Current and emerging therapies in multiple sclerosis: a systematic review

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Wanda Castro-Borrero, Donna Graves, Teresa C. Frohman, Angela Bates Flores, Paula Hardeman, Diana Logan, Megan Orchard, Benjamin Greenberg and Elliot M. Frohman

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

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

Introduction

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

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

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

Correspondence to:
Wanda Castro-Borrero, MD
University of Connecticut Health Center, Neurology Associates, 263 Farmington Ave., Farmington, CT 06030-5357, USA
wcastro@uchc.edu

Donna Graves, MD, Teresa C. Frohman, PAC, Angela Bates Flores, MD, Paula Hardeman, PAC, Diana Logan, RN, FNP-C, BC, MSCN, Megan Orchard, PAC, Benjamin Greenberg, MD, MHS
Elliot M. Frohman, MD, PhD
University of Texas Southwestern Medical Center, Multiple Sclerosis Program, Dallas, TX, USA

FDA- and EMA-approved therapies

Interferon β

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

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

Disease-modifying therapy	Dose/route	Monitoring labs/tests	Side effects*
IFN-β1a (Avonex)	30 μg intramuscularly weekly	CBC, LFTs, TSH	Flu-like symptoms, depression, thyroid dysfunction, liver enzymes abnormalities
IFN-β1a (Rebif)	22 or 44 μg subcutaneously three times a week	CBC, LFTs, TSH	Skin site reactions, flu-like symptoms, depression, thyroid dysfunction, liver enzymes abnormalities
IFN-β1b (Betaseron/ Betaferon/Extavia)	250 μg subcutaneously every other day	CBC, LFTs, TSH	Skin site reactions, flu-like symptoms, depression, thyroid dysfunction, liver enzymes abnormalities
Glatiramer acetate (Copaxone)	20 mg subcutaneously once a day	None	Skin site reactions, immediate postinjection reaction, lipoatrophy
Mitoxantrone	12 mg/m² intravenously over 30 min every 3 months with a lifetime cumulative dose of no more than 140 mg/m²; frequency may vary	CBC, LFTs, U/A, LVEF	Hair loss, cardiotoxicity, leukemia, infertility, increased risk of infections, leukopenia, anemia, nausea, vomiting, thrombocytopenia
Natalizumab (Tysabri)	300 mg intravenously every 28 days	CBC, LFTs	Transient headache fatigue, recurrent UTIs, PML, hypersensitivity reaction
Fingolimod	0.5 mg orally once a day	CBC, LFTs, screen for macular edema	First-degree AV block with first dose, bradycardia, macular edema, shingles, PF dysfunction in selected patients, skin cancer, back pain

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

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

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

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

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

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

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

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

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

Glatiramer acetate

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

Table 3. Multiple sclerosis emerging therapies.

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

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

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

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

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

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

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

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

Mitoxantrone

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

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

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