Perspectives in Medicinal Chemistry

Multiple Sclerosis: Overview of Disease-Modifying Agents

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ABSTRACT: Multiple sclerosis (MS) is a chronic autoimmune disease that usually affects young adults, causing progressive physical and cognitive disability. Since the 1990s, its treatment has been based on parenteral medications known collectively as immunomodulators. This drug class is considered safe and usually prevents 30% of MS relapses. Drugs in this class exert almost the same efficacy and require an inconvenient administration route. New medications have recently been launched worldwide. Thus, new oral drugs are increasingly being administered to MS patients and contributing to a better quality of life, since these have better efficacy than the old immunomodulators. Today, 10 different drugs for MS are marketed worldwide, which requires deep knowledge among neurologists and other healthcare professionals. This paper summarizes all the drugs approved for MS in the US and Europe, emphasizing their mechanism of action, the results from phase II and III studies, and the product safety.

KEYWORDS: multiple sclerosis, therapy, administration, oral

Introduction

Multiple sclerosis (MS) is an autoimmune, chronic inflammatory demyelinating disease of the central nervous system (CNS).[1] It most commonly affects young women between 20 and 40 years of age, and the female/male ratio approaches 3:1.[2] It is the second most common cause of disability in young adults.[3]

MS usually causes the following symptoms in isolation or in certain combinations: acute loss of vision (optic neuritis), reduction of limb strength, sensitivity symptoms, cognitive dysfunction, altered coordination, fatigue, and other less common symptoms.[4] These symptoms can appear as relapses in most cases, and are prone to remission after some days or weeks, thus constituting the so-called "relapsing-remitting" form of disease, which comprises 85% of all MS cases.[2]

MS physiopathology is characterized by lesions of the CNS white matter, with loss of myelin, neuronal axons, and myelin-producing oligodendrocytes.[5] Recently, some gray matter involvement has been proven. The relapses are initiated through peripheral activation of leukocytes that enter the CNS through a breached blood–brain barrier.[6]

MS treatments consist of drugs targeted to prevent relapses of the disease, and consequently, progression of disability. These drugs are so-called "disease-modifying therapies" (DMTs). Ten DMTs have been approved for MS treatment: four forms of interferon (IFN) beta (from four different companies), glatiramer acetate, natalizumab, fingolimod, alemtuzumab, teriflunomide, and dimethyl fumarate (BG-12).

Despite the many options for treatment (Table 1), there are some steps or guidelines that can be followed to assist in choosing the most appropriate DMT for a MS patient. The objectives of this paper were to contribute toward the knowledge of MS therapies, demonstrate the state-of-the-art of all marketed drugs in the US and Europe (last updated on May 24, 2014), and help physicians in choosing the best therapeutic option for their patients. For didactic reasons, all MS therapies

Table 1. Historical of MS drug approval from FDA and EMA.

DRUGS	FDA DATE OF APPROVAL	EMA DATE OF APPROVAL
Interferon beta 1b	23 Jul 1993	30 Nov 1995
Interferon beta 1a 30 μg	17 May 1996	13 Mar 1997
Glatiramer acetate	20 Dec 1996	***
Interferon beta 1a 22 μg	07 Mar 2002	04 May 1998
Interferon beta 1a 44 μg	07 Mar 2002	04 May 1998
Natalizumab	23 Nov 2004	***
Fingolimod	21 Sep 2010	***
Teriflunomide	12 Sep 2012	26 Aug 2013
Dimethyl fumarate	27 Mar 2013	30 Jan 2014
Alemtuzumab	Under analysis	12 Sep 2013
Daclizumab****	Not submitted for approval	Not submitted for approval
Ocrelizumab	Not submitted for approval	Not submitted for approval
Laquinimod	Not submitted for approval	Not submitted for approval

Notes: *FDA: Food and Drug Administration. **EMA: European Medicines Agency. ***Each country has determined specific drug approval, with different dates; this information is not available on the EMA website. ****Daclizumab has already been approved for prophylaxis against organ rejection among kidney transplant recipients, but not for MS yet.

were classified into two groups that are shown in specific tables in this article: established MS treatment drugs (Table 2) and non-established (or emergent) MS treatment drugs (Table 3), according to the availability and routine use of these specific drugs in the US and Europe. Drugs that have been available for more than two years were defined as "established" and those available for less than two years as "non-established."

