Current and emerging therapies in multiple sclerosis: a systematic review

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Abstract: Multiple sclerosis (MS) is a potentially disabling chronic autoimmune neurological disease that mainly affects young adults. Our understanding of the pathophysiology of MS has significantly advanced in the past quarter of a century. This has led to the development of many disease-modifying therapies (DMTs) that prevent exacerbations and new lesions in patients with relapsing remitting MS (RRMS). So far there is no drug available that can completely halt the neurodegenerative changes associated with the disease. It is the purpose of this review to provide concise information regarding mechanism of action, indications, side effects and safety of Food and Drug Administration and European Medicines Agency approved agents for MS, emerging therapies, and drugs that can be considered for off-label use in MS.

Keywords: disease-modifying therapies, emerging therapies, fingolimod, glatiramer acetate, interferon β, multiple sclerosis, natalizumab

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Introduction

Multiple sclerosis (MS) is a chronic autoimmune inflammatory disease of the central nervous system (CNS) that mainly affects young adults and may lead to significant disability over time. Since the first documented case of MS in the nineteenth century the knowledge regarding the pathophysiology of the disease has significantly advanced. The inflammatory cells in MS have been well described and include CD4 and CD8 T lymphocytes, microglia and macrophages [Goverman, 2011]. Also humoral immunity has been described as an important component in the pathophysiology of MS [Boster *et al.* 2010].

Within the past 30 years new and effective therapies have been developed that decreased clinical relapses, reduced new T2 and gadolinium-enhancing (Gad+) lesions and aim to halt the progression of disease. Since the US Food and Drug Administration (FDA) approval of the first disease-modifying therapy (DMT) in 1993, interferon (IFN)-β1b (Betaseron), which was also approved in Europe in 1995 under the name of Betaferon, we now have a total of eight FDA-approved therapies for MS, including an oral agent and a single agent approved for secondary progressive MS (SPMS) (Table 1). Of note, there are two agents approved by the European Medicines Agency (EMA) for the treatment of SPMS, mitoxantrone and IFN-β1b (Betaferon/Extavia). All first-line injectable agents have been studied in clinically isolated syndrome (CIS) and have demonstrated decreased risk of conversion into clinically definite MS (CDMS) (Table 2) [Kappos *et al.* 2006; Jacobs *et al.* 2000; Comi *et al.* 2001, 2009, 2012a]. So far there is no effective therapy to halt progression of disease and reduce disability in primary progressive MS (PPMS).

There are many new agents in the pipeline which will bring great choices into the MS pharmacological armamentarium (Table 3).

FDA- and EMA-approved therapies

Interferon β

IFNs are a family of proteins that play a role in the body's natural defense against microbial, neoplastic and viral insults and have a role in regulating the immune response. IFN-β impacts the immune system in several ways, such as decreasing major histocompatibility complex (MHC) class II expression, upregulation of interleukin 10

Table 1. Current Food and Drug Administration/European Medicines Agency approved therapies for multiple sclerosis (MS)

Disease-modifying therapy	Dose/route	Monitoring labs/tests	Side effects*
IFN-β1a (Avonex)	30 μg intramuscularly weekly	CBC, LFTs, TSH	Flu-like symptoms, depression, thyroid dysfunction, liver enzymes abnormalities
IFN-β1a (Rebif)	22 or 44 μg subcutaneously three times a week	CBC, LFTs, TSH	Skin site reactions, flu-like symptoms, depression, thyroid dysfunction, liver enzymes abnormalities
IFN-β1b (Betaseron/ Betaferon/Extavia)	250 μg subcutaneously every other day	CBC, LFTs, TSH	Skin site reactions, flu-like symptoms, depression, thyroid dysfunction, liver enzymes abnormalities
Glatiramer acetate (Copaxone)	20 mg subcutaneously once a day	None	Skin site reactions, immediate postinjection reaction, lipoatrophy
Mitoxantrone	12 mg/m^2 intravenously over 30 min every 3 months with a lifetime cumulative dose of no more than 140 mg/m^2; frequency may vary	CBC, LFTs, U/A, LVEF	Hair loss, cardiotoxicity, leukemia, infertility, increased risk of infections, leukopenia, anemia, nausea, vomiting, thrombocytopenia
Natalizumab (Tysabri)	300 mg intravenously every 28 days	CBC, LFTs	Transient headache fatigue, recurrent UTIs, PML, hypersensitivity reaction
Fingolimod	0.5 mg orally once a day	CBC, LFTs, screen for macular edema	First-degree AV block with first dose, bradycardia, macular edema, shingles, PF dysfunction in selected patients, skin cancer, back pain

AV, atrioventricular; CBC, complete blood count; IFN, interferon; LFT, liver function test; LVEF, left ventricular ejection fraction; PML, progressive multifocal leukoencephalopathy; PF, pulmonary function; TSH, thyroid-stimulating hormone; U/A, urinalysis; UTI, urinary tract infections.
*Selection of side effects, not full side effects profile.

(IL-10) production, and decreased T helper (Th)-1 and Th17 production, which leads to an overall anti-inflammatory effect [Kieseier, 2011; Kappos *et al.* 2007].

Subcutaneous interferon β1b (Betaseron, Bayer Schering Pharma AG/Betaferon, Bayer Schering Pharma AG/Extavia, Novartis Pharmaceuticals Corp.). The pivotal phase III trial using IFN-β1b was a randomized, double-blind, placebo-controlled, multicenter trial of 372 patients with RRMS over 2 years. This trial demonstrated a 34% reduction in overall relapses compared with placebo. More specifically, there was a 50% reduction in annualized relapses classified as moderate to severe in the treatment group. Patients receiving IFN-β1b were also found to have a lower T2 lesion volume and decreased accumulation of new lesions [IFNB Multiple Sclerosis Study Group. 1993]. Each of the IFN-β therapies, as well as glatiramer acetate, has been shown to delay conversion to CDMS in patients with CIS (Table 2). In the 5-year active treatment extension of the BENEFIT trial, the effects of early *versus* delayed treatment with IFN β1b were investigated. This study showed the risk of conversion to CDMS remained lower in the group receiving early treatment; 46% compared with 57% of patients converting from CIS to CDMS [hazard ratio (HR) 0.63; 95% confidence interval (CI) 0.48–0.83; log rank test $p = 0.003$) [Kappos *et al.*2009].

