

Update on disease-modifying therapies for multiple sclerosis

Diana L Vargas, William R Tyor

Department of Neurology,
Emory University School of
Medicine, Neurology Service,
Atlanta VA Medical Center,
Decatur, Georgia, USA

Correspondence to

Dr William R Tyor,
Department of Neurology,
Emory University School
of Medicine, Neurology
Service, Atlanta VA Medical
Center, 1670 Clairmont Rd.,
Decatur, GA 30033, USA;
William.tyor@va.gov

Accepted 2 January 2017
Published Online First
27 January 2017

Copyright © 2016 American
Federation for Medical
Research

ABSTRACT

Multiple sclerosis (MS) is an autoimmune, demyelinating disease of the central nervous system (CNS). It predominantly affects young women and is one of the most common causes of disability in young adults. MS is characterized by formation of white matter lesions in the CNS as a result of inflammation, demyelination, and axonal loss. Treatment has been a focus of neurological research for over 60 years. A number of disease-modifying therapies (DMTs) have become available making MS a treatable disease. These compounds target the inflammatory response in MS. They work by decreasing the chances of relapse, decreasing the chances of new lesion formation seen on MRI of the CNS and slowing the accumulation of disability. The first drugs for MS to be available were interferon- β and glatiramer acetate. These work by modulating the inflammatory response via different mechanisms that are briefly discussed. Newer agents have since become available and have significantly changed the dynamics of MS treatment. These include fingolimod, dimethyl fumarate and teriflunomide, which are oral agents. Other second-line and third-line Food and Drug Administration (FDA) approved medications include natalizumab and alemtuzumab. Natalizumab is considered one of the most potent treatments for relapse prevention. However, the high risk of progressive multifocal leukoencephalopathy (PML), which is caused by JC virus infection in the brain, tempers the more widespread use of this agent; nevertheless, JC virus antibody tests have helped to stratify the risk of PML. Alemtuzumab, which also has a considerable side effect profile, is likewise highly efficacious. Ocrelizumab, a monoclonal antibody to CD20 on B cells, is a highly effective agent for MS that is likely to be approved soon by the FDA. MS is a major contributor to healthcare costs and it is critical that healthcare providers be aware of the availability and benefits of DMTs. It is imperative that prompt and adequate treatment be established on diagnosis. Changes in therapy should be considered when there is evidence of disease activity as well as accumulation of disability or safety or tolerability concerns.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, autoimmune, demyelinating disease of the central nervous system (CNS) with onset in young and mid adulthood. It is a disease affected by genetic and environmental factors that serve as triggers and activators of the immune response,

which promotes inflammatory and degenerative changes in the CNS.^{1,2} MS is the second most common cause of disability in young adults. Age of onset is usually in the mid to late 20s and the female-to-male ratio is about 3:1.³ It is increasingly more prevalent farther away from the equator and a higher incidence of the disease is seen within families.² Given that it can involve different neuroanatomical locations within the CNS, MS can present with a wide range of symptoms. Patients report problems with ambulation, weakness, sensory loss, loss of balance, problems with urination, fatigue, depression and memory loss, among other things. Given its fairly early onset and its high rate of disability, it is considered to be one of the costliest chronic diseases in the USA.⁴

MS is characterized by the formation of white matter lesions in the CNS that are primarily a result of demyelination, axonal loss, presence of inflammatory cells and loss of oligodendrocytes.¹ It is now known to be a disease that affects gray matter as well as white matter. It is thought that the involvement of gray matter contributes to irreversible disability and progressive symptoms.^{5–7}

The pathophysiology of the disease involves, in part, migration of inflammatory cells into the CNS via the blood–brain barrier (BBB) causing white matter lesions or plaques. These lesions, depending on their exact location in the CNS, are typically manifest symptomatically as ‘attacks’ and denote ‘active’ disease. These white matter lesions tend to predominate in highly myelinated areas, thus giving a variety of clinical symptoms, as aforementioned. Frequent areas affected are the optic nerves, the periventricular and subcortical white matter, and the descending tracts in the pons and midbrain. The spinal cord is also often affected.^{8–10} In relapsing-remitting MS (RRMS), which is the most common form of MS and constitutes 85% of those diagnosed with MS, symptoms tend to evolve over hours to days and often improve after weeks to months. Early in the disease course, symptoms usually completely resolve or leave partial sequelae. Over time, these attacks tend to incompletely resolve causing variable amounts of disability. Most patients with MS eventually experience progressive disability.¹ However, MS is a very heterogeneous disease. Every single patient with the diagnosis behaves differently and the severity of disease can range



CrossMark

To cite: Vargas DL,
Tyor WR. *J Investig Med*
2017;**65**:883–891.

widely. The frequency and severity of relapses are unpredictable as well as the degree and speed of disability that accumulates. At least 50% or more of RRMS eventually develop progression of baseline symptoms without there being evidence of new lesions. When patients reach this point in the disease, they are categorized as having secondary progressive MS.^{11 12} Primary progressive MS (PPMS) occurs in 15% of patients with MS and usually presents with ongoing progression of symptoms rather than acute attacks and episodes of remission.¹³ Progressive relapsing MS is a rare form of MS, but also important in that it may respond to disease-modifying therapies (DMTs). New criteria now define progressive disease as active or not and with or without progression.¹⁴ Differentiation of the different types of MS is important in the clinical setting as most approved therapies for MS target the relapsing disease.

Treatment for MS has been a target of research for the past 50 years and a testament to the advancement of medicine. There have been a number of DMTs that have been proven to help prevent the formation of inflammatory lesions, decrease the number and severity of clinical attacks, and slow the accumulation of disability. There are currently 13 DMTs that have been approved for the treatment of MS and about half of them have only become available in the past 5 years. Given the complexity and novelty of these drugs, it is instrumental to have a good understanding of their utility in MS in order to comfortably treat patients. The purpose of this review is to address current Food and Drug Administration (FDA) approved DMTs as well as therapies that are either used off label or might become FDA approved in the near future; in particular, we will focus on B-cell depleting agents given that ocrelizumab is likely to be approved by the FDA this year and rituximab is already being used off label. These DMTs have dramatically changed treatment strategies in recent years, resulting in complex decision-making for the management of patients with MS.