"First-Generation" Self-Injectable Therapies

This class of drugs is known as immunomodulatory therapy and has been approved for two decades in some countries. There are four IFN beta and one glatiramer acetate preparations (Table 1). IFNs usually inhibit antigen presentation and, as a result, decrease T-cell production of IFN gamma. There may also be a shift from T helper 1 (Th1) to T helper 2 (Th2) in terms of cytokine production, reducing the entry of T-cells into the CNS.[7] Glatiramer has also a complex mechanism of action, but this can be summarized into five interdependent processes: binding to the mean histocompatibility complex; interference with the antigen presentation process; interference with the activation of specific T-cells against myelin basic protein; induction of a shift in glatiramer-reactive T-cells from a Th1 to a Th2 phenotype; migration of glatiramer-specific T-cells into the CNS; and neuroprotection via promotion of neurotrophic factors.[8,9] In the 1990s, they were all tested against placebo; they demonstrated comparable efficacy for prevention of relapses (a mean reduction of 30% in relapses) and moderated the development of new brain MRI lesions.[10–13] In the 2000s, they were compared with each other in two important trials: BEYOND and REGARD.[14,15] The BEYOND study compared two different doses of IFN beta 1b (Betaseron) versus glatiramer. The REGARD study compared IFN beta 1a (Rebif) with glatiramer. The results from these two studies showed that there were no differences in relapses, MRI lesions, or EDSS progression.

IFN beta and glatiramer have favorable long-term safety profiles and still remain the first-choice treatment in many countries. However, with the development of oral drugs for MS, their position has been challenged throughout the world. The most important factor that interferes with the success of injectable drugs is patient adherence.

New developments within the first-generation therapies have been tested. One recent development has been the GALA study,[16] which demonstrated that glatiramer acetate (20 mg) in a daily regimen and the same drug in a double dose (40 mg) thrice a week had similar efficacy.

Natalizumab

Mechanism of action. Natalizumab is a monoclonal antibody that selectively binds to the α4 subunit of the cell adhesion molecule "very late antigen 4" (VLA-4), which is expressed on the surface of lymphocytes and monocytes.[17] It prevents interaction between VLA-4 and its ligand "vascular cell adhesion molecule-1" (VCAM-1) on brain vascular endothelium, thereby blocking the entry of lymphocytes into the CNS.

Phase II studies. In 2003, a phase II trial[18] on 213 MS patients who received natalizumab (3 mg/kg), natalizumab (6 mg/kg), or placebo was published. These patients were followed up for six months with monthly MRI examinations, and the primary endpoint was the number of active lesions on MRI. At the end of six months, there had been a marked reduction in lesions (9.6 per patient with placebo versus 0.7 per patient with natalizumab 3 mg/kg). There was a reduction of around 50% in the number of relapses in patients using natalizumab.

Phase III studies. Two important trials have supported the use of natalizumab for MS. The first one was the SENTINEL study and the second was the AFFIRM study.[19,20] The SENTINEL study compared an association of natalizumab plus IFN beta 1a with an association of placebo plus IFN beta 1a among 1171 patients. The primary endpoints were the relapse rate after one year and the EDSS after two years. The association of natalizumab plus IFN beta 1a produced a 54% reduction in relapses after one year, and a 24% reduction in EDSS progression after 2 years. The AFFIRM study compared natalizumab with placebo among 927 patients. The primary endpoints were relapse rate and EDSS after two years. This study demonstrated a 68% reduction in relapses and a 42% reduction in EDSS progression over a two-year period.