Intramuscular interferon β1a (Avonex, Biogen Idec, Inc.). In the pivotal trial including 301 patients

Table 2. Pivotal trials for approval of disease-modifying therapies in clinically isolated syndrome

Trial	Drug	Result	Reference
BENEFIT	IFN-β1b	Conversion risk at 2 years 28% with interferon β-1b *versus* 45% with placebo	Kappos *et al*. [2006]
CHAMPS	IFN-β1a intramuscularly	Conversion risk at 2 years was 35% with interferon β-1a intramuscularly *versus* 50% with placebo	Jacobs *et al*. [2000]
ETOMS	IFN-β1a subcutaneously	Conversion risk at 2 years was 34% with interferon β-1a subcutaneously *versus* 45% with placebo	Comi *et al*. [2001]
REFLEX	IFN-β1a subcutaneously	Conversion risk at 2 years was 20.6% for three times per week dose, and 21.6% for once a week dose *versus* placebo	Comi *et al*. [2012]
PreCISe	Glatiramer acetate	Conversion risk at 2 years was 25% with glatiramer acetate *versus* 43% with placebo	Comi *et al*. [2009]

BENEFIT, Betaseron/Betaferon in newly emerging multiple sclerosis for initial treatment; CHAMPS, the controlled high risk Avonex multiple sclerosis trial; ETOMS, early treatment of multiple sclerosis; IFN, interferon; PreCISe, effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome; REFLEX, REbif FLEXible dosing in early MS.

with RRMS, IFN-β1a intramuscularly was shown to delay time to progression of disability with fewer treated subjects experiencing disability progression (21.9% *versus* 34.9%; $p = 0.02$) compared with placebo. Annualized relapse rates (ARRs) over a 2-year period were also lower compared with placebo (ARR 0.61 *versus* 0.90; $p = 0.03$). The accumulation of Gad+ lesions was also reduced; however, T2 lesion volume was not significantly different between the two groups at 2 years [Jacobs *et al*. 1996].

Subcutaneous interferon β1a (Rebif, EMD Serono, Inc.). The Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis (PRISMS) trial was a 2-year randomized, double-blind, placebo-controlled, multi-centered trial of 560 patients with RRMS. Subjects treated with either the 22 or 44 μg dose of IFN-β1a subcutaneously showed a significant reduction in ARRs compared with placebo, 27% and 33% respectively. Both treatment groups showed a significant reduction in the number of new or enlarging T2 lesions; 67% reduction in the 22 μg group and 78% reduction in the 44 μg group [PRISMS Study Group, 1998]. An extension study utilizing a crossover design in which placebo-treated patients were randomized to either 22 or 44 μg of IFN-β1a subcutaneously after 2 years revealed patients in both active treatment groups for the entire 4 years continued to show significantly lower number of relapses per year [PRISMS Study Group, 2001]. IFNs have immunogenic properties and treated individuals may develop binding and neutralizing antibodies (NAbs) to these products. NAbs may develop with the use of all formulations of IFN-β; however, they are found more commonly with the high-dose, high-frequency IFNs (IFN-β1b and IFN-β1a subcutaneously). The issue of NAbs is controversial; however, a panel of experts met at the Neutralizing Antibodies on Interferon Beta in Multiple Sclerosis (NABI-NMS) consortium in 2009 in attempts to formulate a practical approach to the evaluation and incorporation of information regarding NAbs in the treatment of MS. The group proposed that both the NAb titer and clinical status of the patient should be considered in the decision regarding the impact of the presence of NAbs on changing DMTs. They also suggested reevaluation of the NAbs status prior to making a change in therapy unless patients were clearly performing poorly clinically [Polman *et al.* 2010].

Glatiramer acetate

Glatiramer acetate (GA) (Copaxone, Teva Neuroscience North America / Teva Pharmaceuticals) is a first-line therapy for relapsing forms of MS

Table 3. Multiple sclerosis emerging therapies.

Current agents in the pipeline	Mechanism of action	Phase	Administration	Results	Adverse effects
Laquinimod	May modulate Th1 to Th2 cytokine shift	III	Oral 0.6 mg daily	23% reduction in relapse rate; 37% reduction in contrast enhancing lesions	LFT elevation
Teriflunomide	Inhibits DNA pyrimidine synthesis in dividing cells such as T and B cells	III	Oral 7 and 14 mg daily	61% reduction in contrast enhancing lesions, reduces ARR by 30%, reduces disability progression by 23–30%	Nasopharyngitis, headache, diarrhea, fatigue, back pain, influenza, hair thinning, LFT elevation, nausea, UTI
Dimethyl fumarate (BG-12)	Modulates oxidative pathways and decreases autoimmunity	III	Oral 120–240 mg three times a day	69% reduction in contrast enhancing lesions (phase II trial); DEFINE phase III trial showed 53% reduction in ARR; 38% reduction in disability progression, and reduced disability progression in 2 years by 49%	Diarrhea, cramps, LFT elevation, nausea and flushing
Alemtuzumab	Antibody binds CD52 to cause destruction of circulating immune cells	III	Intravenous infusion 12 or 24 mg daily for 5 days on month 0 and 12 or 24 mg daily for 3 days on month 12	Up to 75% reduction in sustained accumulation disability; up to 74% reduction in relapse rate	Immune thrombocytopenic purpura, autoimmune thyroid-related problems, headaches, flushing
Daclizumab	Block the IL-2 receptor/ anti-CD25	II	Subcutaneous 2 mg/kg every 2 weeks	72% reduction in contrast enhancing lesions, decreased disease progression by up to 57% in 1 year, decreased ARR by 50–54%	Infusion reaction, serious skin rash, lymphadenopathies, LFT abnormalities, liver toxicity, diarrhea, constipation
Ocrelizumab	Antibody targets CD20 and mediates destruction of B cells	II	600 mg, 2000 mg intravenous infusions	Reduced brain lesions by 89% and 96%, reduced ARR by 80% and 73%	Systemic inflammatory response (one lethal case), infusion site reactions