FDA APPROVED INJECTABLE DMTS

Interferon- β

The first treatment for RRMS became available in 1993.¹⁵ This is a subcutaneous (SC) preparation of interferon- β (IFN- β) called Betaseron. The IFN- β preparations (table 1) are composed of the same amino acids as the natural occurring cytokine except for Betaseron which is one amino acid different in its formulation. IFN- β 's mechanism of action includes induction of several anti-inflammatory cytokines like interleukin (IL)-10 and IL-4, as well as decreasing proinflammatory cytokines like IFN- γ , IL-17, tumor necrosis factor- α and others. It also modulates B-cell trafficking across the BBB.^{15 16} Several similar preparations later became available that offered different alternatives in the route and frequency of dosing but with similar safety, efficacy and side effect profile (table 1). These drugs help in preventing clinical relapses, formation of acute T2 white matter lesions, which are seen as enhancing when using gadolinium (Gd), on brain MRI and some of the IFN- β preparations have been shown to slow the progression of overall disability. Efficacy, across studies, seems to be of around 30% reduction in relapse rate at 2 years over all different agents and the safety profile is very favorable in terms of long-term adverse effects (table 1). Patients may experience influenza-type symptoms

after dosing as well as injection site reactions (with the SC administered preparations), which can be debilitating and affect compliance.^{15–21} Liver enzymes and white cell count should be monitored on a regular basis as needed.

In the INCOMIN trial, which compared higher dose IFN- β 1b (Betaseron) and IFN- β 1a (Avonex), IFN- β 1b was associated with significantly greater percentages of relapse-free patients ($p=0.02$).²² IFN- β 1b, with its higher dose of IFN versus IFN- β 1a (Avonex), was associated with a greater risk of development of antibodies that can neutralize the effect of IFN- β . In the EVIDENCE trial, Rebif was more effective than Avonex at lowering the risk of relapse, reducing active inflammation (as seen on MRI), and increasing the time to first exacerbation.²³

Glatiramer acetate

Glatiramer acetate (GA) was the second DMT approved for prevention of MS relapses in 1996 and is marketed as Copaxone and Glatopa (table 1). GA is a mixture of four amino acids, which combine to form a polymer. It is a synthetic protein that simulates myelin basic protein and seems to block myelin-damaging T cells through a mechanism that is not completely understood.²⁴ GA is similar to the IFNs (see above) with regard to efficacy, reducing relapse rate by 29% at 2 years. Injection site reactions using the SC route are less severe than IFN- β . GA is considered the safest of all DMTs with a category B pregnancy label and long-term monitoring requirements are minimal (table 1). Copaxone was initially marketed as a once daily injection, while now it is available at a higher dose given three times weekly. Glatopa is a once daily injection.^{19 25–28}

In the REGARD trial, GA was compared with IFN- β 1a (Rebif) for 96 weeks. Both drugs were equally effective in increasing time to first exacerbation. Rebif was associated with significantly fewer Gd-enhancing lesions ($p=0.0002$).²⁹ GA and IFN- β 1b again went head to head in the BEYOND trial. Both drugs were equally effective in lowering risk for relapse. IFN- β 1b resulted in significantly better changes in T2 lesion volume and number of new T2 lesions on MRI.³⁰ The use of both agents (GA and IFNs) in combination was reported in the COMBI study with no significant clinical benefit with the use of dual therapy compared with each agent alone.¹⁴

Daclizumab

Daclizumab (Zynbrite) is a humanized monoclonal antibody that works by binding to CD25, the α subunit of the IL-2 receptor of T cells. Daclizumab increases the number of other cell types, particularly regulatory CD56+ natural killer cells, which have a regulatory role in controlling autoimmune cells and their inflammatory consequences.^{31–34} This represents a novel mechanism of action compared with other MS DMTs. Daclizumab was originally approved and used for transplant rejection. It is the latest drug to be approved by the FDA (2016) as a once every 28-day SC injection (table 1). It can only be used after failure of two previous DMTs and is therefore approved as a second-line or third-line therapy. The efficacy of daclizumab was demonstrated in two phase III clinical trials. In the DECIDE study, daclizumab was compared with IFN- β 1a (Avonex) and results showed fewer clinical relapses with daclizumab. In the SELECT study, two doses of daclizumab were compared with placebo and the relapse rate reduction was

Table 1 Injectable DMTs

Treatment	Dose/administration	FDA approval	Common side effects
Interferon β -1a Avonex	30 μ g intramuscular weekly	Decrease disability and reduces frequency of clinical exacerbations by 32% in RRMS at 2 years Approved 1996 Pregnancy category C	Headache, influenza-like symptoms, depression Mild decrease in WCC and elevation in LFTs although rare
Interferon β -1b Betaseron	0.25 mg SC every other day	To reduce frequency of clinical exacerbations by 31% in RRMS at 2 years Approved 1993 Pregnancy category C	Headache, influenza-like symptoms, depression Injection site reactions Mild decrease in WCC and elevation in LFTs
Interferon β -1b Extavia	0.25 mg SC every other day	To reduce frequency of clinical exacerbations by 34% in RRMS Approved 2009 Pregnancy category C	Headache, influenza-like symptoms, depression Injection site reactions Mild decrease in WCC and elevation in LFTs
Interferon β -1a Rebif	22 μ g or 44 μ g SC 3xweekly	To reduce frequency of clinical exacerbations by 33% in RRMS at 2 years Approved 2002 Pregnancy category C	Headache, influenza-like symptoms, depression Injection site reactions Mild decrease in WCC and elevation in LFTs with one fatal case reported
Pegylated interferon β -1a Plegridy	125mcg SC once in 14 days	To reduce frequency of clinical exacerbations by 35.6% in RRMS Approved 2014 Pregnancy category C	Headache, influenza-like symptoms, depression Injection site reactions Mild decrease in WCC and elevation in LFTs
Glatiramer acetate Copaxone	20 mg SC once daily or 40 mg SC three times weekly	To reduce frequency of clinical exacerbations by 29% in RRMS at 2 years Approved 1997 3 times weekly 2014 Pregnancy category B	Injection site reactions are usually mild 10% with one time palpitations, chest pain, and SOB Injection site reactions including lipoatrophy
Glatiramer acetate Glatopa	20 mg SC once daily	To reduce frequency of clinical exacerbations by 30% in RRMS Approved 2015 Pregnancy category B	Approximately 10% of patients may experience transient symptoms after an injection such as palpitations, chest pain, diaphoresis, and shortness of breath
Daclizumab Zinbrya	150 mg SC once every 28 days	To reduce frequency of clinical exacerbations by 45% in RRMS As a second-line or third-line therapy Approved 2016 Pregnancy category None	Colds, URI, rash, eczema, skin hypersensitivity reactions, subcutaneous infections and infestations, depression, lymphadenopathy, colitis, and acute hepatitis Elevation of LFTs, some cases being severe

DMT, disease-modifying therapy; FDA, Food and Drug Administration; LFTs, liver function tests; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous; SOB, shortness of breath; URI, upper respiratory infections; WCC, white cell count.