Safety. Despite a very good efficacy profile, natalizumab has been shown to be correlated with a few cases of progressive

Table 2. Established MS DMTs.

ESTABLISHED MULTIPLE SCLEROSIS DISEASE-MODIFYING THERAPIES						
	INTERFERON BETA 1B		INTERFERON BETA 1A		GLATIRAMER ACETATE	NATALIZUMAB	FINGOLIMOD
Brand name	Betaseron/Betaferon (µg)	Extavia (µg)	Avonex (µg)	Rebif (µg)	Copaxone (mg)	Tysabri	Gilenya
Mechanism of action	Inhibits antigen presentation and promotes a shift from Th1 cells towards Th2 cells	Inhibits antigen presentation and promotes a shift from Th1 cells towards Th2 cells	Inhibits antigen presentation and promotes a shift from Th1 cells towards Th2 cells	Inhibits antigen presentation and promotes a shift from Th1 cells towards Th2 cells	Promotes a shift from Th1 cells towards Th2 cells	Selectively binds to α4 subunit of (VLA-4), preventing the interaction between VLA-4 and VCAM-1	Antagonist of sphingosine-1-phosphate receptor, interfering in the egress of lymphocytes from the lymph nodes
Year approved	1993	2009	1996	2002	1997	2004, 2006	2010
Dose	250	250	30	22 or 44	20	300 mg	0.5 mg
Route	SC	SC	IM	SC	SC	IV	Oral
Frequency	Every 48 h	Every 48 h	Weekly	Three times weekly	Daily	Every four weeks	Daily
Most relevant side effects	Flu-like symptoms*, hepatitis	Flu-like symptoms, hepatitis	Flu-like symptoms, hepatitis	Flu-like symptoms, hepatitis	Local skin reactions	High risk of progressive multifocal leukoencephalopathy	High rates of herpesvirus infections and bradycardia at the first dose

Notes: *Flu-like symptoms: fever, chills, myalgia, and articular pain.
Abbreviations: IV, intravenous; IM, intramuscular; SC, subcutaneous.

multifocal leukoencephalopathy (PML) [a CNS infection caused by the John Cunningham virus (JCV)] and subsequent death. This led to temporary withdrawal of natalizumab from the market, followed by its reintroduction in 2006 with a risk mitigation strategy (the TOUCH program), in order to provide continuous adverse event vigilance. Over the past eight years, much information on PML risk factors has been accumulated, and three important risk factors for PML to become established have been recognized: evidence of prior JCV seropositivity; duration of natalizumab use greater than two years; and prior use of immunosuppressant.[21] In daily practice, there is a data system for risk stratification that is used to advise individual MS patients regarding initiation or discontinuation of natalizumab.[22]

Fingolimod

Mechanism of action. Fingolimod is a modulator of the sphingosine-1-phosphate receptor. After phosphorylation, fingolimod acts as antagonist of this receptor, through inducing its internalization and inactivation and preventing lymphocyte egression from secondary lymphoid tissues (eg, lymph nodes). The resulting redistribution to lymph nodes reduces recirculation of autoaggressive lymphocytes to the CNS.[23]

Phase II studies. An important phase II trial was undertaken for six months,[24] and compared fingolimod 1.25 or 0.5 mg with placebo. The primary endpoint was the number of GD+ lesions on MRI. A total of 255 patients completed the study. There was a marked reduction of brain lesions in patients with the 1.25 mg dose. The annualized relapse rate was verified, and fingolimod at either dose reduced it by 50%.