ARR, annualized relapse rate; DEFINE, efficacy and safety of oral BG00012 in relapsing remitting multiple sclerosis; HZV, Herpes Zoster virus; LFT, liver function test; Th, T helper; UTI, urinary tract infection.

and CIS. GA contains an incalculable number of active amino acid sequences and is composed of a large number of synthetic peptides. The usual dose of GA is 20 mg subcutaneously once a day.

The mechanism of action (MOA) of GA is not completely understood, but consists of an antigen-presenting cell (APC) incorporating peptides of GA and presenting them to a lymphocyte, similar to the process of a vaccine. This process creates a unique population of lymphocytes circulating in the blood which are responsive to GA. It inhibits the multiplication of human lymphocytes that are capable of reacting to myelin basic protein. Researchers have been able to show that GA binds directly to the portion of the APC that is required to stimulate the T lymphocyte, thus

blocking direct immunologic attack. It was in the late 1980s that the immunologic concept of Th1 (proinflammatory) and Th2 (anti-inflammatory) lymphocytes gained momentum. These two types of lymphocytes can be identified by the chemicals that they manufacture and then secrete. These chemicals are known as cytokines, and can be divided into inflammatory and proinflammatory. In 1997, Aharoni and colleagues published a paper that described how GA could stimulate the production of Th2 (anti-inflammatory) cells that inhibited the inflammatory response by secreting anti-inflammatory cytokines [Aharoni *et al.* 1997]. The GAs' effect begins in the peripheral tissues in a population of specific lymphocytes which circulate in the blood and are capable of migrating into the CNS tissue by crossing the blood–brain barrier (BBB). These cells then encounter fragments of several myelin proteins that stimulate the glatiramer cells to multiply and begin to produce anti-inflammatory cytokines. Since the glatiramer-activated lymphocytes can suppress inflammation under way in the diseased area of CNS tissue, this process has been given the name bystander suppression [Johnson, 2010]. To date, data suggest that GA treatment is associated with a broader immunomodulatory effect on cells of not only the innate but also the adaptive immune system. Recent investigations indicate that GA treatment may also promote regulatory B-cell properties [Lalive *et al.* 2011].

GA has a relatively narrow adverse effect profile. Most frequently patients complain of mild pain and pruritis at the injection site. Lipoatrophy and skin site reactions are also seen and may lead to discontinuation of therapy. A transient reaction called immediate postinjection reaction consists of chest tightness, flushing and dyspnea beginning soon after the injection and lasting no longer than 20 min. If no history or evidence of coronary artery disease, the patient can be reassured that such a reaction is benign [DiPiro *et al.* 2005].

Multicenter trials with GA have demonstrated statistically significant reductions in mean ARR that are comparable to those of the IFNs [DiPiro *et al.* 2005]. In two recent studies the efficacy of GA was compared with high-dose/high-frequency IFN-β. In the Rebif *versus* Glatiramer Acetate in Relapsing MS Disease (REGARD) study [Mikol *et al.* 2008], subcutaneous IFN-β1a was compared with GA, and in the Betaseron/Betaferon Efficacy Yielding Outcomes of a New Dose (BEYOND) study [O'Connor *et al.* 2009], subcutaneous IFN-β1b was compared with GA. In both trials, there was no significant difference between IFN and GA in the primary endpoints or in any clinical endpoints, although some differences in magnetic resonance imaging (MRI) measures of disease activity have been claimed.

The results from a 15-year analysis of the US prospective open-label study of GA indicate that long-term continuous use is safe. It also indicates that the majority of patients continuing on GA therapy in the study have had few relapses and minimal disease progression. Of the initial 232 patients that received at least one GA dose since study initiation in 1991, only 100 (43%, ongoing cohort) patients continued. Of the 100 patients receiving continuous GA as sole immunomodulatory therapy for 15 years (mean disease duration of 22 years and mean patient age of 50 years) have not transitioned to SPMS, 57% have retained stable or improved the Expanded Disability Status Scale (EDSS) scores over the course of the study and 82% remain ambulatory without mobility aids. There was no occurrence of any unforeseen adverse events in patients receiving GA therapy. The study will continue for 20 years of prospective follow up [Ford *et al.* 2010].

Mitoxantrone

Mitoxantrone is an anthracenedione initially developed as an anti-neoplastic agent that reduces lymphocyte proliferation. Mitoxantrone intercalates into DNA strands, inducing strand breakage and inhibition of the DNA repair enzyme topoisomerase II. It is an immunosuppressive agent used as a second-line treatment for SPMS, primary relapsing multiple sclerosis and worsening RRMS. Mitoxantrone was approved for the treatment of SPMS based on the study by Hartung and colleagues [Hartung *et al.* 2002].