~50% with the higher dose. Reduction in the accumulation of disability was also seen.^{35–39}

Side effects of the medication include a small, increased risk of infections, frequent skin eruptions such as erythema and eczema, and, importantly, elevation of liver enzymes (table 1). In fact, various skin reactions, most of which were not severe or were satisfactorily managed, occurred in 77% of daclizumab treated patients.⁴⁰ Given the risk of liver enzyme elevation, the FDA requires monitoring of patient's liver enzymes on a monthly basis. Like natalizumab, physicians must be certified in order to prescribe the daclizumab.^{32–39} Given the drug's efficacy but strict monitoring, daclizumab may be used prior to treatment with natalizumab but after having failed two other FDA approved therapies with respect to escalation of therapy.

ORAL DMTs

Fingolimod

Fingolimod (Gilenya) was the first FDA approved oral agent for the treatment of RRMS. It is given once daily. It was initially approved by the FDA in 2010 as first-line therapy and in

2011 by the European Medicines Agency (EMA) as second-line therapy (table 2). It is a first in class lymphocyte migration modulator that binds to four of the five sphingosine-1-phosphate (S1P) receptors on lymphocytes and prevents them from exiting lymphatic tissue. Therefore, it blocks lymphocytic invasion of the brain.^{41–43} There have been suggestions that fingolimod might also have neuroprotective properties since it is able to enter the CNS and bind to neurons and glia expressing S1P receptors. However, it failed to show efficacy in PPMS, which may primarily have a neurodegenerative pathophysiology. Both the FREEDOMS and TRANSFORMS phase III trials showed superiority of fingolimod to placebo as well as to intramuscular IFN-1 β (Avonex), respectively. Fingolimod effectively reduced relapse rate by 50% compared with IFN-1 β ($p < 0.001$).⁴⁴ There was no significant difference between fingolimod and IFN-1 β in progression of disability, but MRI results showed a significant decrease in CNS damage for fingolimod compared with IFN-1 β .^{41–42–44–48}

Fingolimod has several safety issues that have limited its use. Given that it sequesters lymphocytes within lymph nodes, it can cause mild immunosuppression and

Table 2 Oral DMTs

Treatment	Dose/administration	FDA approval	Common side effects
Teriflunomide Aubagio	7 mg or 14 mg orally once daily	To reduce frequency of clinical exacerbations by 31–36% in RRMS at 2 years Approved 2012 Pregnancy category X	Headache, hair thinning, diarrhea, nausea Mild elevation LFTs and decreased WCC
Fingolimod Gilenya	0.5 mg orally QDAY	Decrease disability and reduces frequency by 54% of clinical exacerbations in RRMS Approved 2010 Pregnancy category C	Headache, influenza-like symptoms, diarrhea, back pain, pain in extremities, cough Bradycardia and/or increased BP on first dose Rare macular edema Mild elevation LFTs and decreased WCC
Dimethyl fumarate Tecfidera	120 mg orally two times a day first week, then 240 mg orally two times a day	To reduce frequency of clinical exacerbations by 45–50% in RRMS Approved 2013 Pregnancy category C	Flushing, diarrhea, nausea, abdominal pain Mild increase LFTs and decreased WCC

BP, blood pressure; DMT, disease-modifying therapy; FDA, Food and Drug Administration; LFTs, liver enzyme tests; RRMS, relapsing-remitting multiple sclerosis; WCC, white cell count.

lymphopenia. It also has side effects as a result of off-target effects of S1P receptors in other tissues (eg, cardiomyocytes) uncommonly causing cardiac symptoms like bradycardia and atrioventricular conduction block. These complications are usually seen on the first dose, which has led to a mandatory 6-hour monitoring of blood pressure and heart rate, followed by a repeat ECG. Fingolimod is contraindicated in patients with ischemic heart disease and heart failure, as well as those who have Mobitz type II second-degree or third-degree atrioventricular heart block, sick sinus syndrome, prolonged QT interval, or current treatment with class Ia or class III antiarrhythmic agents. It also increases risk of viral infections including herpes virus encephalitis, cryptococcal meningitis, and disseminated varicella zoster. Immunization for varicella zoster virus is mandatory if patients have not developed antibodies to the virus prior to initiating treatment. The retina also expresses S1P receptors, thus presenting a risk (0.5%) of development of macular edema that requires pretreatment evaluation with an ophthalmologist and a 3-month follow-up after initiating treatment. Patients who have diabetes mellitus have a higher risk of developing macular edema, thus requiring annual ophthalmological assessments while the patient is on therapy.^{41 43 49} Recently, there have been a very small number of cases of progressive multifocal leukoencephalopathy (PML) in patients with fingolimod. PML is a CNS infection by John Cunningham virus (JCV) that can lead to death or irreversible neurological deficits for which there is no proven treatment. JCV is a ubiquitous virus that is harbored in 50–60% of the general population and usually does not cause infection unless there is an immunodeficiency disorder or in patients who receive immunosuppressive therapy. Most cases developed PML after having switched from natalizumab to fingolimod, although three cases of PML have been reported during fingolimod monotherapy.^{50–52} There are no specific recommendations for testing of JCV antibody testing in patients with fingolimod as the risk for PML is very low. Patients should contact their provider with any new or worsening MS symptoms.

Dimethyl fumarate

Dimethyl fumarate (DMF), formerly known as BG-12 and commercially available as Tecfidera, was approved in 2013 as a first-line agent by the FDA and EMA (table 2). It is a

twice daily oral agent that was initially used for the treatment of psoriasis. The mechanism of action of DMF is not completely understood but it is known to activate the nuclear-related factor 2 transcriptional pathway, which reduces oxidative stress as well as modulates nuclear factor κ B, which could have anti-inflammatory effects as well as it ameliorates hydroxycarboxylic acid receptor 2-regulated invasion of neutrophils into the CNS.^{53 54}

The delayed release DMF formulation was found to be superior in relapse rate reduction to placebo and comparable to or slightly better than GA in two large controlled phase III trials (table 2). The DEFINE trial compared DMF to placebo for a 2-year period. DMF had an annual relapse rate reduction of 48%, a reduction in sustained progression of disability of 38% and a reduction in the number of new or enlarging white matter lesions on T2-weighted images by 85%.⁵⁵ These efficacy results are consistent with those of the CONFIRM trial demonstrating that DMF had a reduction in the annualized relapse rate by 44% with the twice daily regimen as compared with placebo. Similarly, in the CONFIRM trial, there were fewer MS lesions on MRIs in patients who received DMF than in those who received placebo.⁵⁶ The safety and tolerability profile of DMF appears favorable, although it can cause lymphopenia requiring white cell count done every 3 months for the first year and every 6 months in subsequent years. Patients with sustained lymphopenia on DMF may have an elevated risk of PML and discontinuation of the drug should be considered. About 50% of patients experience non-severe but potentially unpleasant side effects such as gastrointestinal irritation with diarrhea and abdominal pain, and flushing of the skin with redness, itching or rash (table 2). These side effects usually resolve without treatment and last 1–4 weeks after initiating DMF. They are reduced when taken with food or aspirin or other more specific treatments such as dicyclomine (cramping) or diphenoxylate/atropine (diarrhea).^{53 57–61} Of concern is the possibility of an association of PML with the use of fumarates, which was reported in the European community after four patients developed PML with the use of Fumaderm (compounded fumaric acid used to treat psoriasis). An important distinction to the typical patient with MS is that these cases had confounding factors such as previous immunosuppressive use,

presence of cancer and excessive drug dosing that caused profound leukopenia. Until now, four cases of PML have been reported with DMF since FDA approval while on treatment for MS, aside from those reported in patients without MS treated with Fumaderm.^{62–66}