Phase III studies. There have been two important phase III trials with fingolimod. The FREEDOMS trial compared fingolimod with placebo in patients with relapsing-remitting MS. A total of 1272 patients were randomized to fingolimod 0.5 mg, fingolimod 1.25 mg, or placebo, over a 24-month period. The primary endpoint was the relapse rate, and the secondary endpoint was the time that elapsed until disease progression. There was a 70% reduction in the relapse rate in the fingolimod group. The TRANSFORMS trial compared fingolimod 0.5 or 1.25 mg with IFN beta 1a administered intramuscularly (Avonex). A total of 1292 patients were included in the study. The main endpoint was the relapse rate. Fingolimod reduced the relapse rate by 52%.[25]

Safety. During the trial, one patient with disseminated varicella zoster died. Because of this, recommendations regarding the dosage of varicella zoster antibodies (IgG) have been made. If these are absent in serum samples, specific vaccine should be prescribed and the patient should wait 30 days before taking the first fingolimod dose. Another important concern is the cardiovascular risk during the first dose. Bradycardia almost always occurs, but it is asymptomatic in most cases. The US Food and Drug Administration (FDA) has requested that the first dose of fingolimod should be administered in a clinic with advanced cardiac life support available, in order to

Table 3. Emerging MS DMTs.

EMERGING MULTIPLE SCLEROSIS DISEASE-MODIFYING THERAPIES				
	TERIFLUNOMIDE	**DIMETHYL FUMARATE**	**ALEMTUZUMAB**	**LAQUINIMOD**
Brand name	Aubagio	Tecfidera	Lemtrada	–
Mechanism of action	Selectively and reversibly inhibits a mitochondrial enzyme necessary for de novo pyrimidine synthesis: dihydroorotate dehydrogenase (DHODH)	Activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) antioxidant response pathway	Anti-CD52 monoclonal antibody	Reduces leukocyte migration into the CNS through downregulation of VLA-4- mediated adhesiveness
Year approved	2012	2013	2013*	–
Dose	7 or 14 mg	240 mg	12 mg	–
Route	Oral	Oral	Intravenous	Oral
Frequency	Daily	Twice daily	Annual course	Daily
Most relevant side effects	Lymphopenia, elevated liver enzymes, hypertension, nausea, diarrhea, peripheral neuropathy, acute renal failure, hair thinning and teratogenicity	Flushing, gastrointestinal events (diarrhea, nausea and upper abdominal pain: higher in the first month of treatment, decreasing thereafter), reduction in lymphocyte counts and elevated liver enzymes	Infusion reactions, thyroid disease and thrombocytopenia	Elevated liver enzymes

Note: *Approved only by EMA; pending approval by FDA.

monitor heart rate, blood pressure, and electrocardiogram. The FREEDOMS trial did not show any differences in the overall adverse event rate, except in relation to macular edema (which was usually resolved through drug discontinuation) and brady-cardia (which was usually asymptomatic). Despite a statistical difference in comparison with the placebo group, cases of macular edema or bradycardia were infrequent.

Alemtuzumab

Mechanism of action. Alemtuzumab is an anti-CD52 monoclonal antibody, and a single course of the drug causes robust peripheral depletion of lymphocytes and mono-cytes. The monocytes are the first lineage to recover (after one month), whereas B-cells recover after three months. T-cells recover much more slowly: 11 months for CD8 and 12 months for CD4. Changes to the activity of T-cell subsets after alemtuzumab-induced lymphopenia may also contribute toward long-lasting suppression of disease activity. There is additional evidence that alemtuzumab causes "neuroprotection." This has been suggested based on findings from stimulation of neurotrophin production: BDNF (brain-derived neurotrophic factor) and PDGF (platelet-derived growth factor).[26]

Phase II studies. The most important phase II study has been the CAMMS223 trial, which comparatively evaluated alemtuzumab (12 mg/day), alemtuzumab (24 mg/day), and IFN beta 1a (44 μg) (Rebif; Merck Serono).[27] This study randomized 334 patients, and the main outcome was the EDSS progression. Alemtuzumab significantly reduced the rate of sustained accumulation of disability, in comparison with IFN beta 1a (9 versus 26.2%). Additionally, the brain volume increased in the alemtuzumab group. There were no

significant differences in outcomes between the 12-mg dose and the 24-mg dose of alemtuzumab.