Several studies have shown it to be efficacious in reducing exacerbations and number of Gad+ lesions on MRI, and it seems to have effects on disease course up to 5 years after discontinuing therapy [Martinelli *et al.* 2009; Goodin *et al.* 2003]. Mitoxantrone is given as an intravenous infusion over 30 min every 3 months at 12 mg/m^2 for a 2- to 3-year period with a maximum cumulative dose of 140 mg/m^2. Common side effects include alopecia, nausea and vomiting, an increased risk of infection (particularly urinary and respiratory tracts infections) and amenorrhea. Mitoxantrone, though effective, remains second line due to its

risk of two serious adverse effects that can occur at any time after the first dose is given. The first, acute leukemia has an incidence of approximately 0.81% [Marriott *et al*. 2010]. Regular monitoring of complete blood counts is recommended. Mitoxantrone can also cause decreased left ventricular ejection fraction (LVEF) and congestive heart failure at a rate of approximately 12% and 0.4%, respectively [Marriott *et al*. 2010]. To monitor cardiotoxicity, a baseline LVEF must be obtained and any patient with an ejection fraction less than 50% should not receive mitoxantrone. It was previously believed that cardiotoxicity could only occur with cumulative doses over 96–140 mg/m^2; however, several reports of cardiotoxicity below this threshold have caused the FDA to recommend monitoring cardiac function before every infusion. The therapy must be discontinued if the LVEF ever falls below 50% or decreases by 10% [Martinelli *et al*. 2009].

Natalizumab

Migration of leukocytes from the vasculature into the parenchyma involves the interaction between leukocyte adhesion molecules and their complementary ligands on vascular endothelial cells. Leukocyte integrins are heterodimeric glycoproteins that contain an α and β chain [Ransohoff, 2007]. Vascular cell adhesion molecule 1 (VCAM-1) is expressed on the surface of vascular endothelial cells in the blood vessels within the CNS and interacts with α4β1 integrin on lymphocytes to allow for extravasation across the BBB. Also, the interaction of α4β1 integrin with fibronectin and osteopontin may modulate the survival, priming and activation of leukocytes that have entered into the parenchyma of the brain and spinal cord. Natalizumab (Tysabri, Biogen Idec, Inc.) contains humanized immunoglobulin G4κ monoclonal antibodies against leukocyte α4 integrins, including α4β1 and α4β7 integrins, and blocks binding to their endothelial receptors (VCAM-1 and mucosal addressin cell adhesion molecule 1, respectively) [Polman *et al*. 2006]. By blocking α4 integrins, natalizumab inhibits the migration of leukocytes into the brain, which results in reduced inflammation.

Natalizumab was evaluated for the treatment of RRMS in two phase III clinical trials. The Natalizumab Safety and Efficacy in relapsing remitting multiple sclerosis (AFFIRM) study evaluated 942 patients who were randomly assigned to receive natalizumab *versus* placebo every 4 weeks for 2 years. The primary endpoints were the rate of clinical relapse at 1 year and the rate of sustained progression of disability, measured by the EDSS, at 2 years. Natalizumab reduced the risk of sustained disability by 42% over 2 years (HR 0.58; 95% CI 0.43–0.77; $p < 0.001$). It reduced the rate of clinical relapse at 1 year by 68% ($p < 0.001$). MRI scans were obtained at baseline, 1 year and 2 years. Treatment with natalizumab resulted in an 83% reduction of new or enlarging hyperintense T2 lesions over 2 years (mean number of lesions 1.9 with natalizumab and 11 with placebo; $p < 0.001$). There were 92% fewer Gad+ lesions in the natalizumab group than in the placebo group at 1 and 2 years ($p < 0.001$). There was also a significant effect on Gad+ lesions seen after 6 weeks of natalizumab treatment [Polman *et al*. 2006].

The Safety and Efficacy of Natalizumab in combination with IFN-β1a in patients with RRMS (SENTINEL) trial was a 2-year phase III trial evaluating treatment with natalizumab or placebo in combination with IFN-β1a. The primary endpoints were the rate of clinical relapse at 1 year and accumulative probability of disability progression, measured by the EDSS, at 2 years. The study showed that treatment with both drugs was more effective than treatment with IFN-β1a alone. Patients on combination treatment were less likely to have sustained disability progression (23% *versus* 29%) and were more likely to remain relapse free (61% *versus* 37%). Combination treatment resulted in fewer new or enlarging T2 lesions (0.9 *versus* 5.4; $p < 0.001$) [Rudick *et al*. 2006]. The study ended a month early due to the occurrence of progressive multifocal leukoencephalopathy (PML) in two patients who received natalizumab with IFN-β1a.

The most notable potential adverse effect of natalizumab treatment is the development of PML. Following the observation that three patients treated with natalizumab developed PML, it was withdrawn from the market in February 2005 and reintroduced in July 2006 as monotherapy treatment for RRMS. The original risk of PML was estimated to be approximately one per 1000 patients receiving natalizumab [Berger, 2010]. As of 4 January 2012, approximately 96,582 patients have received natalizumab since it was marketed and there have been 201 confirmed cases of PML worldwide. Approximately 20% of patients who have developed PML have died. Those that survived have varying levels of disability, ranging

from mild to severe. Fewer patients treated and wide confidence intervals result in questionable estimates beyond 30 months of treatment.

PML is a rare demyelinating disease of the brain due to the John Cunningham (JC) virus. It is almost always seen in association with an underlying immunosuppressive condition. The precise explanation for the increased risk of PML with natalizumab therapy remains unknown.

In the natalizumab clinical trials, there was a small increase in the rate of infections, including herpes infections, pneumonia and urinary tract infections. There were no other opportunistic infections or increase cases of cancer reported [Ransohoff, 2007]. Post-release monitoring disclosed one case of fatal herpes encephalitis, one nonfatal case of herpes meningitis, cryptosporidium gastroenteritis, pneumocystis carinii pneumonia, varicella pneumonia and mycobacterium avium intracellular complex pneumonia [Ransohoff, 2007; Gorelik *et al*. 2010].

Natalizumab infusions were complicated by serious hypersensitivity reactions, including fever, rash and anaphylaxis, in less than 1% of patients and less serious infusion reactions in about 4% of patients [Ransohoff, 2007; Polman *et al*. 2006; Rudick *et al*. 2006]. Patients with infusion reactions were more likely to have persistent NAbs. The presence of antibodies lessoned natalizumab's clinical efficacy and resulted in clinical and radiographic disease activity equivalent to patients in the placebo group [Ransohoff, 2007].

