# Disease Modifying Agents for Multiple Sclerosis

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**Abstract:** *Objective*: To summarize major clinical trials which evaluate the efficacy and safety data of approved disease modifying agents for the treatment of various types of multiple sclerosis.

*Data Sources*: A MEDLINE (1966 to August 2008) search of clinical trials using the terms multiple sclerosis, interferon, glatiramer, mitoxantrone and natalizumab was performed. A manual bibliographic search was also conducted. English-language articles identified from the searches were evaluated. New agents under investigation in phase 3 clinical trials were identified using www.clinicaltrials.gov.

*Study Selection & Data Extraction*: Relevant information was identified and selected based on clinical relevance and evidence-based strength. Prescribing information leaflets were used to provide usual dosage, contraindications, precautions, monitoring parameters and other relevant drug-specific information.

*Data Synthesis*: Interferon beta products are more efficacious for the treatment of relapsing-remitting multiple sclerosis. Interferon beta 1-b also delayed the time to diagnosis of definite multiple sclerosis and reduced brain lesion burden in patients with clinical isolated syndrome. Glatiramer and natalizumab have both established efficacy in relapsing forms of multiple sclerosis; whereas mitoxantrone is more commonly used in patients with advanced disease. There are limited data the comparative efficacy among different disease modifying agents. New agents currently under investigation have showed promising results and may offer more treatment options in the future.

*Conclusions*: MS is a complex and devastating disease with challenging treatment considerations and approaches. Interferon beta products continue to be the mainstay of therapy in many patients, however, other treatments are proving to be at least as effective in the management of various types of MS. Newer compounds are being developed and studied with much anticipation and promise for the clinical management of the disease.

**Keywords:** Multiple sclerosis, disease modifying therapy, immune modulators, interferon beta, glatiramer, mitoxantrone, natalizumab.

## INTRODUCTION

Multiple sclerosis (MS) is a debilitating condition that affects approximately 400,000 Americans and 2.5 million people worldwide [1-3]. It is usually diagnosed between age 20 and 50, and affects women twice more often than men [1]. Risk factors include geographic location, ethnicity and genetics [2]. Scandinavian descent and persons who live further away from the equator are more likely to be inflicted [4, 5]. Although the familial recurrence rate of MS is low (~ 5%), a positive family history can increase the risk by 30 to 50 times [2, 6]. About 15% of patients with MS have at least one additional relative suffering from the disease [2, 6]. Concordance data shows a higher prevalence of MS among monozygotic (25%) than among dizygotic twins (3-5%) [5, 7]. Disability due to MS can accumulate and reduce life span by 6 to 7 years and patients survive for about 35-40 years from the time of diagnosis [2, 8]. This article provides an overview of MS, as well as a review of the agents commonly used to manage its symptoms and progression.

## PATHOPHYSIOLOGY AND ETIOLOGY

The exact causes of MS are unclear. Autoimmune and microbial etiologies have been proposed to explain the pathophysiology of MS. In the autoimmune etiology theory, a patient's own immune system attacks against myelin or oligodendrocyte antigens [1, 2, 9]. This leads to the stripping of myelin sheath which is a protein-lipoid substance surrounding the neuronal axons. Myelin sheath insulates, protects, and helps to conduct nerve impulses. Demyelination, together with inflammatory responses, leads to the formation of characteristic lesions in the central nervous system (CNS).

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This destructive process leads to axonal damage even early in the disease and may result in neurologic symptoms, which typically reflect the affected area of the CNS [1, 2, 9].

In the microbial etiology theory, bacteria or viruses are responsible for the pathogenesis of MS. Suspected organisms include varicella zoster, rubella, Epstein-Barr, human herpes virus 6, mycoplasma, rabies virus, canine distemper virus, retrovirus, mumps, measles, *Chlamydia pneumoniae*, and others. Nevertheless, no one particular pathogen has been fully established as a causal agent for MS symptoms [1, 2, 9-12].

Environmental factors may also contribute to the pathogenesis [13]. MS is more prevalent in countries with moderate or cool climate, areas with greater distances from the equator in both the northern and southern hemispheres [1]. Interestingly, the environmental influence is more important between the ages of 10 and 15 years [13, 14].

## CLINICAL MANIFESTATIONS

MS has a variable clinical presentation with its clinical course or disease progression related to the type of MS [2, 15]. The disease consists of four distinct types or stages: (1) relapsing-remitting MS (RRMS); (2) secondary progressive MS (SPMS); (3) primary progressive MS (PPMS); and progressive-relapsing MS (PRMS) [2, 15, 16, 20].