Phase III studies. The most important phase III trial has been the CARE study.[28] In this trial, MS patients were randomized to receive alemtuzumab or IFN beta 1a (44 μg). The endpoint was the relapse rate after two years. The alemtuzumab group had significantly fewer relapses (54%).

Safety. The most common adverse events have been infusion reactions, autoimmune secondary diseases, and infections. The infusion reactions were mild to moderate and occurred during the infusion or within 24 hours after infusion, were more frequent during the first course of alemtuzumab, and usually occurred on the first day of infusion. The most common autoimmune disease was thyroid disease, with an incidence of 23% among alemtuzumab-treated patients. The second most common autoimmune disease was thrombo-cytopenia, in 3% of the patients. The infection rate was 66% in the alemtuzumab group, whereas in the IFN group, this proportion was 47%.[27]

Dimethyl Fumarate (BG-12)

Mechanism of action. In the pathogenesis of MS, in addition to pathogenic adaptive autoimmunity processes, the release of free radicals (oxygen and nitrogen) by infiltrating monocytes leads to mounting oxidative stress.[29] Dimethyl fumarate (BG-12) has been shown to have beneficial effects in neuroinflammation models and appears to exert its effects through activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) antioxidant response pathway.[30–32]

Phase II studies. This study evaluated 257 patients with relapsing-remitting MS and assigned them to receive placebo,

120 mg of BG-12 once a day, 120 mg of BG-12 thrice a day, or 240 mg of BG-12 thrice a day, for 24 weeks. The main outcome was the total number of new GD-enhancing lesions on MRI. Treatment with BG-12 240 mg thrice a day reduced the mean total number of new GD-enhancing lesions by 69%, in comparison with placebo.[33]

Phase III studies. There have been two phase II studies on BG–12. The first one was the DEFINE trial, which evaluated the effects of BG-12 240 mg twice a day, BG-12 240 mg thrice a day, or placebo on the proportion of patients who had a relapse within two years. The estimated proportion of patients who had a relapse was significantly lower in the two BG-12 groups than in the placebo group (27% with BG-12 twice a day and 26% with BG-12 thrice a day, versus 46% with placebo).[34]

The other phase III study – the CONFIRM trial – compared the effect of using BG-12 240 mg twice a day, BG-12 240 mg thrice a day, placebo, and glatiramer acetate.[35] A total of 1430 relapsing-remitting MS patients were randomly assigned between the treatment groups. The main outcome was the annualized relapse rate over two years. It was observed that the annualized relapse rate and relative risk were significantly lower with BG-12 twice a day (0.22; RR = 44%), BG-12 thrice a day (0.20; RR = 51%), and glatiramer (0.29; RR = 29%) than with placebo (0.40). The differences between BG-12 and glatiramer acetate were not significant.

Safety. Treatment with BG-12 was safe. The adverse events that occurred at higher incidence with BG-12 were flushing, gastrointestinal events (diarrhea, nausea, and upper abdominal pain – higher in the first month of treatment and decreasing thereafter), reduced lymphocyte counts, and elevated liver enzymes.[35]

Laquinimod

Mechanism of action. The exact mechanism of action of laquinimod has not been fully elucidated. This drug reduces leukocyte migration into the CNS through downregulation of VLA-4-mediated adhesiveness, thereby inhibiting Th 17-proinflammatory responses, and also through modulating the cytokine balance in favor of Th2 interleukins.[36–38]

Phase II studies. An important phase II trial on laquinimod was published in 2008. This was a randomized, double-blind, placebo-controlled trial on 306 patients, who were assigned to receive laquinimod 0.3 mg/day, laquinimod 0.6 mg/day, or placebo, over a 36-week period. The main outcome was the cumulative number of GD-enhancing lesions. Laquinimod 0.6 mg/day significantly reduced the number of GD-enhancing lesions, by 40.4%, in comparison with placebo. Laquinimod 0.3 mg/day showed no significant results versus placebo.[39]

Phase III studies. There have been two important phase III studies: the ALLEGRO and BRAVO trials.. The ALLEGRO trial[40] was a randomized, double-blind, placebo-controlled trial on 1105 patients. They were assigned to receive laquinimod

0.6 mg/day or placebo. The main outcome was the annualized relapse rate during the 24-month period. Laquinimod was associated with a modest reduction in mean annualized relapse rate (0.30 versus 0.39).

