successfully treated with minimal residual disability, establishing regular MRI screening as an important tool for minimizing PML-related disability in at-risk patients. PML has no cure, and treatment strategies focus on restoring immunocompetence. Natalizumab-associated PML is typically treated by withdrawal of natalizumab in combination with plasmapheresis to accelerate drug clearance (20) as, on its own, natalizumab may persist in the circulation for over 200 days after the last infusion (21).

Rapid discontinuation of natalizumab in the setting of JC virus infection is almost universally associated with immune reconstitution inflammatory syndrome (IRIS) and subsequent clinical deterioration (22, 23). IRIS was first identified in HIV patients who paradoxically worsened after starting highly active anti-retroviral therapy, despite reduction in their viral load and improvement of CD4 counts. IRIS may affect any organ system including the CNS; CNS-IRIS has been defined as paradoxical neurologic worsening during immune recovery in a person with an underlying CNS infection (24). It is exceedingly common in the setting of natalizumab-induced PML once the drug has been discontinued (23). In patients undergoing plasmapheresis for natalizumab removal, IRIS often develops within days; in other patients, symptoms may develop months after stopping the drug as the immune system reconstitutes (15). IRIS is identified by worsening of clinical symptoms and enlargement of lesions on MRI, frequently with corresponding contrast enhancement. On biopsy or autopsy, inflammatory changes are predominant, particularly CD8+ lymphocyte and macrophage infiltration with accompanying tissue necrosis (25). Patients who develop CNS-IRIS often require administration of IV glucocorticoids to diminish the inflammatory response (15, 23, 24); however, this can be counterproductive in cases of PML-IRIS where the only effective treatment is restoration of immunocompetence.

Debate continues as to whether natalizumab cessation causes increased MS activity apart from IRIS. Aggressive MS relapses leading to fulminant neurologic deterioration and sometimes death after discontinuation of natalizumab have been reported (22, 26–29). Since no underlying JC virus infections were identified, it is appropriate to consider such deterioration as MS reactivation rather than IRIS. Despite sporadic reports of aggressive relapses occurring after natalizumab cessation, a longitudinal study of >1800 patients who stopped natalizumab abruptly suggested that MS activity started to return shortly after natalizumab discontinuation and peaked at 4–7 months post-discontinuation. This time course was consistent with the pharmacokinetics of natalizumab clearance (30). Recent data from Cree and colleagues also showed that disease activity returned gradually in proportion to saturation of alpha-4-integrins with natalizumab. As alpha4-integrin saturation dropped below 70%, radiologic disease activity returned [Cree B, De Seza J, Fox R, et al.: Natalizumab effects during a 6-month dose interruption: relationship of pharmacokinetic, pharmacodynamic, and MRI measurements [abstract S41.003]. Presented at 65th American Academy of Neurology meeting. San Diego, CA; March 16–23, 2013]. It appears, therefore, that while MS reactivates upon natalizumab clearance, the severity of the relapses may increase from baseline in at least a subset of patients.

Alemtuzumab

Alemtuzumab is a humanized anti-CD 52 monoclonal antibody that results in marked lymphocyte depletion. CD52 is a cell-surface molecule present on B & T-lymphocytes and monocytes; it is not present on plasma cells or hematological precursors (31). Alemtuzumab was identified as a therapeutic agent in cell-mediated lysis of human lymphocytes in the 1980s (32); it was approved in the US for treatment of B-cell chronic lymphocytic leukemia in 2001. Since then, it has been studied in a variety of autoimmune diseases. A single dose of alemtuzumab in MS patients resulted in undetectable peripheral lymphocytes and monocytes for prolonged periods; while B-cells returned to pretreatment levels by 3 months, CD4+ and CD8+ T-cell counts at 12 months were only 32.9% and 55.4% of baseline values, respectively (33). Subsequent studies have shown that B-cells reach 165% of pre-treatment values by 12 months following treatment, albeit with a more immature phenotype (34). The T-cell depletion induced by even a single dose of alemtuzumab can last for years (35). The clinical relevance of this prolonged CD4+ recovery was demonstrated in a study of 56 patients in which relapse-free patients had lower mean CD4+ counts following treatment compared to those who relapsed (36).

The data supporting the efficacy of alemtuzumab in MS is strong, has been presented and published in a variety of forums and print media over the past several years and is thus best summarized in tabular form (Table 1). In addition, results of a 5-year follow-up to the initial phase 2 study show that the effects of alemtuzumab are sustained. The risk of sustained accumulation of disability and the rate of relapse both remained lower in alemtuzumab-treated patients, even amongst those who received no additional alemtuzumab beyond the two doses in the original study (37).