Natalizumab is an extremely effective therapy for RRMS and is licensed for highly active naïve patients. Due to the potential risk of PML and other opportunistic infections, it is typically reserved for patients with clinically or radiographically extremely active disease either as initial therapy or when initial therapy has been ineffective or poorly tolerated. Treatment with natalizumab requires rigorous ongoing clinical surveillance. To minimize the risk of PML, patients beginning treatment should have no history of immunosuppressive medications in the preceding 3 months and should not have other conditions that may compromise cell-mediated immunity. The FDA and EMA recommend the use of the JC virus antibody for risk stratification on all patients on Tysabri. The risk of PML increases after 24 months on therapy, if there has been prior immunosuppressant use and the presence of JC virus antibody. Patients with positive JC virus antibody, prior treatment with an immunosuppressant and who have received more than 24 doses of Tysabri have an estimated risk of PML of 9–11/1000. However, patients without any of those risk factors for PML have a risk of PML of less than 0.1 per 1000 [Sorensen *et al*. 2012].

Fingolimod

Fingolimod is an oral sphingosine-1 phosphate (S1P) receptor modulator. It was approved by the FDA in September 2010 as first-line therapy for RRMS. However, the EMA has recommended that its use be limited to those whose condition fails to respond to first-line therapy or only in cases of severe, rapidly developing cases of MS. It acts as a sphingosine analogue, binding to the $S1P_1$ receptor on lymphocytes leading to internalization and downregulation of their expression and thereby preventing the egression of lymphocytes from the lymph nodes. Additionally, through interactions with S1P receptors on neural cells, fingolimod has been shown to have potentially neuroprotective effects in the animal experimental autoimmune encephalomyelitis model [Foster *et al*. 2007; Coelho *et al*. 2007; Miron *et al*. 2008].

In the 24-month phase III FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis (FREEDOMS) trial comparing placebo with oral fingolimod at doses of 1.25 mg and the now FDA-approved 0.5 mg daily dose, there was a significant reduction in ARR with both doses of fingolimod (0.16 at 1.25 mg and 0.18 at 0.5 mg) compared with placebo (0.40) which represented a relative reduction of 60% and 54%, respectively. Furthermore, fingolimod also reduced the risk of disability progression with a probability of disability progression (confirmed after 3 months) of 17.7% at the 0.5 mg dose and 16.6% at the 1.25 mg dose compared with 24.1% with placebo. Almost 90% of patients receiving fingolimod, at either dose, were free of enhancing lesions over the course of 2 years and approximately 50% were free of new or enlarging T2 lesions [Kappos *et al*. 2010].

The Trial Assessing Injectable Interferon *versus* FTY720 Oral in RRMS (TRANSFORMS) comparing fingolimod with intramuscular INF-β1a showed a 52% relative reduction in ARR in the patients treated with fingolimod 0.5 mg *versus* IFN. This study showed a similar beneficial

effect on MRI markers compared with IFN-β1a; however, there was no statistically significant difference in the disability progression between the fingolimod and IFN-β1a groups [Cohen *et al*. 2010].

Despite its efficacy, there are additional safety concerns compared with the injectable therapies. Data from the two pivotal trials showed an increased risk of infections, cardiovascular effects, including bradycardia and atrioventricular (AV) block (first and second degree) with initial dosing and macular edema. Each of these was more common with the higher 1.25 mg dose. Of note, there were two deaths related to infections in subjects receiving fingolimod at the 1.25 mg dose in TRANSFORMS. One death was secondary to a dissemination varicella zoster infection and the second was related to herpes simplex encephalitis. While herpes virus infection has been seen at the 0.5 mg dose, cases tended to be mild and were not found to occur at a higher rate than the control arm [Cohen *et al*. 2010].

The EMA recently recommended increased patient monitoring during the first dose of fingolimod, including electrocardiogram monitoring before treatment and then continuously for the first 6 h after the first dose is administered, and measurement of blood pressure and heart rate every hour over the same 6 h.

Off-label therapies

Immunosuppressive agents, chemotherapies and various mAbs have been used off label for many years as DMTs in MS but the potential benefits of these therapies are limited by systemic adverse events, such as increased risk of malignancy and opportunistic infections. These agents have been used in patients who are refractory to or cannot tolerate the side effects of IFN-β and GA, cannot afford FDA-approved therapies, or need intensification of therapy (i.e. used in combination with IFN-β or GA). Also limiting the use of these medications is the lack of large-scale, controlled trials, validating their efficacy.

Mycophenolate mofetil

Mycophenolate mofetil (MMF; Cellcept, Roche Laboratories, Nutley, NJ, USA) is FDA and EMA approved for preventing rejection of cardiac, liver and renal transplants. MMF undergoes rapid and complete metabolism to mycophenolic acid (MA), which is the active metabolite. MA is a potent, selective, noncompetitive and reversible inhibitor of inosine 5' monophosphate dehydrogenase type II. MA inhibits the *de novo* synthesis pathway of guanosine nucleotides without being incorporated into DNA. Because T and B lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines, while other cell types can utilize salvage pathways, MA has potent cytostatic effects on lymphocytes. MA inhibits proliferative responses of T and B lymphocytes to both mitogenic and allospecific stimulation. MA also suppresses antibody formation by B lymphocytes [Product information: Cellcept, 2009].

Potential side effects include hypertension, backache, abdominal pain, diarrhea, nausea, elevated transaminases, vomiting, anxiety and tremor. Serious side effects include gastrointestinal bleeding, thrombocytopenia, skin cancer, opportunistic infection and PML. Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression.