The BRAVO trial[41] enrolled 1331 patients with relapsing-remitting MS and was randomized to receive laquinimod 0.6 mg/day, placebo, or IFN beta 1a weekly (Avonex; Biogen). The main outcome was the annualized relapse rate. There were no significant differences between the treatments. There was a significant reduction in brain atrophy in favor of laquinimod (reduction of 27.5%, in comparison with placebo), but this was a secondary outcome.

Safety. The most common adverse event was elevated liver enzymes, with no clinical signs of liver failure. The enzyme elevations were dose-dependent and reversible after treatment discontinuation.

Teriflunomide

Mechanism of action. Teriflunomide is the principal active metabolite of leflunomide, which is used for treating rheumatoid arthritis. Teriflunomide selectively and reversibly inhibits a mitochondrial enzyme that is necessary for de novo pyrimidine synthesis: dihydroorotate dehydrogenase (DHODH).[42] Inhibition of DHODH limits the expansion of stimulated T- and B-cells and reduces the number of lymphocytes available to enter the CNS.

Phase II studies – monotherapy. The first study to evaluate the efficacy and safety of teriflunomide for relapsing-remitting MS patients was published in 2006. It enrolled 179 patients, who were randomized to receive placebo, teriflunomide 7 mg/day, or teriflunomide 14 mg/day. The primary endpoint was the number of active lesions seen on MRI. Teriflunomide-treated patients had significantly fewer active lesions, new or enlarging T2 lesions, and new T2 lesions during the 36-week double-blind period. The treatment was well tolerated; the numbers of adverse events and serious adverse events were similar in all treatment groups.[43]

Phase II studies – combination therapy. The combination of teriflunomide with IFN beta 1a 44 μg (Rebif; Merck Serono) has been tested in a trial with 116 patients.[44] This combination therapy was well tolerated and was associated with reduced activity seen on MRI at 48 weeks, compared with monotherapy with IFN beta 1a (relative reduction of GD-enhancing lesions of more than 80% for each of two doses of teriflunomide).

Phase III studies – monotherapy. After the promising results of the phase II trial, a larger phase III study was developed: the TEMSO trial.[45] This study recruited 1088 patients with relapsing-remitting MS between 2004 and 2008. Patients were randomly assigned to receive a once-daily oral dose of placebo, low-dose teriflunomide (7 mg/day), or high-dose teriflunomide (14 mg/day) over a 108-week period. The primary outcome from the trial was a reduction of the annualized relapse rate. The effect size was modest (31.2%

reduction in relapse rate for the low-dose group and 31.5% for the high-dose group, compared with placebo).

Another phase III study – the TOWER trial[46] – was similar to the TEMSO trial and showed similar preliminary results. The TOWER trial enrolled 1169 MS patients and assigned them to receive placebo, teriflunomide (7 mg/day), or teriflunomide (14 mg/day). The main outcome was the annualized relapse rate. In this study, a clear dose effect was demonstrated: 36.3% reduction in relapse rate in the 14-mg arm and 22.3% in the 7-mg arm.

The TENERE trial[47] compared the effect of teriflunomide with IFN beta 1a 44 μg (Rebif; Merck Serono). The primary outcome was the time that elapsed until treatment failure (a confirmed relapse under treatment or a permanent treatment discontinuation for any reason). There was no statistical difference between the IFN and the teriflunomide groups (48.6% treatment failure for the 7 mg teriflunomide group, 37.8% for the 14 mg teriflunomide group, and 42.3% for the IFN group; not significant).