Teriflunomide

Teriflunomide, otherwise known as Aubagio, is the newest oral drug approved by the FDA for the treatment of MS (table 2). It comes in a once daily formulation and is the active metabolite of leflunomide, which has been used for the treatment of rheumatoid arthritis since 1998. It exerts immunological effects by inhibiting dihydroorotate dehydrogenase, an enzyme required for de novo pyrimidine synthesis in proliferating, but not resting, lymphocytes.^{67 68}

Efficacy of teriflunomide was superior to placebo in phase III randomized control trials. In these trials (TEMSo and TOWER), there was a reduction in the annual relapse rate of 31% in one and 36% in the other at 2 years compared with placebo. Sixty-four percent of patients were free of new, Gd-enhancing lesions with the higher dose of teriflunomide with an overall decrease in white matter lesions in 80% of patients compared with placebo. There was also a 30% decrease in disability progression.^{69 70} Teriflunomide had better efficacy in annual relapse rate reduction at its lower dose when compared with IFN- β 1a (Avonex) but not at the higher dose.⁷¹ The explanation for this phenomenon is unclear.

Teriflunomide is generally well tolerated. Adverse effects include lymphopenia, elevated liver enzymes (carries a black box warning for potentially serious hepatotoxicity), hypertension, nausea, diarrhea, peripheral neuropathy, alopecia and acute renal failure. These are usually rare except for alopecia and mild elevations of liver enzymes or slight reduction in white cell count. A unique safety consideration for teriflunomide is its teratogenicity. It is considered category X in pregnancy and is excreted in breast milk and semen. It has a long half-life and may take from several

months to up to 2 years to fully eliminate unless an accelerated elimination protocol is used as it is stated in by the manufacturer.^{35 68 72–77} This is a major concern for women and men of childbearing age and usually a significant limitation for considering the drug in this population. In cases when hepatotoxicity is present, cholestyramine or activated charcoal can be given to decrease teriflunomide half-life and aid in more rapid elimination. Of concern, as well, is the safety profile of leflunomide, with three cases of PML having been reported, two of which had been previously treated with immunosuppressants and one in which there is only minimal information available.^{78–80}

INTRAVENOUS DMTs

Natalizumab

Natalizumab (Tysabri) is a humanized monoclonal antibody that binds α 4 β 1-integrin, a cell adhesion molecule expressed on the surface of lymphocytes and monocytes. It inhibits migration of inflammatory cells across the BBB by preventing the adhesion of the integrin to its ligand (cell adhesion molecule-1) on the brain vascular endothelium. Thus, it prevents lymphocytes from entering the brain, contributing to inflammation, and causing white matter lesions.^{8 81}

In 2004, natalizumab was approved by the FDA through an accelerated process, given its proven efficacy and the urgent need for a more effective therapy (table 3). The AFFIRM study showed a relapse reduction rate of 68% as compared with placebo, with a significant reduction in sustained disability progression and presence of new and existent white matter lesions on MRI. The drug was suspended from the market because of two cases of PML. After considerable scrutiny of these PML cases, natalizumab again became available in 2006, but only after the FDA mandated careful monitoring and surveillance for PML through the TOUCH programme.^{82–84} Overall, clinical experiences, as well as patient registry studies, such as the TYSABRI Observational Program or MSBase, have confirmed the superiority of natalizumab over IFN- β and GA; however,

Table 3 Intravenous therapies

Treatment	Dose/administration	FDA Approval	Common side effects
Natalizumab Tysabri	300 mg IV once in 28 days	To reduce frequency of clinical exacerbations by 67% and long-term disability by 42% in RRMS As a second-line or third-line therapy, although sometimes used as a first-line therapy in very aggressive RRMS Approved 2006 Pregnancy category C	Headache, fatigue, joint pain, chest discomfort, UTI, lower respiratory tract infection, gastroenteritis, overall increase risk of infections PML Occasional increase in LFTs and decreased WCC, although rare
Alemtuzumab Lemtrada	12 mg IV once daily \times 5 days, then repeat 12 mg IV once daily \times 3 days in 1 year	To reduce frequency of clinical exacerbations by 49% and reduce long-term disability by 42% in RRMS As a third-line therapy Approved 2014 Pregnancy category C	Rash, headache, fever, nasal congestion, nausea, UTI, fatigue, insomnia, URI, herpes viral infections, hives, itching, thyroid gland disorders (common), fungal infection, pain in joints, extremities and back, diarrhea, vomiting, flushing. Infusion reactions Elevation of LFTs and decreased WCC Can cause other autoimmune disorders that can be fatal like Immune thrombocytopenia and increase risk of malignancies like melanoma, thyroid cancer and lymphoproliferative disorders

DMT, disease-modifying therapy; FDA, Food and Drug Administration; IV, intravenous; LFTs, liver enzyme tests; RRMS, relapsing-remitting multiple sclerosis; PML, progressive multifocal leukoencephalopathy; URI, upper respiratory infections; UTI, urinary tract infection; WCC, white cell count.

the cases of PML in natalizumab treated patients have been increasing at an alarming rate. As of June 2016, 667 cases of PML out of 152 500 patients on natalizumab have been reported. Three of these patients have died; 77% of patients are alive with varying levels of disability. The overall risk of PML with natalizumab treatment seems to be around 4.22:1000, although the risk increases under certain conditions. Patients who have been on prior immunosuppression have a higher risk of PML, as well as patients with antibodies to JCV and those having been on treatment for longer than 2 years. If all three factors are present, the risk increases to ~1:90 patients. If none are present, the risk is 1:10 000.⁸⁵ Testing for the presence of JCV (antibodies not PCR) should be done every 6 months while the patient is on treatment as the seroconversion rate is around 1–2% per year, which will then automatically place the patient in a higher risk category. The risk of PML seems to linger even after cessation of natalizumab; thus, monitoring for PML needs to be continued. If PML is suspected, MRI and cerebrospinal fluid analysis for JCV DNA should be obtained.⁸⁶ These patients should be admitted to a hospital and treatment with plasma exchange should be considered in order to rapidly remove circulating natalizumab.^{50 51 80 84 87} Depending on the presentation of PML, intravenous steroids may also be considered.