RRMS is the most common type, affecting approximately 80 to 85% of patients beginning in their second or third decade of life and clinically manifesting in the third or fourth decade [2, 15, 17]. Women are twice as likely to present with this type of MS [2]. Signs and symptoms usually present over a course of days, typically stabilizing and spontaneously resolving. Disability and CNS dysfunction may present and progress after relapses, and during times of remission [2, 15]. Initial symptoms include sensory, visual, balance and gait disturbances, limb weakness, neurogenic bladder and bowel problems. Temporal fatigue and increases in body temperature have also been reported. In addition, cognitive impairment, depression, emotional lability, dysarthria, dysphagia, vertigo, progressive quadriparesis and sensory loss, ataxic tremors, pain, sexual dysfunction, spasticity, and other apparent CNS problems may arise [2].

An estimated 50% of RRMS patients over a period of 10 years [18] and about 90% over 25 years will experience a stage transition to SPMS [16]. SPMS is characterized by a gradual and worsening disability with or without the presence of superimposed relapses [17, 19]. Exacerbations may or may not be seen during the secondary progressive stage [20].

PPMS affects approximately 10-20% of patients and carries the worst prognosis [2, 17]. The incidence has been reported to be similar among men and women [2]. It is characterized by a gradual and progressive course in which patients experience continuous worsening in disease from onset with no exacerbations or remission periods [2, 20]. Initial presentation includes a slow progressive myelopathy of the legs. Quadraparesis, cognitive decline, visual loss, brain-stem syndromes, and dysfunction of bowel, bladder, and reproductive systems may also occur [2].

A fourth and unusual type, referred to as progressive-relapsing MS (PRMS), has also been introduced as a pro-

gressive disease from onset with clear, acute and superimposed relapses with or without recovery [20]. However, one study found that there was no differentiation between primary progressive and progressive-relapsing based on clinical characteristics and progression of disability [21].

All types of MS can cause significant disability [15]. Although it is difficult to predict the progressive course and development of disability [17], poor prognostic factors have been described: male gender, older age at onset, motor symptoms or cerebellar signs at onset, short interval and incomplete recovery between the initial and subsequent attack, high relapse rate early on in disease, early disability, moderate disability within 5 years and high lesion load revealed on early magnetic resonance imaging (MRI) of the brain [16, 18, 22, 23].

## DIAGNOSIS

Currently, no specific diagnostic test is available for MS. Therefore, appropriate diagnosis depends on thorough history and examination and objective evidence of CNS lesions scattered in space and time [24, 25]. An MRI is utilized to support the clinical diagnosis, confirm dissemination in space, and rule out other potential causes such as metabolic, vascular, psychiatric, genetic, autoimmune, neuropathic, neoplastic and other disorders [2]. It is the most sensitive and specific technique for detecting MS lesions and quantifying their progression over time [26]. Typical findings include multifocal lesions of various ages primarily involving the periventricular white matter, brain stem, cerebellum, and spinal cord white matter. In addition, the presence of gadolinium-enhanced lesions indicates inflammatory demyelination [2].

Cerebrospinal fluid (CSF) analysis and visual evoked potentials (VEP) are also used to further assist in the diagnosis. CSF analysis provides information on inflammatory and immunologic disturbances, while VEP provide physiologic evidence of optic nerve dysfunction. Somatosensory evoked potentials (SEP) detect spinal cord dysfunction, and can provide diagnostic support when used along with spinal MRI [2, 24].

In 2000, the International Panel on the Diagnosis of MS developed the McDonald Criteria [24]. Core features of these diagnostic criteria include: emphasis on objective clinical findings; dependence on evidence of dissemination of lesions in time and space; use of supportive and confirmatory paraclinical examination; focus on specificity rather than sensitivity; and elimination of better explanations for a diagnosis [24, 27]. In the 2005, its revisions called for a particular focus on MRI criteria for dissemination of lesions in time, incorporation of spinal cord lesions into the imaging requirements, and establishing a diagnosis of PPMS by concentrating on clinical and imaging evidence and placing less emphasis on CSF findings [27].

## APPROVED DISEASE MODIFYING AGENTS

### Interferon β

Interferon β (IFNβ) is produced by fibroblasts and has antiviral, antiproliferative, and immunomodulatory effects [28]. Currently, there are two types of IFNβ available: IFNβ-1a and IFNβ-1b (Table **1**). IFNβ-1a is identical to natural IFNβ, while IFNβ-1b has a serine substitution for cysteine at

position 17 [29]. Also of note, IFNβ-1a is glycosylated, while IFNβ-1b is not [29].