Phase III studies – combination therapy. A larger phase III trial – TERACLES[48] – which was designed to evaluate teriflunomide combined with IFN beta 1a was recently prematurely terminated. The main cause was a smaller sample size than what would be required to show reliability in this study. The primary outcome was the reduction in relapse rate under combination therapy with low-dose and high-dose teriflunomide and IFN beta 1, compared with monotherapy with IFN beta 1a.

Safety. Teriflunomide has generally been well tolerated at both doses. Common adverse effects include: lymphopenia, elevated liver enzymes, hypertension, nausea, diarrhea, peripheral neuropathy, acute renal failure, and hair thinning.[49,50] One important consideration is its teratogenicity (pregnancy category X) and prolonged half-life. It is contraindicated during pregnancy. It may take several months to fully eliminate the drug after discontinuation, which is a concern among patients who become pregnant while using the drug. In such cases, cholestyramine may be used to hasten the elimination over a period of 11 days.[50]

Daclizumab

Mechanism of action. Daclizumab is a monoclonal antibody specific for the α subunit (CD25) of the interleukin-2 receptor. After T-cell activation, CD25 is upregulated, thereby enhancing IL-2 signal transduction. Daclizumab exerts antagonism to CD25 and selectively inhibits activated T-cells. In contrast, CD25 antagonism causes expansion of a subset of natural killer cells (CD56), thus favoring cell-mediated lysis of autologous activated T-cells.[51,52]

Phase II studies. The CHOICE study was a phase II trial on 230 patients, who were randomized to receive IFN beta plus high-dose daclizumab (2 mg/kg every two weeks), IFN beta plus low-dose daclizumab (1 mg/kg every four weeks), or IFN beta plus placebo, for 24 weeks. The main

outcome was the mean number of new or enlarged gadolinium contrast-enhancing lesions on MRI. The mean number of these lesions was 4.75 in the placebo group, 3.58 in the low-dose daclizumab group, and 1.32 in the high-dose daclizumab group, which was a significant difference.[53]

Phase III studies. The SELECT trial[54] was published in 2013, with 617 patients, and compared daclizumab 150 mg, daclizumab 300 mg, and placebo over a one-year period. The annualized relapse rate fell by 54% in the daclizumab groups, thus demonstrating that the treatment had a good effect on relapses. The efficacy results were similar for the two doses of daclizumab, with more favorable point estimates of efficacy noted with the dose of 150 mg, for clinical outcomes.

Safety. In the SELECT trial, adverse events occurred in similar proportions of patients in all study groups. Nine patients given treatments (2%) had serious infections, whereas no patient given placebo had infections. There were four occurrences of malignancies during the trial: two cases of cervical carcinoma (one in the placebo group and one in the daclizumab 150 mg group) and two cases of melanoma in the daclizumab 300 mg group. The cases of melanoma were treated with local excision with no reported recurrence.[54]

Ocrelizumab

Mechanism of action. Ocrelizumab is an anti-CD20 monoclonal antibody that targets B lymphocytes.[55] It causes depletion of these cells, thereby interfering in the process of antibody production.

Phase II studies. Ocrelizumab was tested in a phase II trial.[55] This was a 48-week, randomized, placebo-controlled study of ocrelizumab 600 mg or 2000 mg administered intravenously on days 1 and 15 of two cycles, six months apart. The relapse rate and the volume of GD-positive lesions reduced significantly.[55]

Phase III studies. Two trials[56,57] are ongoing and will be published in the near future.

Safety. The adverse events most often reported have been infusion-related reactions. Ocrelizumab has been well tolerated, showing similar rates of serious adverse events between groups.

Therapeutic Strategies

When comparing the efficacy of the established drugs for MS, natalizumab and fingolimod are the most effective ones, almost doubling the efficacy in relation to IFNs and glatiramer acetate. However, natalizumab increases the risk of PML, whereas fingolimod has a bradycardia effect at the time of administration of its first dose.