These positive treatment effects do not come without risks, some of which are life-threatening. The most common adverse effects associated with alemtuzumab were infusion reactions, which occurred in the vast majority of all treated subjects and consisted most frequently of headaches, rash, nausea and fever (38–40). Of great concern was the development of idiopathic thrombocytopenic purpura (ITP), which occurred in 16/1188 patients involved in the phase 2 and 3 studies (38–40). ITP was an unanticipated adverse event, and the association went unrecognized until a patient died from an intracerebral hemorrhage (40). After additional ITP cases were identified, alemtuzumab dosing was suspended for nearly two years (40) and subsequently only the 12 mg dose was given, as the 24 mg dose was more strongly associated with ITP. Most cases of ITP responded to corticosteroids, but several cases also required intravenous immunoglobulins and rituximab; one patient required splenectomy (38–40). More common than ITP were thyroid-related adverse events. These occurred in 16% to 25.9 % (38–40) of subjects treated with 12 mg alemtuzumab in studies and included hyper- and hypo-thyroidism, thyroiditis, goiter and thyrotoxic crisis. Anti-glomerular basement membrane (GBM) disease was reported after alemtuzumab in 3 patients, requiring cyclophosphamide and ultimately renal transplantation in two patients (35, 41, 42). Infection is a concern given the alemtuzumab-induced immunosuppression. The percentage of subjects experiencing any infections ranged from 45–55% in IFN β -treated subjects to 66–77% in alemtuzumab-treated subjects (38–40). The most common events included nasopharyngitis, upper respiratory tract infections, urinary tract infections and herpes infections. Herpes infections were significant at times and one case of herpes meningitis was described (38). Other atypical infections included a case of spirochetal gingivitis and *Listeria* meningitis (35, 42). Most other opportunistic infections (such as PML, cytomegalovirus, etc) have not been observed. Malignancies have not been statistically different in alemtuzumab-treated patients compared to controls. Three cases of thyroid cancer were noted in phase III trials, and one patient in the phase II trial extension died from non-Epstein Barr virus associated Burkett's lymphoma. Another patient developed a prelymphomatous condition, Castleman's disease (38, 39, 42, 43). Cossburn and colleagues analyzed prospective data from 248 alemtuzumab-treated MS patients to identify the rate, time to onset and clinical risk factors for the development of auto-immune diseases (AID). Autoimmunity developed in 22.17% during the 34 month median follow-up. 42 cases (77%) of AID were thyroid, with Grave's disease being most common. In this cohort, there were 5 cases (2%) of ITP and 1 case of GBM disease. Mean time to development of AID from initial treatment was 23 months and the longest interval was 54 months. Two risk factors for AID were identified: family history of AID (11.26%) and smoking (42.7% vs 17.2% for never-smokers). Risk was not influenced by the cumulative dose or dosing interval (44).

Risk mitigation will clearly be imperative with alemtuzumab, and the drug will require close and careful monitoring for infections and AID. The yearly dosing frequency combined with the potential for high therapeutic efficacy pose a unique challenge in this regard. One can envision that treated patients who are doing well may fail to appear for scheduled appointments and lab work, thus placing themselves at risk for adverse events and exposing the practitioner to liability. Thus, in addition to considering the medical appropriateness of this therapy, physicians will also need to consider whether a given patient is likely to be

compliant with the required monitoring. Despite the efficacy of alemtuzumab, the attendant risks make it unlikely to be used frequently as a first-line therapy, and its main use may be in patients with very active MS who have not responded to other DMTs.

Daclizumab

Daclizumab, another humanized monoclonal antibody being evaluated for multiple sclerosis, targets the α subunit (CD25) of the interleukin-2 receptor (IL-2R) found on regulatory T-cells and antigen-activated T-lymphocytes. By targeting CD25, daclizumab interferes with expansion of activated T-cells (45).

In the phase 2 CHOICE study, 230 patients who were taking IFN β were randomized to receive add-on daclizumab 2 mg/kg subcutaneous (SC) every two weeks (high dose group, HDG), 1 mg/kg SC every 4 weeks (low dose group, LDG) or placebo (PBO) for 24 weeks. The primary outcome was number of new or enlarged contrast enhancing lesions (CEL) on brain MRI. Relative to PBO there was a 25% reduction in CEL in the LDG and a 72% reduction in CEL in the HDG. Significant expansion of CD56^{bright} natural killer cells was observed in both daclizumab groups (46).