### Interferon β-1a

IFNβ-1a is available as two different formulations: a once weekly intramuscular (IM) injection (Avonex®) and a three times weekly (TIW) subcutaneous (SC) injection (Rebif®). Intramuscular IFNβ-1a was approved by the FDA in May 1996 following two clinical trials that demonstrated efficacy. In one double-blind, placebo-controlled study, patients with RRMS were randomized to receive either IFNβ-1a 30mcg IM once weekly (n = 158) or placebo (n = 143) for up to 104 weeks [30]. The primary outcome was the time to

**Table 1.    FDA Approved Disease-Modifying Agents for the Management of Multiple Sclerosis**

| Drug | Mechanism of Action | Approved Indication | Usual Dosage | Notes |
|---|---|---|---|---|
| Interferon beta-1a (Avonex®) | Anti-proliferation, immunomodulation | RRMS | 30 mcg SC once weekly | |
| Interferon beta- 1a (Rebif®) | Anti-proliferation, immunomodulation | RRMS | 20% of target dose initially, titrate to 22 mcg or 44 mcg IM TIW over 4 weeks | Administer on the same days each week, at least 48 hours apart |
| Interferon beta-1b (Betaseron®) | Anti-proliferation, immunomodulation | RRMS, CIS with MRI features consistent with MS | 0.0625 mg SC QOD initially; increase to 0.25 mg QOD over 6 weeks | CBC and LFT at baseline and 1,3,6 months thereafter; TFT every 6 months in selected patients |
| Glatiramer (Copaxone®) | Competitive binding with MBP, cytokine modulation & inhibition of free radical | RRMS | 20 mg SC daily | Routine laboratory monitoring is not required |
| Mitoxantrone (Novantrone®) | Intercalates into DNA; interferes with RNA; inhibits topoisomerase II; anti-proliferation; immunomodulation; TNF-α and IL-2 inhibition | SPMS, PRMS, or worsening RRMS | $12mg/m^2$ IV infusion over 5-15 minutes every 3 months | Bone marrow suppression (neuropenia) may occur. CBC should be monitored prior to initial dose, before each subsequent dose, and after discontinuation of therapy<br><br>Assessment of cardiac function recommended prior to initiation, during treatment and yearly after discontinuation (history, physical examination, electrocardiogram and quantitative evaluation of left ventricular ejection fraction via echocardiogram, multi-gated radionuclide angiography (MUGA), MRI, etc.)<br><br>LFT should be monitored prior to initial dose and before each subsequent dose<br><br>Secondary acute myelogenous leukemia (AML) has been reported. Elevated risk of 0.25% has been observed |
| Natalizumab (Tysabri®) | Inhibits the adhesion of molecules onto the surface of immune cells; potentially inhibits the migration of immune cells | Monotherapy for relapsing forms of MS | 300mg IV infusion over approximately one hour every 4 weeks<br><br>(data on the efficacy and safety is limited to two years) | CBC, WBC, LFT (including bilirubin) should be monitored regularly<br><br>Antibody testing upon initiation and at 3 months (if persistent antibodies are suspected)<br><br>Hypersensitivity/ anaphylaxis may occur within 2 hours of infusion<br><br>Gadolinium-enhanced brain MRI and CSF analysis for JC viral DNA are recommended for suspected PML |

MBP = myelin binding proteins; TNF = tumor necrosis factor; IL = interleukin; CIS = clinical isolated syndrome; RRMS = relapsing-remitting multiple scleroris; MRI = magnetic resonance imaging; SPMS = secondary progressive multiple sclerosis; PRMS = progressive relapsing multiple sclerosis; SC = subcutaneously; QOD = every other day; IV = intravenously; CBC = complete blood count; LFT = liver function tests; TFT = thyroid function tests; CSF = cerebrospinal fluid; PML = progressive multifocal leukoencephalopathy.

onset of sustained disease disability, as defined by a decrease from baseline expanded disability status scale (EDSS) scores of at least 1 point for at least 6 months. Other outcomes included the number of exacerbations and brain lesions. Of the patients who completed 104 weeks of the study, 85 received IFNβ and 87 received placebo. The primary outcome, time to sustained progression of disease disability, was significantly prolonged in the interferon group as compared to the placebo group (p = 0.02). The number of exacerbations were significantly lower in the interferon group (0.82 *vs* 0.67 per year per patient; p = 0.04) when looking at all patients. The difference was more pronounced in the patients who completed 104 weeks of treatment, where the number of exacerbations per year per patient was 0.90 in the placebo group and 0.61 in the IFN group (p=0.002). At the end of one year, 29.9% in the IFN group and 42.3% in the placebo group (p=0.05) had positive MRI scans. At the end of year two, the percentages of positive MRI scans were similar: 28.9% *vs* 42.7%, respectively (p=0.02). Overall, IFN was well-tolerated. The adverse events that occurred more often in the IFN group included flu-like symptoms, muscle aches, fever, and chills.

The second study on IM IFNβ-1a was a randomized, double-blind, placebo-controlled, multicenter trial in patients who had recently experienced their first demyelinating event involving the optic nerve, brainstem, cerebellum, or spinal cord, and also had to have subclinical lesions on MRI [31]. Patients first received a regimen of methylprednisolone 1g IV for 3 days, then prednisone 1mg/kg orally for 11 days, then a 4 day period of steroid taper. Patients were then randomized to receive either IFNβ-1a 30mcg IM once weekly (n=193) or placebo (n=190) for 3 years. Cumulative probability of developing clinically confirmed MS during the 3 years was significantly decreased in the IFNβ group (rate ratio 0.56; 95%CI 0.38-0.81; p=0.002). On MRI, the number of new or enlarging lesions was significantly lower in the IFNβ group at months 6 (p=0.001), 12 (p<0.001), and 18 (p<0.001). The volume of lesions seen on MRI also significantly decreased in the IFN group at 6 (p<0.001), 12 (p=0.004), and 18 months (p<0.001). Influenza-like symptoms and depression occurred statistically more often in the IFNβ group.