Given the PML risk, natalizumab has been considered as a second-line or third-line agent, although it has also been used as a first-line agent in patients who present with aggressive MS at onset. If the patient has received prior immunosuppressive treatment and is also JCV antibody positive, natalizumab is discontinued after 1–2 years of treatment. However, even in cases of no prior immunosuppressive treatment but who are JCV antibody positive, natalizumab is also typically discontinued after 1–2 years. Thorough conversations with patients explaining the risks are critical in order to help aid this complex decision process. About 6% of patients on natalizumab can develop neutralizing antibodies that can persist, thus making the drug ineffective. Patients can also develop active disease soon after treatment discontinuation. Some of these patients who develop rebound MS after natalizumab discontinuation have significantly aggressive disease and accumulate disability. Therefore, early transition to another DMT with relatively high efficacy should be strongly considered to reduce the risk of rebound.^{84 88}

Alemtuzumab

Alemtuzumab (Lemtrada) was approved by the EMA in 2013 and later by the FDA for treatment of RRMS as a third-line agent⁸⁹ (table 3). This humanized monoclonal antibody has been available for some time for the use of chronic lymphocytic leukemia. It depletes CD52+ cells (B and T lymphocytes, among others). Its mechanism of action seems to involve the targeting of circulating memory cells, including those prone to penetrate the CNS, resulting in the formation of white matter lesions. One course of treatment depletes T cells, especially CD4 types, B cells and natural killer cells. B cells repopulate after 5–6 months of treatment but T cells are depleted for more than a year. Treatment is repeated once after 1 year.^{31 33} Efficacy was shown to be high with a relapse reduction rate of about 50% compared with IFN-1 β in two different studies

(CARE-MS I and CARE-MS II).^{35 89–91} Given that it is approved as a third-line therapy; patients must have failed at least two or more DMTs in order for this agent to be considered. An important advantage of alemtuzumab is that its efficacy seems to be maintained for years after delivery of two cycles.^{92 93}

Alemtuzumab is associated with significant adverse effects, especially secondary autoimmune disorders such as autoimmune thyroid disease, which was reported in 34% of patients, idiopathic thrombocytopenic purpura in 2% of cases and Goodpasture syndrome in 0.3%. Infusion reactions, herpes infection and other common infections were also more frequently reported in patients receiving alemtuzumab. It is recommended in patients with herpes infection that they be treated with acyclovir for 28 days after alemtuzumab infusion.^{89–91 94} There are no reported cases of PML in patients with MS treated with alemtuzumab. Since the FDA requires careful long-term monitoring, most complications are managed satisfactorily. Alemtuzumab is an important option for patients manifesting severe RRMS.

OFF LABEL TREATMENTS NOT YET FDA APPROVED FOR MS

Anti-CD20 agents

It is now widely known that MS is a T-cell mediated disease and that B cells are intimately involved in the pathogenesis of the disease.^{95–97} Therefore, agents targeting B cells have been used as effective treatments for MS. Currently, there are three agents that target the CD20 cell surface marker on B cells that are under study. These are rituximab, ocrelizumab and ofatumumab.^{31 33 98}

Rituximab is a human–mouse chimeric monoclonal antibody against CD20 that is approved to treat B-cell lymphomas and rheumatoid arthritis, among other autoimmune disorders. It has been widely used off label as a treatment in MS as well as in neuromyelitis optica (an antibody-mediated (against aquaporin 4) autoimmune demyelinating disease similar to MS). The HERMES trial (phase II study) examined the use of rituximab in RRMS as compared with placebo. It was shown to reduce new Gd-enhancing lesions on MRI by 91% as well as a significant reduction in relapse rate for up to 48 weeks. There was no notable increase in infection rate but there were very high (78%) infusion-related symptoms like fever, chills, rigors, hypotension and influenza-like symptoms, probably due to the release of cytokines from B-cell lysis. The OLYMPUS trial, though, did not meet its end point of delaying disability in patients with PPMS. However, the pathogenesis of MS in this patient subset is probably different from RRMS. There is unlikely to be a phase III trial of rituximab in MS because of the development of new CD20 monoclonals likely to be licensed specifically for the MS indication.^{31 35 97}

Newer, completely humanized anti-CD20 monoclonal antibodies have been designed to reduce infusion-related reactions and are currently in trial for the various forms of MS. Ocrelizumab showed favorable results in the phase III trial, ORATORIO, where efficacy and safety were studied in patients with PPMS. Ocrelizumab significantly reduced clinical disease progression in patients with PPMS for at least 12 weeks by 24% (compared with placebo). OPERA II and III compared ocrelizumab to IFN- β 1a. Results showed that ocrelizumab was superior to IFN β -1a, reducing the

annualized relapse rate by nearly 50% over a 2-year controlled treatment period.^{99–100} Ofatumumab just recently completed a phase II trial of safety and efficacy showing no unexpected safety concerns and a 99% suppression of new brain lesions on MRI at 24 weeks. A phase III trial is currently underway.

CONCLUSION

MS is the second leading cause of disability among young adults and represents a major health burden. In the past several years, there has been a tremendous change in the management of the disease, raising expectations for better disease control and ultimately reduction in long-term disability. With the multitude of DMTs now FDA approved for RRMS, the clinician can individually tailor the treatment plan based on individual factors, severity of disease, side effects and long-term safety.

The options available for de novo treatment of newly diagnosed patients remain the IFN- β preparations, GA and the oral agents. Teriflunomide and DMF and fingolimod have been approved for first-line therapy. Deciding on a DMT depends on the side effect profile, preference of orals over injectables, age, gender and desire of pregnancy, among other things. Patients now have options to switch to therapies of equal or similar efficacy based on tolerability. Escalation of treatment when there is concern for disease activity is now center stage, given the availability of second-line and third-line agents. Given the availability of these newer drugs, many clinicians switch therapy if there is any evidence of disease activity. In addition to relapses, motor deficits, walking and tremor, factors like brain atrophy, cognition, fatigue, depression and quality of life are now being factored into decisions to switch DMT. Depending on the severity of breakthrough disease, one might opt for one treatment over the other based on the patient's prior failed therapies, if any, and efficacy of other more potent drugs.

The challenge now is to master, as clinicians, the different alternatives in therapy as well as to identify and monitor side effects as they arise. Familiarizing ourselves with these new agents is important in order to make the best treatment decision, consider drug or other disease interactions, and educate patients concerning compliance and expectations. Existing and emerging therapies will ultimately improve our management of MS and improve the lives of our patients.