The phase 2 SELECT study evaluated the efficacy of daclizumab high-yield process (DAC-HYP) as monotherapy for RRMS. In this multicenter, multinational, double-blind, placebo-controlled trial, over 600 subjects were randomized 1:1:1 to receive SC injections of DAC-HYP 150 mg or 300 mg, or PBO every 4 weeks for 52 weeks (47). The primary endpoint was annualized relapse rate (ARR). Relative to PBO, there were 54% and 50% reductions in ARR with the 150 mg and 300 mg doses, respectively. New CELs were reduced by 69% (150 mg) and 78% (300 mg) vs PBO. DAC-HYP also reduced the risk of 3 month sustained disability progression by 57% (150 mg) and 43% (300 mg) compared to PBO. Expansion of CD56^{bright} NK cells was again observed.

Complications of daclizumab included infections and liver dysfunction. A higher incidence of serious infections occurred in patients treated with DAC-HYP (2%) vs. PBO (0). The frequency of herpes infections was similar among all treatment groups. Serious cutaneous events emerged in both DAC-HYP groups (1%) but not with PBO. While recovering from a serious cutaneous reaction one subject died from complications of a psoas abscess that was only identified post-mortem. Modest elevations of transaminases were observed across all groups; increases >5x the upper limit of normal were seen only in those treated with DAC-HYP (4%). These all resolved in a median of 62 days and some subjects continued dosing during this time (47).

Subjects who completed the SELECT study had the option of entering an extension study (the SELECTION study) to further evaluate the safety and efficacy of DAC-HYP. 517 patients chose to participate in this 52-week study [Giovannani G, Gold R, Selmaj K et al. The safety and efficacy of daclizumab HYP in relapsing remitting multiple sclerosis in the SELECTION extension study: primary results [abstract S01.001]. Presented at the 65th American Academy of Neurology meeting, San Diego, CA; March 16–23 2013]. Patients on PBO in the SELECT study were randomized to monthly 150 mg or 300 mg SC DAC-HYP. Patients who had originally been on DAC-HYP were randomized to stay on their current treatment vs. a 24-week washout followed by re-initiation of their original dose. In patients previously on PBO, the 52-week ARR was reduced by 59% and the proportion of patients with 3-month disability progression was reduced by 50% compared to the previous year. Patients remaining on DAC-HYP showed sustained benefit as measured by ARR and T2-weighted MRI lesions in year 2 vs. year 1; 88% showed no disability progression at 2 years. Importantly, there was no evidence of disease rebound at the end of the washout period. One

patient died from autoimmune hepatitis. Serious infections and serious cutaneous events occurred at similar rates with transaminitis being less common than in the SELECT study.

A phase 3 study comparing DAC-HYP 150 mg SC every 4 weeks to IFN β -1a 30 mcg IM once weekly in individuals with RRMS for up to 144 weeks is ongoing, and expected to conclude in 2014. Effects on relapses, disability and MRI are being measured (48).

Anti B-cell Monoclonal Antibodies

The contribution of B cells and their products to the pathogenesis of MS has been studied and debated for decades. Kabat established in the 1940s that immunoglobulins were elevated in the cerebrospinal fluid (CSF) of most MS patients (49). Immunoglobulins, B cells, and plasma cells are present in and around active MS lesions (50, 51). Meningeal ectopic lymphoid follicles containing B and T lymphocytes, follicular dendritic cells, and CXCL13 are associated with cortical demyelination and worse clinical MS outcomes (52). However, it was not until treatments that specifically targeted B cells were applied to MS that the critical importance of B cells in relapsing MS was proven.

Rituximab

Trials of rituximab, a monoclonal antibody therapy that targets the B-cell surface molecule CD20, were a key step forward. This Ig G1 κ chimeric mouse/human antibody binds CD20 and lyses B cells, primarily via complement-dependent mechanisms (53). A phase 2 trial of 104 relapsing MS patients showed that patients treated with rituximab had a ten-fold reduction in the number of CELs compared to placebo (54). This effect on MRI activity was rapid, with reductions noted at 4 weeks, maximal at 12 weeks and sustained for 48 weeks. The proportion of subjects with relapses was also reduced by rituximab at week 24 (14.5% versus 34.3% for placebo, $p=0.02$) and week 48 (20.3% versus 40.0%, $p=0.04$).