Subcutaneous IFNβ-1a was approved by the FDA in May 2002 following the completion of two clinical trials: Prevention of Relapses and Disability by IFNβ-1a Subcutaneously in Multiple Sclerosis (PRISMS-2) and Evidence of Interferon Dose-Response: European North American Comparative Efficacy (EVIDENCE). The PRISMS-2 was a multicenter, double-blind, placebo-controlled trial enrolling 560 patients with RRMS [32]. Patients were randomly assigned to receive SC IFNβ-1a 22mcg, 44mcg, or placebo TIW for 2 years. Ninety percent of patients completed this study. The mean number of relapses decreased significantly in the IFN groups: 2.56 placebo, 1.82 IFN 22mcg (p<0.005 *vs* placebo), and 1.73 IFNβ 44mcg (p<0.005 *vs* placebo). Time to progression was longer in both IFNβ groups compared to placebo (p<0.05). The percentage of relapse-free patients over 2 years was 27% in the 22mcg group (p<0.05 *vs* placebo), 32% in the 44mcg group (p<0.005 *vs* placebo), and 16% in the placebo group. Statistically significant responses were seen in the IFNβ groups for decreased positive MRI scans and other endpoints. Overall, IFNβ-1a was well-tolerated. Injection-site reactions, lymphopenia, increased liver function test

(LFT), and granulocytopenia were reported more often among the IFN groups.

Results of a 2 year follow up study (PRISMS-4) were later published [33]. During years 3 and 4 of the study, patients originally receiving placebo were randomized in a double-blind fashion to receive IFNβ-1a 22mcg TIW or 44mcg TIW; data for this group was pooled as the "crossover" group. Patients originally receiving either dose of IFNβ continued that dose through years 3 and 4. Results showed that patients who received IFNβ-1a for the entire 4 years had fewer relapses per year (22 mcg, 0.80 per year; 44mcg, 0.72 per year) than patients who received 2 years of placebo and 2 years of IFNβ (1.02 per year).

The EVIDENCE study was an active-controlled, multi-center trial that compared three times weekly SC IFNβ-1a with once weekly IM IFNβ-1a (Avonex®) for 2 years in patients with RRMS [34]. Patients were randomly assigned to receive either IFNβ-1a SC 44mcg TIW (n=33) or IFNβ-1a IM 30mcg once weekly (n=388). At the end of 2 years, 75% in the SC group and 63% in the IM group were relapse-free (OR 1.9; 95%CI 1.3-2.6; p=0.0005). Patients in the SC group had fewer lesions on MRI than the IM group (p<0.0001). The time to first relapse was prolonged for the patients in the SC group as compared to the IM group (HR 0.70; 95%CI 0.55-0.88; p=0.003). Lower relapse rates were seen in the SC group (0.29 *vs*. 0.40 relapses/patient; p=0.022). Adverse events were more common in the SC group than in the IM group, with injection-site reactions, systemic influenza-like symptoms, LFT abnormalities, and white blood cell abnormalities occurring more often.

An extension of the EVIDENCE study was later published in which patients were followed for an average of 32 additional weeks [35]. In this phase of the study, patients originally assigned to receive IM IFNβ-1a were switched to the SC form, while those originally receiving the SC form continued in that group. The primary outcome was the change in relapse rate from pre-transition to post-transition. A total of 223 patients who were originally receiving the IM dose were switched to SC (IM to SC group), and 272 continued their originally SC dose (continuing SC group). Post-transition, the relapse rate per year decreased from 0.64 to 0.32 in the IM to SC group (p<0.001), and decreased from 0.46 to 0.34 in the continuing SC group (p=0.03). Patients in the continuing SC group had fewer T2-weighted lesions on MRI after the switch (p=0.02), while the SC continuing group had no change in number of lesions. Patients in the IM to SC group had more adverse events, and more patients in this group stopped treatment due to an adverse event. Injection-site reactions, influenza-like symptoms, LFT abnormalities, and white blood cell abnormalities occurred more often post-transition in the IM to SC group.

Both forms of IFNβ-1a are indicated for the treatment of relapsing forms of MS [36, 37]. The frequency of administration may affect the expression of biologic effect markers, indicating differences in therapeutic efficacy. In a study conducted in 1999, subjects were administered IFNβ-1a 22mcg once weekly, 22mcg TIW, or 66mcg once weekly. Levels of proinflammatory cytokines including tumor necrosis factor-α, interferon-γ, interleukin-1β, interleukin-6, and tumor necrosis factor-β decreased with the increase in dosing frequency (22mcg once weekly *vs*. TIW), not by the increase in

absolute dose (22mcg once weekly *vs* 66mcg once weekly) [38].