Competing interests None declared.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES

- Noseworthy JH, Lucchinetti C, Rodriguez M, et al. Multiple sclerosis. *N Engl J Med* 2000;343:938–52.
- Handel AE, Giovannoni G, Ebers GC, et al. Environmental factors and their timing in adult-onset multiple sclerosis. *Nat Rev Neurol* 2010;6:156–66.
- Magyari M, Koch-Henriksen N, Pflieger CC, et al. Gender and autoimmune comorbidity in multiple sclerosis. *Mult Scler* 2014;20:1244–51.
- Adelman G, Rane SG, Villa KF. The cost burden of multiple sclerosis in the United States: a systematic review of the literature. *J Med Econ* 2013;16:639–47.
- Freeman L, Garcia-Lorenzo D, Bottin L, et al. The neuronal component of gray matter damage in multiple sclerosis: A [(11)C]flumazenil positron emission tomography study. *Ann Neurol* 2015;78:554–67.
- van Munster CE, Jonkman LE, Weinstein HC, et al. Gray matter damage in multiple sclerosis: Impact on clinical symptoms. *Neuroscience* 2015;303:446–61.
- Grothe M, Lotze M, Langner S, et al. The role of global and regional gray matter volume decrease in multiple sclerosis. *J Neurol* 2016;263:1137–45.
- Loma I, Heyman R. Multiple sclerosis: pathogenesis and treatment. *Curr Neuropharmacol* 2011;9:409–16.
- Weissert R. The immune pathogenesis of multiple sclerosis. *J Neuroimmune Pharmacol* 2013;8:857–66.
- Lehmann PV, Rottlaender A, Kuerten S. The autoimmune pathogenesis of multiple sclerosis. *Pharmazie* 2015;70:5–11.
- Lorscheider J, Buzzard K, Jokubaitis V, et al. Defining secondary progressive multiple sclerosis. *Brain* 2016;139(Pt 9):2395–405.
- Plantone D, De Angelis F, Doshi A, et al. Secondary progressive multiple sclerosis: definition and measurement. *CNS Drugs* 2016;30:517–26.
- Lassmann H, van Horssen J, Mahad D. Progressive multiple sclerosis: pathology and pathogenesis. *Nat Rev Neurol* 2012;8:647–56.
- Lublin FD, Cofield SS, Cutter GR, et al. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. *Ann Neurol* 2013;73:327–40.
- TIMSS Group. Interferon beta-1b is effective in relapsing-remitting—multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993;43:655–66.
- Jongen PJ, Sindic C, Carton H, et al. Improvement of health-related quality of life in relapsing remitting multiple sclerosis patients after 2 years of treatment with intramuscular interferon-beta-1a. *J Neurol* 2010;257:584–9.
- Patti F, Amato MP, Bastianello S, et al. Effects of immunomodulatory treatment with subcutaneous interferon beta-1a on cognitive decline in mildly disabled patients with relapsing-remitting multiple sclerosis. *Mult Scler* 2010;16:68–77.
- Jankovic SM. Injectable interferon beta-1b for the treatment of relapsing forms of multiple sclerosis. *J Inflamm Res* 2010;3:25–31.
- Doggrell SA. Good results for early treatment of clinically isolated syndrome prior to multiple sclerosis with interferon beta-1b and glatiramer group. *Expert Opin Pharmacother* 2010;11:1225–30.
- Baker DP, Pepinsky RB, Brickelmaier M, et al. PEGylated interferon beta-1a: meeting an unmet medical need in the treatment of relapsing multiple sclerosis. *J Interferon Cytokine Res* 2010;30:777–85.
- Limmroth V, Putzki N, Kachuck NJ. The interferon beta therapies for treatment of relapsing-remitting multiple sclerosis: are they equally efficacious? A comparative review of open-label studies evaluating the efficacy, safety, or dosing of different interferon beta formulations alone or in combination. *Ther Adv Neural Disord* 2011;4:281–96.
- Barbero P, Bergui M, Versino E, et al. INCOMIN Trial Study Group. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis (INCOMIN Trial) II: analysis of MRI responses to treatment and correlation with Nab. *Mult Scler* 2006;12:72–6.
- Schwid SR, Panitch HS. Full results of the Evidence of Interferon Dose-Response-European North American Comparative Efficacy (EVIDENCE) study: a multicenter, randomized, assessor-blinded comparison of low-dose weekly versus high-dose, high-frequency interferon beta-1a for relapsing multiple sclerosis. *Clin Ther* 2007;29:2031–48.
- Racke MK, Lovett-Racke AE, Karandikar NJ. The mechanism of action of glatiramer acetate treatment in multiple sclerosis. *Neurology* 2010;74(Suppl 1):S25–30.
- Karussis D, Teitelbaum D, Sicsic C, et al. Long-term treatment of multiple sclerosis with glatiramer acetate: natural history of the subtypes of anti-glatiramer acetate antibodies and their correlation with clinical efficacy. *J Neuroimmunol* 2010;220:125–30.
- Bains SN, Hsieh FH, Rensel MR, et al. Glatiramer acetate: successful desensitization for treatment of multiple sclerosis. *Ann Allergy Asthma Immunol* 2010;104:321–5.
- Messina S, Patti F. The pharmacokinetics of glatiramer acetate for multiple sclerosis treatment. *Expert Opin Drug Metab Toxicol* 2013;9:1349–59.
- Garcia Bujalance L, Kelly M, Blackney M, et al. Glatiramer acetate 40 mg/ml three times a week for the treatment of relapsing forms of multiple sclerosis: potential cost benefits of a regimen with infrequent injections which may minimise switching to the newly-introduced first-line and second-line disease modifying therapies. *Value Health* 2015;18:A751.
- Mikol DD, Barkhof F, Chang P, et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REBif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. *Lancet Neurol* 2008;7:903–14.
- O'Connor P, Filippi M, Arnason B, et al. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting


- multiple sclerosis: a prospective, randomised, multicentre study. *Lancet Neurol* 2009;8:889–97.
- 31 Trebst C, Voss E, Skripuletz T, *et al.* Specific immune intervention with monoclonal antibodies for the treatment of multiple sclerosis. *Curr Med Chem* 2010;17:640–50.
- 32 Reardon J, Perumal JS. Review of daclizumab and its therapeutic potential in the treatment of relapsing-remitting multiple sclerosis. *Drug Des Devel Ther* 2013;7:1187–93.
- 33 Lycke J. Monoclonal antibody therapies for the treatment of relapsing-remitting multiple sclerosis: differentiating mechanisms and clinical outcomes. *Ther Adv Neurol Disord* 2015;8:274–93.
- 34 Wiendl H, Gross CC. Modulation of IL-2Ralpha with daclizumab for treatment of multiple sclerosis. *Nat Rev Neurol* 2013;9:394–404.
- 35 Fernandez O, Alvarez-Cermenon JC, Arroyo-Gonzalez R, *et al.* Review of the novelties presented at the 27th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) (II). *Rev Neurol* 2012;54:734–49.
- 36 Gold R, Giovannoni G, Selmaj K, *et al.* Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. *Lancet* 2013;381:2167–75.
- 37 Giovannoni G, Gold R, Selmaj K, *et al.* Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECTION): a multicentre, randomised, double-blind extension trial. *Lancet Neurol* 2014;13:472–81.
- 38 Kappos L, Wiendl H, Selmaj K, *et al.* Daclizumab HYP versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med* 2015;373:1418–28.
- 39 Gold R, Radue EW, Giovannoni G, *et al.* Safety and efficacy of daclizumab in relapsing-remitting multiple sclerosis: 3-year results from the SELECTED open-label extension study. *BMC Neurol* 2016;16:117.
- 40 Cortese I, Ohayon J, Fenton K, *et al.* Cutaneous adverse events in multiple sclerosis patients treated with daclizumab. *Neurology* 2016;86:847–55.
- 41 Vasilou S. Oral fingolimod for the treatment of relapsing-remitting multiple sclerosis. *Drugs Today* 2010;46:315–25.
- 42 Kappos L, Radue EW, O'Connor P, *et al.* A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010;362:387–401.
- 43 Singh M, Cugati G, Singh P, *et al.* Fingolimod: the first oral drug approved by food and drug administration; a breakthrough in treatment of multiple sclerosis. *J Pharm Bioallied Sci* 2011;3:460–1.
- 44 Cohen JA, Barkhof F, Comi G, *et al.* TRANSFORMS Study Group. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010;362:402–15.
- 45 Link H, Martin R. New drugs may improve, complicate treatment for multiple sclerosis. *Nat Med* 2010;16:272.
- 46 Doggrell SA. Oral fingolimod for relapsing-remitting multiple sclerosis. Evaluation of: Kappos L, Radue E-M, O'Connor P, *et al.* A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010;362:387–401; and Cohen JA, Barkhof F, Comi G, *et al.* Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010;362:402–15. *Expert Opin Pharmacother* 2010;11:1777–81.
- 47 Grutzke B, Hucke S, Gross CC, *et al.* Fingolimod treatment promotes regulatory phenotype and function of B cells. *Ann Clin Transl Neurol* 2015;2:119–30.
- 48 Khatri BO. Fingolimod in the treatment of relapsing-remitting multiple sclerosis: long-term experience and an update on the clinical evidence. *Ther Adv Neurol Disord* 2016;9:130–47.
- 49 Singer BA. Fingolimod for the treatment of relapsing multiple sclerosis. *Expert Rev Neurother* 2013;13:589–602.
- 50 Killestein J, Vennegoor A, van Golde AE, *et al.* PML-IRIS during fingolimod diagnosed after natalizumab discontinuation. *Case Rep Neurol Med* 2014;2014:307872.
- 51 Giovannoni G, Naismith RT. Natalizumab to fingolimod washout in patients at risk of PML: when good intentions yield bad outcomes. *Neurology* 2014;82:1196–7.
- 52 Gyang TV, Hamel J, Goodman AD, *et al.* Fingolimod-associated PML in a patient with prior immunosuppression. *Neurology* 2016;86:1843–5.
- 53 Linker RA, Gold R. Dimethyl fumarate for treatment of multiple sclerosis: mechanism of action, effectiveness, and side effects. *Curr Neurol Neurosci Rep* 2013;13:394.
- 54 Lundy SK, Wu Q, Wang Q, *et al.* Dimethyl fumarate treatment of relapsing-remitting multiple sclerosis influences B-cell subsets. *Neurol Neuroimmunol Neuroinflamm* 2016;3:e211.
- 55 Gold R, Kappos L, Arnold DL, *et al.* Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012;367:1098–107.
- 56 Fox RJ, Miller DH, Phillips JT, *et al.* Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med* 2012;367:1087–97.
- 57 Stangel M, Linker RA. Dimethyl fumarate (BG-12) for the treatment of multiple sclerosis. *Expert Rev Clin Pharmacol* 2013;6:355–62.
- 58 Kawalec P, Mikrut A, Wisniewska N, *et al.* The effectiveness of dimethyl fumarate monotherapy in the treatment of relapsing-remitting multiple sclerosis: a systematic review and meta-analysis. *Curr Neuropharmacol* 2014;12:256–68.
- 59 Bompreszi R. Dimethyl fumarate in the treatment of relapsing-remitting multiple sclerosis: an overview. *Ther Adv Neurol Disord* 2015;8:20–30.
- 60 Vigiotta V, Miller D, Bar-Or A, *et al.* Efficacy of delayed-release dimethyl fumarate in relapsing-remitting multiple sclerosis: integrated analysis of the phase 3 trials. *Ann Clin Transl Neurol* 2015;2:103–18.
- 61 Gold R, Giovannoni G, Phillips JT, *et al.* Efficacy and safety of delayed-release dimethyl fumarate in patients newly diagnosed with relapsing-remitting multiple sclerosis (RRMS). *Mult Scler* 2015;21:57–66.
- 62 van Oosten BW, Killestein J, Barkhof F, *et al.* PML in a patient treated with dimethyl fumarate from a compounding pharmacy. *N Engl J Med* 2013;368:1658–9.
- 63 van Kester MS, Bouwes Bavinck JN, Quint KD. PML in patients treated with dimethyl fumarate. *N Engl J Med* 2015;373:583–4.
- 64 Rosenkranz T, Novas M, Terborg C. PML in a patient with lymphocytopenia treated with dimethyl fumarate. *N Engl J Med* 2015;372:1476–8.
- 65 Nieuwkamp DJ, Murk JL, van Oosten BW, *et al.* PML in a patient without severe lymphocytopenia receiving dimethyl fumarate. *N Engl J Med* 2015;372:1474–6.
- 66 Lehmann-Horn K, Penkert H, Grein P, *et al.* PML during dimethyl fumarate treatment of multiple sclerosis: How does lymphopenia matter? *Neurology* 2016;87:440–1.
- 67 Palmer AM. Teriflunomide, an inhibitor of dihydroorotate dehydrogenase for the potential oral treatment of multiple sclerosis. *Curr Opin Investig Drugs* 2010;11:1313–23.
- 68 Miller AE. Teriflunomide: a once-daily oral medication for the treatment of relapsing forms of multiple sclerosis. *Clin Ther* 2015;37:2366–80.
- 69 O'Connor P, Wolinsky JS, Confavreux C, *et al.* Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med* 2011;365:1293–303.
- 70 Confavreux C, O'Connor P, Comi G, *et al.* Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014;13:247–56.
- 71 Vermersch P, Czlonkowska A, Grimaldi LM, *et al.* Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. *Mult Scler* 2014;20:705–16.
- 72 Warnke C, Meyer zu Horste G, Hartung HP, *et al.* Review of teriflunomide and its potential in the treatment of multiple sclerosis. *Neuropsychiatr Dis Treat* 2009;5:333–40.
- 73 Wood H. Multiple sclerosis: teriflunomide shows promise for MS treatment in phase III trial. *Nat Rev Neurol* 2011;7:657.
- 74 Antochi F. Teriflunomide—a new oral agent for multiple sclerosis treatment. *Maedica (Buchar)* 2013;8:404–5.
- 75 Brunetti L, Wagner ML, Maroney M, *et al.* Teriflunomide for the treatment of relapsing multiple sclerosis: a review of clinical data. *Ann Pharmacother* 2013;47:1153–60.
- 76 Oh J, O'Connor PW. Teriflunomide in the treatment of multiple sclerosis: current evidence and future prospects. *Ther Adv Neurol Disord* 2014;7:239–52.
- 77 Bar-Or A. Teriflunomide (Aubagio(R)) for the treatment of multiple sclerosis. *Exp Neurol* 2014;262(Pt A):57–65.
- 78 Warnatz K, Peter HH, Schumacher M, *et al.* Infectious CNS disease as a differential diagnosis in systemic rheumatic diseases: three case reports and a review of the literature. *Ann Rheum Dis* 2003;62:50–7.
- 79 Rahmlow M, Shuster EA, Dominik J, *et al.* Leflunomide-associated progressive multifocal leukoencephalopathy. *Arch Neurol* 2008;65:1538–9.
- 80 Schmedt N, Andersohn F, Garbe E. Signals of progressive multifocal leukoencephalopathy for immunosuppressants: a disproportionality analysis of spontaneous reports within the US Adverse Event Reporting System (AERS). *Pharmacoepidemiol Drug Saf* 2012;21:1216–20.
- 81 Bermel RA, Cohen JA. Multiple sclerosis: advances in understanding pathogenesis and emergence of oral treatment options. *Lancet Neurol* 2011;10:4–5.
- 82 Coyle PK. The role of natalizumab in the treatment of multiple sclerosis. *Am J Manag Care* 2010;16:S164–170.
- 83 Ferreira ML. Natalizumab treatment for multiple sclerosis. *Arq Neuropsiquiatr* 2014;72:911–12.