A retrospective review of experience in treating 79 patients with MS with MMF showed that this agent was well tolerated by the majority of patients. Patients were initiated on 500 mg twice a day, which was titrated up by 500 mg weekly to a maximum of 1000 mg twice a day. While the observations were uncontrolled, some of the patients demonstrated either stabilization or improvements in their activities of daily living, ambulation and relapse rate [Frohman *et al*. 2004]. In a randomized, MRI-blinded, parallel group, pilot trial of MMF compared with IFN-β1a, both drugs appeared safe and well tolerated in the majority of patients. The trial also showed a trend toward a lower accumulation of combined active MRI lesions. MMF showed a nonstatistically significant increase in infections [Frohman *et al*. 2010]. The dose generally used in patients with RRMS is 1000 mg twice daily. Large, randomized clinical trials are needed to better evaluate the safety and efficacy of this agent in patients with MS.

Azathioprine

Azathioprine is FDA approved for rejection prophylaxis (as monotherapy or adjunct) of renal transplant and rheumatoid arthritis (RA). Although not FDA approved, it has been used in the USA to treat MS since 1971 [La Mantia *et al*. 2007]. Azathioprine is licensed for MS therapy in

Germany. Azathioprine is an imidazole derivative of 6-mercaptopurine and acts as an immunosuppressive antimetabolite. It is a purine antagonist and affects DNA replication. It impairs T-cell lymphocyte function and is more selective for T lymphocytes than for B lymphocytes [Casetta *et al.* 2009]. The Cochrane MS Group concluded that azathioprine is an appropriate maintenance treatment for patients with MS and could be a fair alternative to IFN. It is recommended that cumulative doses do not exceed 600 g due to possibly increasing the risk of malignancies [Casetta *et al.* 2009].

Methotrexate

Methotrexate (MTX) is a chemotherapeutic agent used for the treatment of severe psoriasis, juvenile RA (JRA), severe RA, acute lymphoid leukemia and other malignancies. MTX reversibly inhibits dihydrofolate reductase. Via this mechanism, MTX sodium interferes with DNA synthesis, repair and cellular replication [Product information: methotrexate, 2000, 2005].

On a systematic review of oral MTX for MS, for the Cochrane Multiple Sclerosis Group, the authors do not recommend the use of MTX for progressive MS or RRMS due to a lack of high-quality evidence. Future trials need to be performed using standard outcome measures and objective measures, such as MRI [Gray *et al.* 2004].

Rituximab

Rituximab is FDA approved for the treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, refractory moderate to severe RA, Wegener's granulomatosis and microscopic polyangiitis [Prescribing information, 2010]. It is EMA approved for diffuse large B-cell lymphoma and autoimmune arthritis. Rituximab is a chimeric murine/human mAb that targets and selectively binds CD20, an antigen present on pre-B cells and B cells, but not on antibody-producing plasma cells or stem cells in the bone marrow. By binding CD20, rituximab depletes circulating B-cell populations (but not stem cells or plasma cells) through a combination of cell-mediated and complement-dependent cytotoxicity and possibly promoting apoptosis [Bar-Or *et al.* 2008].

Common side effects of rituximab include nasopharyngits, urinary tract infections, nausea, leucopenia, fever, fatigue, headache, muscle spasms and diarrhea. Cases of PML, severe mucocutaneous reactions, tumor lysis syndrome and fatal infusion reactions have been documented. Other severe adverse reactions include fulminant hepatitis, hepatic failure, bacterial, fungal or viral infections, cardiac arrhythmias, renal toxicity and bowel obstruction or perforation [Prescribing information, 2010].

In a 72-week, open-label phase I trial the safety and tolerability of rituximab were evaluated in 26 patients with RRMS. The authors indicated that no serious adverse events were reported in this small cohort with active RRMS and all the adverse events including infections were mild to moderate and did not lead to medication withdrawal. No efficacy conclusions were noted due to the absence of a control group but they noticed a reduction in relapses, Gad+ lesions, new T2 lesion number and T2 lesion volumes through 72 weeks [Bar-Or *et al.* 2008]. In a phase II randomized, placebo-controlled trial with 104 patients there was a reduction in Gad+ lesions and relapses in patients on rituximab *versus* placebo [Hauser *et al.* 2008]. Rituximab has shown efficacy in the treatment of patients with RRMS. A recently completed randomized clinical trial using a standard dose of rituximab in patients with RRMS demonstrated a 91% reduction in the number of Gad+ lesions on MRI, as well as a significant reduction in the number of clinical relapses [Hauser *et al.* 2008]. In a recent trial of patients with PPMS, rituximab appeared to have efficacy only in young patients (primarily male) with signs of active inflammation on MRI scans [Hawker *et al.* 2009]. Manufacturers of rituximab decided not to go forward with phase III trials, but other CD20 molecule manufacturers are undertaking phase III trials.

Immunoglobulin

While several studies have suggested a beneficial effect of intravenous immunoglobulin (IVIG) in RRMS [Fazekas *et al.* 1997; Achiron *et al.* 1998; Lewanska *et al.* 2002] and CIS [Achiron *et al.* 2004] in terms of relapse rate, MRI and disability progression, there were limitations in terms of methodology and sample size. The most recent published trial from the Prevention of Relapse with Intravenous Immunoglobulin (PRIVIG) study group brought the efficacy of IVIG as a preventative agent in MS into question [Fazekas *et al.* 2008]. Current guidelines

from the European Federation of Neurological Societies recommend that IVIG be considered as a second- or third-line therapy in RRMS if conventional immunomodulatory therapies are not tolerated [Elovaara *et al*. 2008]. However, IVIG is widely used to reduce relapse rate following pregnancy [Achiron *et al*. 1996; Haas and Hommes, 2007].