Considering the non-established drugs, laquinimod has a low relapse reduction rate and is the least effective representative of this group. Teriflunomide has a good effect on MS relapses, but the reduction rates are comparable to IFNs. The most effective drugs of this group are dimethyl fumarate and alemtuzumab.

After approval of the non-established drugs, dimethyl fumarate may compete for the same target market with

fingolimod, whereas alemtuzumab may share the same target with natalizumab.

Sequential DMT monotherapy has been the usual strategy over the last two decades and is partially supported by the trials available. The aim should be to achieve a condition with no further relapses, no changes in EDSS, and no new lesions or GD-enhancement seen on MRI. This should be attained together with a good tolerability profile, thus resulting in good safety and adherence. However, this ideal situation, which was recently described, is not common in the daily practice of MS treatment. Even if treatment with some DMTs is going very well, it is common to experience some degree of relapse or activity seen on MRI owing to the partial effect of all DMTs.[58,59] In order to help physicians understand the appropriate time to change from one DMT therapy to another, the concept of treatment failure has been defined. This concept has sometimes changed over the last few years, but Freedman et al.[60] have now proposed criteria for categorizing the evidence for treatment failure into situations of low, medium, and high propensity for changing DMT, depending on the combination of clinical, imaging, and other parameters.

After defining the existence of treatment failure in a patient, the next step is to select another DMT. This strategy is called treatment escalation. There are few head-to-head DMT trials evaluating the best drug therapy in the setting of treatment failure.

There are some classic scenarios that should be discussed. The first one is a patient who has been using any first-line agent (IFN or glatiramer) and presents treatment failure. The next options are fingolimod or natalizumab, in accordance with the algorithm from Río et al.[61] The choice between fingolimod or natalizumab will depend on the patient's JCV status. If positive for JCV antibodies in serum tests, natalizumab should be avoided because of the higher risk of PML. The second scenario is a patient who has been using fingolimod or dimethyl fumarate and presents failure. In this case, the best option is to change to natalizumab or alemtuzumab. Changing between oral drugs such as fingolimod and dimethyl fumarate is not recommended. The third scenario is a patient who has been using natalizumab or alemtuzumab and presents treatment failure. In this case, there are no support guidelines directing toward the next treatments.

After defining the next DMT, some issues still remain to be resolved, for example, the time to allow for washout between the previous and the new DMT and the real-life risks of these new DMTs, including opportunistic infections, cardiovascular risks, and malignancy risks. Therefore, it is to be hoped that further published studies will soon be able to help in answering these questions.

In daily neurological practice, there has been a tendency to use oral drug therapy as a first-line option. This trend has been driven by MS patients worldwide, and physicians should be prepared to discuss the pros and cons concerning this issue. Despite evidence-based medicine, the innovation of oral therapy – and consequently better quality of life – has influenced patients and physicians toward using fingolimod or dimethyl fumarate, especially the former because it was the first to be marketed in most countries. Continuing this trend, further cohort studies following MS patients who are using fingolimod or dimethyl fumarate as first-line therapy are recommended, in order to demonstrate their long-term efficacy and safety.

Conclusions and Unmet Needs

The availability of increasing numbers of DMTs has provided patients and physicians with a multiplicity of therapeutic options, thereby nurturing hope among people suffering from MS. Despite these possibilities, there are no trials or guidelines to support strong evidence-based strategies for selecting the best DMT at such moments, or for ordering the best treatment escalation strategy in cases of failure. Therefore, further DMT escalation studies need to be conducted within the setting of treatment failure. These studies should ideally be controlled trials, or even cohort studies, in order to best guide patients and physicians in selecting the most appropriate therapy.

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Author Contributions

Conceived the concepts: AF. Analyzed the data: AF. Wrote the first draft of the manuscript: AF. Made critical revisions: AF. The author reviewed and approved of the final manuscript.

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