- 84 Kornek B. An update on the use of natalizumab in the treatment of multiple sclerosis: appropriate patient selection and special considerations. *Patient Prefer Adherence* 2015;9:675–84.
- 85 Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med* 2012;366:1870–80.
- 86 McGuigan C, Craner M, Guadagno J, et al. Stratification and monitoring of natalizumab-associated progressive multifocal leukoencephalopathy risk: recommendations from an expert group. *J Neurol Neurosurg Psychiatr* 2016;87:117–25.
- 87 Wingerchuk DM, Carter JL. Multiple sclerosis: current and emerging disease-modifying therapies and treatment strategies. *Mayo Clin Proc* 2014;89:225–40.
- 88 Al-Khamis FA. The use of immune modulating drugs for the treatment of multiple sclerosis. *Neurosciences (Riyadh)* 2016;21:4–9.
- 89 Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* 2012;380:1819–28.
- 90 Jones DE, Goldman MD. Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis: a review of its clinical pharmacology, efficacy and safety. *Expert Rev Clin Immunol* 2014;10:1281–91.
- 91 Tuohy O, Costelloe L, Hill-Cawthorne G, et al. Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy. *J Neurol Neurosurg Psychiatr* 2015;86:208–15.
- 92 Jones JL, Anderson JM, Phuah CL, et al. Improvement in disability after alemtuzumab treatment of multiple sclerosis is associated with neuroprotective autoimmunity. *Brain* 2010;133:2232–47.
- 93 Hersh CM, Cohen JA. Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis. *Immunotherapy* 2014;6:249–59.
- 94 Fox EJ. Alemtuzumab in the treatment of relapsing-remitting multiple sclerosis. *Expert Rev Neurother* 2010;10:1789–97.
- 95 Diebold M, Derfuss T. Immunological treatment of multiple sclerosis. *Semin Hematol* 2016;53(Suppl 1):S54–57.
- 96 Martin R, Sospedra M, Rosito M, et al. Current multiple sclerosis treatments have improved our understanding of MS autoimmune pathogenesis. *Eur J Immunol* 2016;46:2078–90.
- 97 Claes N, Fraussen J, Stinissen P, et al. B cells are multifunctional players in multiple sclerosis pathogenesis: insights from therapeutic interventions. *Front Immunol* 2015;6:642.
- 98 Palavra F. Monoclonal antibodies for multiple sclerosis treatment. *Acta Med Port* 2015;28:640–51.
- 99 Montalban X, Hemmer B, Rammohan K, et al. Efficacy and safety of ocrelizumab in primary progressive multiple sclerosis: results of the Phase III double-blind, placebo-controlled ORATORIO Study (S49.001). *Neurology* 2015;86(Supplement S49.001:16).
- 100 Sorensen PS, Lisby S, Grove R, et al. Safety and efficacy of ofatumumab in relapsing-remitting multiple sclerosis: a phase 2 study. *Neurology* 2014;82:573–81.

AFMR

American Federation
for Medical Research


Develop and mentor tomorrow's leaders in medical research



We Support You, The Physician Scientist, by...


- Fostering excellence in training and successful development of medical investigators
- Disseminating scholarly, multidisciplinary, ethical research on human disease and health care delivery
- Educating public and government leaders about medical research and the importance of funding

What can your AFMR Membership do for you?




Publications

- **Journal of Investigative Medicine (JIM): 8 Issues**
No page charges for accepted manuscripts
- **Journal of Investigative Medicine HIGH IMPACT CASE REPORTS** online
50% discount on publishing fees
- **AFMR Insights e-newsletter**
Membership, scientific and legislative updates




Meetings

- **Network present Abstracts & earn CME at reduced rates**
- **Translational Science** –
National meeting cosponsored by AFMR
- **Experimental Biology** –
AFMR symposia on translational research
- **4 Regional Meetings:**
Eastern, Midwestern, Southern, Western




AFMR Awards

- **Henry Christian Award**
- **Outstanding Investigator Award**
- **Junior Physician-Investigator Awards**
- **Regional Scholars**
- **Research Day Awards**
with Departmental Memberships




Advocacy

- **FASEB Membership**
Established NIH K Awards and the Loan Repayment Program with AFMR
- **Research!America**
Alliance member



Volunteering

- **Join a regional or national committee**
- **Participate on a FASEB committee**
- **Become a mentor or mentee**

admin@afmr.org
 @AFMRResearch
www.afmr.org/membership

Bridging the gap from bench to bedside...