### Interferon β-1b

IFNβ-1b (Betaseron®) is the first disease modifying agent approved by the FDA in 1993. It is indicated for RRMS initially, and then also for clinical isolated syndrome (CIS) with MRI features consistent with MS [39].

In a multi-center, double-blind, placebo-controlled trial, IFNβ-1b reduced exacerbation rates, severity of exacerbations, and accumulation of MRI abnormalities. There was also an insignificant reduction of disability [40, 41]. In this trial, 372 patients with RRMS were randomized to receive placebo and IFNβ-1b (1.6 or 8 MIU SC every other day) for 2 years. IFNβ-1b demonstrated dose-dependent efficacy in annual exacerbation rates (1.27, 1.17 and 0.84, respectively). More patients receiving IFNβ-1b remained exacerbation-free (36 *vs.* 18 placebo; p = 0.007). IFNβ-1b also significantly delayed the time to first exacerbation by up to 142 days. Overall, IFNβ-1b had a persistent beneficial effect on exacerbation rate for up to 3 years and MRI burden of disease for up to 5 years [42]. Reported side effects include lymphopenia, liver enzyme elevation inflammation at injection site, fever, and myalgia.

The efficacy and safety of IFNβ-1b in patients with CIS has been demonstrated in a multi-center, randomized, double-blind, placebo-controlled, 2-year trial involving 468 patients [43]. Enrolled patients experienced a first clinical demyelinating event and at least two clinically silent brain MRI lesions. Treatment with IFNβ-1b significantly delayed the time to diagnosis of clinically definite MS by 50% and McDonald MS by 46%. It also significantly reduced secondary MRI endpoints, including newly active lesions and change in T2 lesion volume. Most common reported side effects were injection site reactions, flu-like syndrome, and headache. Incidence of depression was comparable in both groups (10% *vs.* 11%).

Treatment with IFNβ-1b provided conflicting results in patients with SPMS in two multi-center, randomized, double-blind, placebo-controlled trials [44, 45]. In EU-SPMS trial, IFNβ-1b significantly delayed the progression of disability in European patients with SPMS. The study was terminated one month early due to a compelling evidence of efficacy. Fewer patients receiving IFNβ-1b had confirmed disease progression (39% *vs.* 50%, p = 0.0048). Overall, treatment with IFNβ-1b delayed progression for 9-12 months (OR 0.65; 95% CI 0.52-0.83). This beneficial effect was seen in patients with superimposed relapses and those with only progressive deterioration without relapses. IFNβ-1b also provided beneficial effects on relapse rate, relapse severity, MRI variables and time to becoming wheelchair-bound in this 3-year study [44]. The most common reported side effects were flu syndrome, injection site inflammation, injection site reaction, fever, and hypertonia.

Unfortunately, this efficacy was not reproducible in a similar study involving North Americans (NA-SPMS trial) [45] that enrolled 939 subjects with SPMS, but was halted approximately 3 months early due to a lack of efficacy. Although IFNβ-1b improved clinical relapses and MRI variables, it did not delay the time to confirmed progression of disability [45].

There are no clear explanations for the contrasting results seen in EU-SPMS [44] and NA-SPMS [45] trials, but differences in patient baseline characteristics may have played an important role [46]. Evidences suggested that patients with ongoing inflammatory activity, as evidenced by pronounced disability progression and ongoing relapses, may benefit more from IFNβ-1b therapy [47]. It has been speculated that subjects in the EU-SPMS trial were more subject to treatment benefit compared to those in the NA-SPMS trial. The pooled analysis of both trials showed that treatment with IFNβ-1b provided a 20% risk reduction in EDSS progression confirmed at 6 months (p = 0.008). Higher risk reduction (30% to 40%) was seen in patients with at least one relapse or change in EDSS by >1 in the 2 years prior to study entry [47].

Even though all IFNβs induce neutralizing antibodies, IFNβ-1a seems to be less immunogenic that IFNβ-1b, possibly due to its glycosylation [29, 48, 49]. In one study conducted in 2006, IM IFNβ-1a induced neutralizing antibodies at a lower rate (5%; p<0.0001) than SC IFNβ-1a (29%) and interferon β-1b (31%) [49]. The frequency of binding antibodies followed the same pattern. However, in the subgroup of patients testing positive for neutralizing antibodies, more patients receiving IFNβ-1a had high titers compared to patients receiving IFNβ-1b (p=0.04). This may be the reason that many patients who develop neutralizing antibodies to IFNβ-1b eventually return to negative neutralizing antibody titers, since higher antibody levels indicate that the antibodies will persist [50]. The IFNβs also differ in the extent of liver injury they can cause. A retrospective chart review published in 2004 evaluated aminotransferase levels in 835 patients receiving the three IFNβs [51]. The authors concluded that SC IFNβ-1b and IFNβ-1a led to similar elevations of aminotransferase levels, and these were higher than the levels caused by IM IFNβ-1a.