Corticosteroids

The use of corticosteroids in MS has primarily focused on treatment of exacerbations, but there is evidence to support the use of steroids as a preventative therapy. Data from the Optic Neuritis Treatment Trial (ONTT) suggest that the use of high-dose steroids reduces the risk of development of MS at 2 years following the initial optic neuritis event [Beck *et al*.1993]. Further, a randomized, controlled phase II trial utilizing pulsed high-dose methylprednisolone over the course of 5 years showed a reduction in brain atrophy, T1 lesion volume and disability progression, but failed to show a difference in annualized relapse rate or T2 lesion volume [Zivadinov *et al*. 2001].

Methylprednisolone in combination with IFN-β1a did not show reduction in disability progression compared with IFN-β1a alone [Ravnborg *et al.* for The MECOMBIN study, 2010]. A similar study by Sorensen and colleagues showed a decrease relapse rate when methylprednisolone was used in combination with IFN-β1a subcutaneously compared with IFN-β1a alone [Sorensen *et al.* 2009]. The advent of new immunomodulatory therapies and concerns for long-term adverse effects of steroids largely limit their use as a long-term preventative therapy.

What is in the pipeline?

At this time, six new drugs have entered or completed phase II and III clinical trials, three of which are oral drugs. These include laquinimod, teriflunomide and dimethyl fumarate, and three mAbs—alemtuzumab, daclizumab and rituximab.

Laquinimod

Laquinimod is an orally administered immunomodulator being studied in patients with RRMS and SPMS. The anti-inflammatory properties of laquinimod are thought to be secondary to downregulation of MHC class II gene transcription factors, stimulation of neurotrophic factors, activation of the anti-inflammatory IL-4 pathway in CD4+ T cells, promotion of apoptosis in CD8+ T cells and B cells, and suppression of the metabolic activity of CD14+ and natural killer cells [Thöne *et al.* 2011]. Therefore, it is proposed that laquinimod acts by affecting the Th1 to Th2 cytokine shift. Two phase II trials in patients with RRMS and SPMS have been completed, with varying results [Comi *et al*. 2008; Polman *et al*. 2005]. In the phase III Assessment of Oral Laquinimod in Preventing Progression in Multiple Sclerosis (ALLEGRO study), laquinimod significantly improved clinical and radiologic outcomes, resulting in a 23% reduction in relapse rate, and a 37% reduction in mean cumulative number of Gad+ lesions [Comi *et al*. 2012b]. The Benefit Risk Assessment of Avonex and Laquinimod (BRAVO) study is another phase III study comparing laquinimod at 0.6 mg/day with weekly intramuscular IFN-β1a at 30 μg in patients with RRMS. At the 5th Joint Triennial Congress of the European and Americas Committees for Treatment and Research in Multiple Sclerosis (ECTRIMS/ACTRIMS), the results of a randomized, placebo-controlled, double-blind, active-comparator phase III study, BRAVO, were presented. This study did not achieve its primary endpoint of reducing the ARR. Laquinimod appears to be well tolerated, with only transient and dose-dependent increases in liver enzymes [Vollmer *et al*. 2011].

Teriflunomide

Teriflunomide is an oral agent that inhibits the synthesis of DNA pyrimidine bases in rapidly dividing cells such as T and B cells and macrophages, and may thereby reduce inflammation (and likely produce immune suppression). It reversibly inhibits dihydroorotate dehydrogenase, a key enzyme involved in *de novo* pyrimidine synthesis. Because activated lymphocytes largely depend on *de novo* pyrimidine synthesis, pyrimidine depletion might result in inhibition of immune-cell proliferation [Korn *et al*. 2004]. There is some evidence from *in vitro* studies suggesting that teriflunomide induces Th2-mediated anti-inflammatory cytokine activation. A phase II study examined the efficacy of teriflunomide daily doses of 7 and 14 mg compared with placebo over 36 weeks in patients with RRMS and SPMS. Teriflunomide efficacy was measured by the number of new lesions (T2 and Gad+) as observed on MRI scans. Active treatment resulted in a 61% reduction in MRI activity compared

with placebo. Teriflunomide was generally well tolerated and occurrence of adverse events was similar between the two treatment groups. Serious adverse events included elevated liver enzyme levels, hepatic dysfunction, neutropenia, rhabdomyolysis and trigeminal neuralgia. A 2-year, double-blind, placebo-controlled phase III study in RRMS (The Teriflunomide Multiple Sclerosis Oral [TEMSO] study) was recently published. The study showed that at 7 and 14 mg the ARR was approximately 30% compared with placebo. Teriflunomide significantly reduced disability progression compared with placebo [O'Connor *et al*. 2011].

Dimethyl fumarate

A novel oral therapy under development is dimethylfumaric acid (BG-12), which is related to fumaric acid, an agent used for many years in psoriasis (principally in Europe). BG-12 is thought to inhibit immune cells and molecules involved in MS attacks on the brain and spinal cord. Fumarates appear to modulate a number of oxidative pathways and thereby may influence the mechanisms by which autoimmune mechanisms provoke downstream pathways of tissue damage. *In vitro* studies with the ester dimethyl fumarate (DMF) described an inhibitory effect on nuclear factor κB dependent transcription of tumor necrosis factor α induced genes in human endothelial cells [Moharregh-Khiabani *et al.* 2009]. Although its exact MOA is not known, BG-12 is thought to inhibit immune cells by stimulating the expression of anti-inflammatory cytokines, such as IL-10, IL-4 and IL-5. Hence, it is thought that DMF can induce a shift from a proinflammatory Th1 to an anti-inflammatory Th2 T-cell response [Wierinckx *et al*. 2005]. In addition, BG-12 may have a neuroprotective therapeutic effect by inducing phase II detoxification genes and upregulation of the phase II detoxification enzyme, nicotinamide adenine dinucleotide phosphate oxidase:quinone oxidoreductase-1 [Wierinckx *et al*. 2005]. In an earlier phase II study, compared with placebo, the BG-12 dose of 240 mg three times a day led to a 69% reduction in active inflammation on MRI scans from weeks 12 to 24 [Kappos *et al*. 2008]. A phase III pivotal trial showed that 240 mg of BG-12, administered twice a day, met the primary study endpoint, demonstrating a highly statistically significant reduction in relapses in patients with RRMS, as well as providing a statistically significant reduction in ARR in the number of new or newly enlarging T2 hyperintense lesions, in new Gad+ lesions, and in the rate of disability progression at 2 years as measured by the EDSS [Biogen Idec, 2011]. Side effects of BG-12 included abdominal pain, flushing, headache and fatigue [Schimrigk *et al.* 2006].

