ORIGINAL RESEARCH PAPER

Volume-8 | Issue-8 | August - 2019 | PRINT ISSN No. 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

MULTIPLE SCLEROSIS: NEWER TREATMENTS

Neurology

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ABSTRACT

Multiple sclerosis (MS) is a chronic autoimmune disease of central nervous system that usually affects young adults, causing progressive physical and cognitive disability. Its treatment has been based on parenteral medications known collectively as immunomodulators since the 1990s . This drug class is considered safe and usually prevents 30% of MS relapses. Drugs in this class exert almost the same efficacy but require an inconvenient administration route i.e. parenteral leading to decrease compliance . New medications have recently been launched worldwide. New oral drugs are increasingly being used in MS patients contributing to a better quality of life, since these have better efficacy than the old immunomodulators with easier method of administration. Today, 10 different drugs for MS are marketed worldwide, which requires deep knowledge among neurologists and other healthcare professionals. This review article summarizes all the drugs approved for MS in the US and Europe, emphasizing their mechanism of action and the product safety.

KEYWORDS

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune, chronic inflammatory demyelinating disease of the central nervous system (CNS).(1)

Multiple sclerosis affects about 400,000 people in the United States, and about 2 1/2 million worldwide. In the United States, the prevalence of the condition- that is, the number of people who have it compared with the general population is nearly 90 cases per 100,000 people.

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 :**MS plaques**. The usual **evolution of the MS plaque** is as follows: in the acute phase (active plaque), activated mononuclear cells, including lymphocytes, microglia, and macrophages destroy myelin and, to a variable degree, oligodendrocytes. Myelin debris are picked up by macrophages and degraded. At an early stage, macrophages contain myelin fragments; later, they contain proteins and lipids from chemical degradation of myelin. With time, gliosis develops, and plaques reach a burned-out stage consisting of demyelinated axons traversing glial scar tissue (inactive plaque). Remaining oligodendrocytes attempt to make new myelin. If the inflammatory process is arrested at an early phase, plaques are partially remyelinated (shadow plaque). In more advanced lesions, remyelination is ineffective because gliosis creates a barrier between the myelin producing cells and their axonal targets. The pathological process may be arrested at any time, sometimes after partial demyelination. Demyelination causes **loss of saltatory conduction.** Linear conduction along demyelinated axons is slow because the internodal axon membrane has few ion channels. In addition, lack of insulation of axons allows impulses to disperse laterally to adjacent demyelinated axons. The abnormal physiology of demyelinated axons results in **inefficient conduction or conduction block.** This is reflected by **abnormal evoked response potentials,** an electrodiagnostic test that measures conduction velocity in the CNS. Loss of axons, which occurs during the acute inflammatory phase of the disease, explains the permanent disability.(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)

"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:

1. Interferon beta 1b
2. Interferon beta 1a 30 µg
3. Glatiramer acetate
4. Interferon beta 1a 22 µg
5. Interferon beta 1a 44 µg

Mechanism of Action: IFNs usually inhibit antigen presentation thereby 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)

IFN beta and glatiramer have favorable long-term safety profiles and still remain the first-choice treatment. 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.

Established treatments for MS (Table 1):

	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
Dose	250	250	30	22 or 44	20	300mg	0.5mg
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 pro-gressive multifocal leukoencephalopathy	High rates of herpesvirus infections and bradycardia at the first dose

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.(10) 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.

Safety:

Despite a very good efficacy profile, natalizumab has been shown to be correlated with a few cases of progressive multifocal leukoencephalopathy (PML) and subsequent death. This led to temporary withdrawal of natalizumab from the market. 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.(11)

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.(12)

Safety:

Increased cardiovascular risk especially bradycardia with first dose has been noticed. 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 monitor heart rate, blood pressure, and electrocardiogram.

NEWER TREATMENTS FOR MS (Table 2):

	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

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 monocytes. 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).(13)

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 thrombocytopenia, in 3% of the patients. The infection rate was 66% in the alemtuzumab group, whereas in the IFN group, this proportion was 47%.(14)

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.(15) 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.(16-18)

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.(19)

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.(20-22)

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).(23) Inhibition of DHODH limits the expansion of stimulated T- and B-cells and reduces the number of lymphocytes available to enter the CNS.

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.(24,25) 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.(25)

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.(26,27)

Safety:

Common side effects of Zinbryta include: abnormal liver function test, decreased lymphocyte count, diarrhea, dry skin, skin redness, hair bumps (folliculitis) ,increased liver enzymes ,laryngitis ,enlarged lymph nodes ,pneumonia ,Itching ,psoriasis ,skin peeling, toxic skin eruption, and viral infection.

Ocrelizumab

Mechanism of action:

Ocrelizumab is an anti-CD20 monoclonal antibody that targets B lymphocytes.(28) It causes depletion of these cells, thereby interfering in the process of antibody production

Safety:

The adverse events most often reported have been infusion-related reactions. Ocrelizumab has been well tolerated.

CONCLUSION

The availability of increasing number of Disease Modifying therapies has provided patients and physicians with a multiplicity of therapeutic options, thereby nurturing hope among people suffering from MS. 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 these possibilities, there are no trials or guidelines to support strong evidence-based strategies for selecting the best DMT at such moments. Therefore, further studies should be conducted and 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.