### Glatiramer

Glatiramer, or copolymer-1 (Copaxone®) is the acetate salt of a random mixture of synthetic polypeptides composed of L-glutamic acid, L-lysine, L-tyrosine, and L-alanine (Table **1**) [52]. It reduces relapses and MRI findings in patients with RRMS [53-56]. In a double-blind, randomized, placebo-controlled 2-year pilot trial that involved 48 patients, glatiramer reduced relapse rate by about 4-fold (0.6 *vs* 2.7 placebo) [54]. Significantly more patients receiving glatiramer remained exacerbation-free at the end of the study (56% *vs.* 26%). Similar results were noted in a double-blind, placebo-controlled, 2-year, phase 3 trial in 251 patients with RRMS [55]. Glatiramer significantly reduced annualized relapse rate by 29% (0.59 *vs.* 0.84; p = 0.007) with a more profound benefit in subjects with lower EDSS scores of 0 to 2. Nevertheless, glatiramer did not provide benefit in sustained disability progression, defined as a 1.0 point or greater increase in EDSS maintained for 90 days. Drug-related side effects were injection-site reactions (90% *vs.* 59% placebo) and transient self-limiting systematic reactions, characterized by flushing, chest pain, palpitation, anxiety and dyspnea (15% *vs.* 3%). In a randomized, placebo-controlled extension trial [56], glatiramer provided similar benefit in relapse rate reduction (32%), and demonstrated benefit on disability progression, defined as worsening by 1.5 or greater on the EDSS (p = 0.001). Local injection site reactions occurred

more commonly in the glatiramer group (66% *vs*. 37% placebo). Immediate systemic reactions were noted with glatiramer use (1%% *vs*. 3.2% placebo) [56].

Follow-up analyses compared the neurologic status of subjects who remained on glatiramer therapy with those who withdrew from therapy in a 10-year period [57]. Results showed that more patients who remained on glatiramer therapy had stable or improved EDSS scores (68% *vs*. 28%). Still, glatiramer was associated with injection site reactiosn (erythema, pain, mass, edema) and immediate post-injection reaction (vasodilation, chest pain, palpitation, tachycardia or dyspnea) [57]. Unlike interferons, glatiramer is not associated with flu-like reactions or depression and does not seem to worsen headaches [58, 59]. Glatiramer is a Category B drug but use during pregnancy and breast-feeding is not recommended [52].

Glatiramer has also reduced MRI-measured disease activity and burden among RRMS patients in a randomized, placebo-controlled, 9-month study that involved 239 patients [60]. The glatiramer group had a significant reduction in the total number of enhancing lesion In another study, glatiramer significantly reduced the likelihood of new T2 lesions after 7 and 8 months, and provided a favorable effect on tissue disruption in MS lesions [61]. In addition, a small study showed that glatiramer may be an option for continuing disease modification in patients with RRMS who received prior treatment with mitoxantrone [62], or IFNβ treatments [63, 64].

A randomized, placebo-controlled, 3-year (PROMISE) trial was planned to evaluate the effect of glatiramer in delaying time to confirmed disease progression in 943 patients with PPMS. Unfortunately, it was halted early due to significant dropout of patients (26.4%) and marked slower annual progression rate in the placebo group (16.1% compared to an expected rate of 50%) [65].

**Mitoxantrone**

Mitoxantrone was approved by the FDA in October 2000, and is indicated for the reduction of neurologic disability and/or frequency of clinical relapses in patients with SPMS, PRMS, or worsening RRMS (Table **1**). The approval of mitoxantrone was based on two phase III clinical trials. The first study was a multicenter, double-blind, placebo-controlled, trial conducted in patients with SPMS or PRMS [66, 67] A total of 194 patients were enrolled and 188 patients were included in an intent-to-treat analysis at 24 months. Patients were randomized to receive either mitoxantrone 5mg/m$^2$, mitoxantrone 12mg/m$^2$ or placebo IV every 3 months for 24 months.

In comparing mitoxantrone 5mg/m$^2$, mitoxantrone 12mg/m$^2$ or placebo, the mean EDSS changes was 0.23, 0.13 and 0.23, mean ambulation index changes was 0.41, 0.30 and 0.77, mean number of relapses treated with corticosteroids was 0.73, 0.40 and 1.20, median months to first relapse requiring corticosteroids was 6.9, 20.4, 6.7, and mean standardization neurological status change was 0.38, 1.07, 0.77, respectively (all p values significant).

In regards to the subset of patients undergoing MRI assessment, the number of patients with new gadolinium-enhancing lesions was 11%, 0% and 18% in the mitoxan-

trone 5mg/m$^2$, mitoxantrone 12mg/m$^2$ and placebo groups, respectively (p=0.022). The mean number of patients in which a change in the number of T2-weighted lesions were 34, 28 and 32, respectively.