Our group conducted an open-label investigator-initiated trial of rituximab as an add-on therapy in 30 relapsing MS patients with a suboptimal response to disease modifying therapy (55). The primary endpoint was number of CELs on brain MRIs done prior to versus after rituximab, and an 88% reduction in number of CELs post-treatment was seen ($p<0.0001$). CSF B-cell numbers declined by 95% 6 months after treatment, though numbers of oligoclonal bands and IgG indices did not change significantly.

Rituximab was tested in a multi-center Phase II/III trial of 450 patients with primary progressive MS (PPMS) (56). While the primary endpoint of reduction in disability progression sustained for 12 weeks was not met, a pre-planned analysis of those patients who were younger (< 51 years) and had active baseline MRIs (CELs present) revealed a significant benefit of treatment on progression. A secondary endpoint of changes in T2-weighted lesion volume on brain MRI also revealed a benefit in the rituximab-treated group ($p<0.001$).

An open-label phase I study of 26 RRMS patients evaluated the safety of rituximab (57). There were no serious adverse events. Most reported adverse events consisted of infusion reactions, a side effect that is thought to be caused by cytokine release during B-cell lysis. Infections noted were mild to moderate. However, despite the established safety and efficacy of rituximab, the drug is not currently approved for MS and is not widely used for its treatment. FDA approval is not currently being sought due to the development of other humanized monoclonal antibodies targeting B cells, which are expected to have fewer side effects and a lower incidence of neutralizing antibody formation.

Ocrelizumab

Like rituximab, ocrelizumab is an anti-CD20 IgG1 monoclonal antibody. It is unique in that it is more fully humanized, differentially glycosylated, and has a modified Fc portion that potentially reduces side effects related to complement activation. In Phase 2 studies, 220 subjects were randomized to one of two doses of ocrelizumab, placebo, or β -IFN. In the intention-to-treat analysis CEL numbers were reduced by 89%–96% ($p<0.0001$) in the ocrelizumab groups compared to placebo after 24 weeks. This effect was rapid, with near maximum effects on CELs by week 8 in both ocrelizumab dosing groups (58). Phase 3 trials of ocrelizumab are underway in patients with both relapsing and primary progressive MS.

Ocrelizumab has not been associated with opportunistic infections in MS clinical trials, but studies of this drug in rheumatoid arthritis and lupus patients were stopped due to increased serious and opportunistic infections, including some deaths. The increase in infection in the rheumatoid arthritis trials was mainly seen at a higher 2,000mg dose, which is no longer being used (59). Side effects reported in MS trials to date have been limited to mild-to-moderate infusion reactions during the initial infusions.

Ofatumumab

Ofatumumab is also a humanized mAb that targets B cells, but at a different epitope of CD20 (60). In vitro, ofatumumab binds CD20 better than rituximab with a slower rate of dissociation. A small Phase II study of 38 active RRMS patients randomized to ofatumumab or placebo used escalating doses and showed that the mean cumulative number of new CELs was reduced by >99% for ofatumumab compared to placebo after 24 weeks [Soelberg-Sorenson P, Drulovic J, Havrdova E, et al. Magnetic resonance imaging (MRI) efficacy of ofatumumab in relapsing-remitting MS - 24 week results of a phase II study [abstract 136]. Presented atECTRIMS. Gothenburg, Sweden; October 13–16, 2010]. Currently, ofatumumab remains in Phase II clinical trials. No safety concerns have yet emerged.

Failed Monoclonal Antibodies in Multiple Sclerosis

It is useful to bear in mind that many biologic agents tested in MS have been unsuccessful. For example, elevation of tumor necrosis factor (TNF)- α is associated with MS relapses (61, 62). In animal models, treatment with TNF exacerbated disease and inhibiting TNF ameliorated disease (63–65). However, a phase I trial of anti-TNF antibodies in two MS patients showed increased MRI activity, CSF leukocyte counts and IgG indices after each anti-TNF infusion (66). A phase II trial of lenercept, a TNF- α receptor IgG1 fusion protein showed that patients treated with active drug had significantly more MS exacerbations compared to those that received PBO (67). Demyelinating disease has also developed as a complication of the anti-TNF treatments infliximab, etanercept and adalimumab (68), although the mechanism by which these TNF inhibitors promote demyelination is not clear. Anti-TNF agents are contraindicated in MS patients.

Early phase trials also attempted to ameliorate MS activity by targeting CD4 “helper” T-cells (69), or the cytokine IL-12/23 (70). Despite supportive basic science and promising results from animal studies (71–73), these monoclonal antibodies did not affect disease activity in humans and have not been pursued.