REFERENCES

1. Sospedra M, Martin R. Immunology of multiple sclerosis. Annu Rev Immunol. 2005;23:683–747.[PubMed] [Google Scholar]
2. Noseworthy JH, Lucchinetti CF, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med. 2000;343:938–52. [PubMed] [Google Scholar]
3. Compston A, Coles A. Multiple sclerosis. Lancet. 2002;359:1221–31. [PubMed] [Google Scholar]
4. Calabresi PA. Diagnosis and management of multiple sclerosis. Am Fam Physician. 2004;70:1935–44.[PubMed] [Google Scholar]
5. Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mork S, Bo L. Axonal transaction in the lesions of multiple sclerosis. N Engl J Med. 1998;338:278–85. [PubMed] [Google Scholar]
6. Lassmann H. The pathology of multiple sclerosis and its evolution. Philos Trans R Soc Lond B Biol Sci. 1999;354:1635–40. [PMC free article] [PubMed] [Google Scholar]
7. Yong VW, Chabot S, Stuve O, Williams G. Interferon beta in the treatment of multiple sclerosis: mechanisms of action. Neurology. 1998;51:682–9. [PubMed] [Google Scholar]
8. Kipnis J, Yoles E, Porat Z, et al. T cell immunity to copolymer 1 confers neuroprotection on the damaged optic nerve: possible therapy for optic neuropathies. Proc Natl Acad Sci U S A. 2000;97:7446–51. [PMC free article] [PubMed] [Google Scholar]
9. Moalem G, Leibowitz-Amit R, Yoles E, Mor F, Cohen IR, Schwartz M. Autoimmune T cells protect neurons from secondary degeneration after central nervous system axotomy. Nat Med. 1999;5:49–55.[PubMed] [Google Scholar]
10. Ransohoff RM. Natalizumab for multiple sclerosis. N Engl J Med. 2007;356(25):2622–9. [PubMed] [Google Scholar]
11. Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N Engl J Med. 2012;366:1870–80. [PubMed] [Google Scholar]
12. 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. [PubMed] [Google Scholar]
13. 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. [PubMed] [Google Scholar]
14. The CAMMS223 Trial Investigators. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med. 2008;359:1786–1801. [PubMed] [Google Scholar]
15. Witherick J, Wilkins A, Scolding N, et al. Mechanisms of oxidative damage in multiple sclerosis and a cell therapy approach to treatment. Autoimmune Dis. 2010;2011:164608. [PMC free article] [PubMed] [Google Scholar]
16. Scannevin RH, Chollate S, Jung MY, et al. Fumarate promotes cytoprotection of central nervous system cells against oxidative stress via the Nrf2 pathway. J Pharmacol Exp Ther. 2012;341:274–84.[PubMed] [Google Scholar]
17. Nguyen T, Sherratt PJ, Pickett CB. Regulatory mechanisms controlling gene expression mediated by the antioxidant response element. Annu Rev Pharmacol Toxicol. 2003;43:233–60. [PubMed] [Google Scholar]
18. Lukashev M, Zeng W, Goelz S, et al. Activation of Nrf2 and modulation of disease progression in EAE models by BG00012 (dimethyl fumarate) suggests a novel mechanism of action combining anti-inflammatory and neuroprotective modalities. Mult Scler. 2007;13:S149–P503. [Google Scholar]
19. 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. [PubMed] [Google Scholar]
20. Wegner C, Stadelmann C, Pförtner R, et al. Laquinimod interferes with migratory capacity of T cells and reduces IL-17 levels, inflammatory demyelination and acute axonal damage in mice with experimental autoimmune encephalomyelitis. J Neuroimmunol. 2010;227:133–43. [PubMed] [Google Scholar]
21. Yang J, Xu L, Xiao B, Hedlund G, Link H. Laquinimod (ABR-215062) suppresses the development of experimental autoimmune encephalomyelitis, modulates the Th1/Th2 balance and induces the Th3 cytokine TGF-beta in Lewis rats. J Neuroimmunol. 2004;156:3–9. [PubMed] [Google Scholar]
22. Aharoni R, Saada R, Eilam R, Hayardeny L, Sela M, Arnon R. Oral treatment with laquinimod augments regulatory T-cells and brain-derived neurotrophic factor expression and reduces injury in the CNS of mice with experimental autoimmune encephalomyelitis. J Neuroimmunol. 2012;251:14–24.[PubMed] [Google Scholar]
23. Warnke C, Meyer zu, Hörste G, Hartung HP, Stüve O, Kieseier BC. Review of teriflunomide and its potential in the treatment of multiple sclerosis. Neuropsychiatr Dis Treat. 2009;5:333–40.[PMC free article] [PubMed] [Google Scholar]
24. Alcom N, Saunders S, Madhok R. Benefit-risk assessment of leflunomide: an appraisal of leflunomide in rheumatoid arthritis 10 years after licensing. Drug Saf. 2009;32:1123–34. [PubMed] [Google Scholar]
25. Oh J, O'Connor PW. Teriflunomide. Neurol Clin Pract. 2013;3(3):254–60. [PMC free article][PubMed] [Google Scholar]
26. Bielekova B, Catalfamo M, Reichert-Scrivner S, et al. Regulatory CD56 (bright) natural killer cells mediate immunomodulatory effects of IL-2R alpha-targeted therapy (daclizumab) in multiple sclerosis. Proc Natl Acad Sci U S A. 2006;103:5941–6. [PMC free article] [PubMed] [Google Scholar]
27. Airas L, Saraste M, Rinta S, et al. Immunoregulatory factors in multiple sclerosis patients during and after pregnancy: relevance of natural killer cells. Clin Exp Immunol. 2008;151:235–43. [PMC free article][PubMed] [Google Scholar]
28. Kappos L, Li D, Calabresi PA, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomized, placebo-controlled, multicentre trial. Lancet. 2011;378:1779–87. [PubMed] [Google Scholar]