Mitoxantrone was most frequently reported to cause mild or moderate nausea, urinary tract infections, menstrual disorders including amenorrhea, and mild alopecia, compared to the placebo group. Approximately 9.7% (6/60) of patients in the mitoxantrone 12mg/m$^2$ group discontinued treatment due to the occurrences of leukopenia, depression, decreased left ventricular function, bone pain, emesis, renal failure and prevention of recurrent urinary tract infections, compared to the 3.1% (2/64) in the placebo group due to hepatitis and myocardial infarction. No deaths or serious drug-related events occurred during the study.

The second study was a controlled trial conducted to assess the efficacy and safety of combination mitoxantrone and methylprednisolone in patients with SPMS or worsening RRMS who experienced residual neurological deficit between relapses [66]. At screening, patients were initiated on a two-month protocol consisting of monthly doses of methylprednisolone 1g IV, as well as monthly MRI scans. Patients who had developed at least one new gadolinium-enhancing lesion during this time were randomized and included in the study, A total of 42 patients were then randomized to receive either methylprednisolone 1g IV monthly or approximately 12mg/m$^2$ of mitoxantrone IV plus methylprednisolone 1g IV for a total of 6 months. All completed the study except five patients in the methylprednisolone group, due to lack of efficacy,

More patients in the mitoxantrone plus methylprednisolone group had no new gadolinium-enhancing lesions at 6 months (90% *vs* 31%; p=0.001). In addition, the mean EDSS change among the groups was -1.1 and -0.1 (p=0.013), mean annual relapse rate per patient was 0.7 and 3.0 (p=0.003) and percentage of patients without relapses was 67% and 33% (p=0.031) for combination and methylprenidolone alone groups, respectively.

The most frequently reported adverse effects reported in the mitoxantrone plus methylprednisolone group, versus the methylprednisolone alone group included amenorrhea, alopecia, nausea, and asthenia. Leukopenia, neutropenia, and mild to moderate infections were also reported at a higher rate in the combination therapy group.

In a multicenter study, the efficacy of mitoxantrone over 24 months was compared to placebo in the proportion of patients with confirmed progression of MS [68]. Fifty-one patients with clinically definite or laboratory-supported RRMS were were randomized to receive either mitoxantrone 8mg/m$^2$ IV over 30 minutes monthly for 1 year or placebo.

A statistically significant difference in the proportion of patients with confirmed progression of MS as measured by at least one point on the EDSS was seen at 24 months and the total study period (baseline to 24 months) between the treatment and placebo groups (0% *vs*. 25%, p=0.01; 7% *vs* 37%, p=0.02). No significant differences were noted on the mean change of EDSS scores between the two groups at 12 or 24 months. A significant decrease in the mean number of annual exacerbations was reported when comparing mitaxontrone to placebo at 12 months (0.52 *vs*. 1.54, p=0.001) and

at 24 months (0.37 *vs*. 1.1, p=0.005). The number of exacerbation-free patients were also found to be statistically significant between the groups at 12 months (70% *vs*. 25%, p=0.003) and at 24 months (78% *vs*. 42%, p =0.01). All 51 patients completed the MRI study except 9 patients due to perceptions of treatment inefficacy, lack of compliance or non-medical reasons. No significant differences in the development of new or enlarged lesions were noted at 12 or 24 months between the two study groups, however, a greater reduction in the number of new lesions was noted in the mitoxantrone group.

The most frequently reported side effects in the mitoxantrone group were mild or moderate nausea, urinary tract and upper respiratory infections, headache, and diarrhea. Five women experienced transient amenorrhea.

**Natalizumab**

Natalizumab (Tysabri®) is the first recombinant humanized monoclonal antibody that was approved by the FDA in November 2004 for use in RRMS (Table **1**). It was voluntarily withdrawn from the market by the manufacturer in February 2005 due to 2 reports of progressive multifocal leukoencephalopathy (PML), including one fatal case. In addition, a third patient developed PML in another open label trial involving the use of natalizumab in Crohn's disease [69]. In July 2006, after a thorough review of all patients exposed to this agent and additional clinical trials evaluating its safety and efficacy, the FDA allowed natalizumab to return to the market with a block-box warning of PML and under strict safety restrictions and provisions. This agent is only available to certified practitioners, infusion centers and pharmacies registered through a special restricted distribution program known as the TOUCH™ (Tysabri® Outreach: Unified Commitment to Health) Prescription Program [69, 70]. Most recently, two European patients were reported to develop PML prompting the FDA to report an alert in August 2008. Natalizumab is currently indicated for monotherapy in the treatment of relapsing forms of MS. It is used to delay the accumulation of physical disability and to reduce the frequency of clinical exacerbations.

Two phase III clinical trials were pivotal in the approval of natalizumab for use in patients with MS. In the first study, 942 patients with a diagnosis of relapsing MS were included [71, 72]. This was a multicenter, double-blind, placebo-controlled, trial which enrolled patients who had not received INFβ or glatiramer for the previous 6 months. Eligible patients were randomly assigned (2:1) to receive either natalizumab 300mg or placebo by IV infusion every 4 weeks for up to 116 weeks.