Conclusion

Monoclonal antibodies are an exciting treatment option for patients with MS, and many of the mAbs currently approved or under development appear to be singularly effective in reducing disease activity. Natalizumab, the only mAb currently approved for MS, appears to be one of the most efficacious drugs available. Alemtuzumab, currently under FDA review,

also has exciting implications for MS treatment, as yearly infusions essentially halted disease activity in many patients. Early data for daclizumab and ocrelizumab, both in phase III trials, have been very promising (Table 2).

The potent disease modifying abilities of these mAbs come with a unique set of agent-specific risks. Natalizumab is associated with PML. Over the last decade, we have begun to understand how to mitigate this risk, but much remains to be learned and PML remains a very real concern for practitioners prescribing the drug and for patients taking it. Similarly, alemtuzumab-treated patients are at risk for a variety of AID, specifically thyroid disorders and ITP. The profound and long-lasting reduction in T-cell numbers following alemtuzumab also raises questions about its long-term safety.

Each biologic agent will likely be associated with different and agent-specific risks and complications, and it will remain necessary for providers to be vigilant in monitoring patients undergoing therapy with monoclonal antibodies for MS. Similar to what happened with natalizumab, some treatment-related complications may not become evident until the new drug is put into widespread use.

Acknowledgments

Dr. Longbrake is supported by a Sylvia Lawry Fellowship from the National Multiple Sclerosis Society.

Dr. Cross was supported in part by the Manny and Rosalyn Rosenthal-Dr. John Trotter Chair in Neuroimmunology of the Barnes-Jewish Hospital Foundation.

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Table 1

Clinical trials of alemtuzumab

Population	Design	Impact on Relapse	Impact on Disability	Impact on MRI	Other Findings
Early MS (40)	Alem (brief cycles of 12 or 24mg IV given yearly) vs. IFN β -1a (44 mcg 3x/week)	74% reduced relapse rate; increased relapse-free survival in Alem (80%) vs. IFN β (52%)	Sustained disability risk decreased 71%	Greater reduction in lesion volume on T2-weighted MRI	none
Relapsing/ remitting MS (38)	Phase III Alem (brief cycles of 12mg IV yearly) vs. IFN β -1a (44 mcg 3x/week) as first-line therapy	54.9% reduced relapse risk; increased relapse free in Alem (77.6%) vs. IFN β (58.7%)	None	Decreased CELs; 40% decrease in loss of brain volume; no difference in lesion volume on T2-weighted MRI	Increased clinically disease-free with Alem (74%) vs. IFN β (56%); increased MRI and clinically disease-free in Alem (39%) vs. IFN β (27%)
Relapsing MS (39)	Phase III Alem (brief cycles of 12 or 24mg IV given yearly) vs. IFN β -1a (44 mcg 3x/week) in previously treated MS patients	49.4% reduced relapse risk; increased relapse-free with Alem (65.4%) vs. IFN β (46.7%)	42% reduced disability progression	Decrease in new T2 and CELs; decreased loss of brain volume; no difference in lesion volume on T2-weighted MRI	Increased clinically disease-free with Alem (60%) vs. IFN β (40%); increased MRI and clinically disease-free in Alem (32%) vs. IFN β (14%)

Alem – alemtuzumab; CEL – contrast enhancing lesion; IFN – interferon;

TABLE 2

Monoclonal antibody treatments approved or in development for MS

Agent	Type of MS (delivery)	Target	Mechanism of Action	Year approved
Natalizumab (Tysabri [®])	Relapsing (monthly infusion)	Alpha-4 integrins	Blocks leukocyte migration into CNS	2004/2006
Alemtuzumab (Lemtrada [®])	Relapsing (yearly infusions)	CD52	Depletes CD52+ cells (e.g. mature lymphocytes, monocytes, dendritic cells)	Under review by FDA
Daclizumab	Relapsing (s.c. injections q4 weeks)	CD25 (IL-2 receptor α subunit)	Antagonizes CD25-mediated signaling, thus blocking T-cell activation & expansion; expands regulatory CD56 ^{bright} natural killer cells	Phase III trials
Rituximab	Relapsing (twice yearly infusions)	CD20	Lyses B-cells (early pro-B-cells and plasma cells are spared)	Approval for MS not being pursued
Ocrelizumab	Relapsing, PPMS (twice yearly infusions)	CD20		Phase III trials
Ofatumumab	Relapsing (infusion, injections)	CD20		Phase II trials