Results of the phase III Efficacy and Safety of Oral BG00012 in Relapsing-Remitting Multiple Sclerosis (DEFINE) trial were presented at the 5th Joint Triennial Congress of the European and Americas Committees for Treatment and Research in Multiple Sclerosis (ECTRIMS/ACTRIMS). It showed that BG-12 at 24 mg twice or three times a day reduced the relapse rate by 49% and 50%, respectively.

Alemtuzumab

Alemtuzumab is a mAb that binds to CD52, an epitope common to most cells within the immune system. Treatment with this agent essentially results in an antibody-mediated ablation of the circulating immune system. Alemtuzumab binds to B and T lymphocytes, resulting in antibody-dependent cell lysis, and subsequent elimination from the bone marrow and blood, with the effect lasting up to 16 months. This agent appears to rapidly and profoundly establish both clinical and radiographic remission of MS; however, alemtuzumab has been associated with the risk of developing new autoimmune disorders (autoimmunity), including thyroiditis, idiopathic thrombocytopenic purpura and Goodpasture's syndrome. Cossburn and colleagues found that the cumulative risk of autoimmunity in MS following the use of alemtuzumab was 22.2%, most frequent between 12 and 18 months following the first dose and evident for up to 5 years [Cossburn *et al.* 2011].

Other adverse events associated with alemtuzumab include infections, increased cancer risk, organ toxicity and infusion-associated hypersensitivity reactions with potentially resultant neutralizing antibodies. Studies of alemtuzumab in the treatment of patients with RRMS and SPMS have suggested efficacy in the suppression of ARR, but with variable results in preventing progression of disability, depending on stages of the disease [Corboy *et al*. 2010].

The phase II trial CAMMS223 compared alemtuzumab (12 or 24 mg intravenously on 5 consecutive days during the first month and on 3 consecutive days at months 12 and 24) with

IFN-β1a, 44 μg subcutaneously three times a week. Alemtuzumab demonstrated a decrease in sustained disability (75% at 12 mg dose and 67% at 24 mg dose) and a decrease in relapse rate (69% at 12 mg and 79% at 24 mg) compared with IFN-β1a subcutaneously [Panitch *et al.* 2008].

Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis Study 1 (CARE MS I), a 2 year phase III trial comparing alemtuzumab with subcutaneous IFN-β1a in treatment-naïve patients showed a reduction in relapse rate by 55% but did not show statistical significance regarding slowing disease process. A second phase III trial (CARE MS II) is currently in progress.

Daclizumab

Daclizumab is an engineered human antibody that blocks the IL-2 receptor on immune cells. IL-2 is a potent immune stimulator and thus by blocking it, this therapy putatively dampens immune responses (including autoimmune responses).

The clinical benefit derived from daclizumab has been linked to the expansion of immunoregulatory CD56 natural killer cells, and the resulting downregulation of adaptive T-cell responses [Bielekova *et al.* 2006]. A recent open-label phase II trial using subcutaneous daclizumab at 2 mg/kg in patients with MS whose condition showed an inadequate response to IFN-β therapy demonstrated a 72% reduction in the number of new or enlarged contrast-enhancing lesions at week 24 compared with patients receiving IFN-β alone [Wynn *et al.* 2011]. A phase III trial of daclizumab *versus* IFN-β1a is ongoing (DECIDE study). Daclizumab is currently FDA approved for use in organ transplant patients.

Ocrelizumab

Ocrelizumab, the humanized version of rituximab, is an antibody that targets CD20, a cell surface epitope on developing B cells. Upon binding to its target, these agents provoke rapid destruction of circulating B cells via two principal mechanisms, antibody-dependent and complement-dependent cellular cytotoxicity.

The effect of CD20 targeting has ramifications for both B- and T-cell immune function, and as such, these treatments can be associated with risk of infection (including PML), and organ toxicity. Ocrelizumab, a humanized mAb against human CD20, is currently under investigation in a phase III program called ORCHESTRA (OPERA I and II in RRMS and ORATORIO in PPMS) evaluating its efficacy in patients with MS. A phase II trial comparing ocrelizumb 600 mg and 2000 mg with placebo showed a significant reduction in brain lesions (89% and 96%, respectively) and ARR (80% and 73%, respectively) [Kappos *et al.* 2011].

Discussion

The pharmacological armamentarium for MS has significantly expanded in the past 20 years and many new drugs are on the horizon. Each of these drugs has their own niche for utilization. There are significant data about long-term safety and efficacy of all the IFN-β and GA agents which should be considered first line in newly diagnosed patients. For patients whose condition fails to respond to first-line agents (i.e. recurrent clinical exacerbations, significant disease burden with new and enhancing lesions) or with an aggressive disease course at onset alternatives such as natalizumab or fingolimod are appropriate. MOAs, adverse events and compliance issues should be considered when choosing a therapy. Off-label agents also have a place for patients who are unable to tolerate FDA-approved therapies. These agents also offered options for intensification of therapy, although large clinical trials are needed to determine ideal dosing. The results of efficacy and safety profiles of emergent oral and intravenous agents are essential to determine their place in the treatment of patients with MS. With the advent of new therapies, the need for biomarkers that can predict a patient's response to therapy is imperative. More studies are needed to develop therapies for halting neurodegeneration, promoting remyelination and promoting neuronal repair.

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