Results revealed better clinical and MRI endpoints for patients in the natalizumab group at 2 years (p<0.001). Seventeen percent of the natalizumab group *versus* 29% of the placebo group had a sustained increase in disability. There was a relative risk reduction of 42% at 2 years in the natalizumab group (0.22 *vs*. 0.67 annual relapse rate). More patients in the natalizumab group remained relapse free at two years (67% *vs*. 41%).

The most frequently reported serious adverse effects among the natalizumab and placebo groups were infections, acute hypersensitivity reactions, depression, and cholelithiasis. Other adverse events which were significantly more common in the natalizumab group included headache, fatigue, arthralgia, pain in extremity, abdominal discomfort, diarrhea and rash.

The second multicenter, double-blind, placebo-controlled parallel-group trial [71, 73] enrolled patients with RRMS (n = 1196), however, only 1171 of these patients were included in data analysis. All patients received treatment with INFβ-1a for at least 12 months and experienced at least one relapse during the 12-month period prior to study initiation. Patients were randomly assigned to receive either 300mg of natalizumab or placebo IV every 4 weeks, in addition to 30mcg of INFβ-1a administered IM once weekly for up to 116 weeks. Combination therapy was reported to have a 24% reduction in the relative risk of sustained disability (p=0.02), with a lower cumulative probability of sustained disability progression at two years (23% *vs*. 29%; p=0.02). Combination therapy was also associated with a lower annualized rate of relapse as compared to INFβ-1a (0.38 *vs*. 0.82 at one year, p<0.001; 0.34 *vs*. 0.75 at two years; p<0.001). The risk of relapse was reported to be 50% lower with combination therapy (p<0.001); 54% in the combination group and 32% in the INFβ-1a group alone (p<0.001) were relapse-free at two years. In addition, natalizumab produced a 92% reduction in gadolinium-enhancing lesions (2.4 *vs*. 0.2; p<0.001), an 83% reduction in new or enlarging T2-hyperintense lesions (11.0 *vs*. 1.9; p<0.001) and a 76% reduction in new T1-hypointense lesions (4.6 *vs*. 1.1; p<0.001) over the two year period.

Commonly reported adverse events of the combination group included anxiety, pharyngitis, sinus congestion and peripheral edema. The incidence of infection was similar in both the combination and INFβ-1a alone group. The most common serious adverse event among both study groups was MS relapse. Appendicitis was also more common in natalizumab patients. The trial was stopped approximately one month prior to the anticipated date due to 2 cases of natalizumab associated PML.

In another multicenter, double-blind, placebo-controlled trial, a total of 213 patients with clinically definite or laboratory-supported definite RRMS or SPMS were enrolled and included in the intent-to-treat analysis [74]. Patients were randomized to receive either natalizumab 3mg/kg, natalizumab 6mg/kg, or placebo administered by IV infusion every 28 days for a total of 6 months. Physical and neurological examinations were performed at monthly, at which time adverse events were also recorded.

Over 6 months, reductions in the number of new lesions in the natalizumab 3mg/kg, 6mg/kg and placebo groups were 0.7, 1.1 and 9.6 per patient, respectively)p<0.001;). Relapses were seen in 13, 13 and 27 patients respectively, (p=0.02). The placebo group reported a slight worsening in well-being with a mean decrease of 1.38mm (on a 100-mm visual-analogue scale). An improvement in well-being was reported in both the 3mg/kg natalizumab and 6mg/kg natalizumab groups (a mean increase of 9.49mm and 6.21mm, respectively). The 3mg/kg natalizumab group had a mean of 0.7 new gadolinium-enhancing lesions per patient (p<0.001), 1.1 in the 6mg/kg natalizumab group, and 9.6 in the placebo group (p<0.001). No significant difference in values was detected between the two natalizumab groups.

Subgroup analysis demonstrated the efficacy of natalizumab over placebo in reducing new enhancing lesions in both RRMS and SPMS patients. Natalizumab also caused marked reductions in the numbers of persistent enhancing lesions and new active lesions, the total volume of enhancing lesions, and the percentage of scans showing activity. In addition, fewer natalizumab-treated patients requires corticosteroid treatment for relapses. No significant changes in the EDSS scores were observed in any group during the six-month treatment period.

Adverse effects were similar in all groups and included headache, infection, urinary tract infection, pharyngitis, myasthenia, paresthesia, rash, pruritis, back pain, diarrhea and sinusitis. One death due to pleural carcinomatosis complicated by hemothorax was reported in the placebo group.

### Comparative Studies

INFβ-1b has been directly compared to INFβ-1a 30 mcg IM formulation in patients with RRMS in a multi-center, randomized, 2-year trial (INCOMIN trial), which enrolled 188 patients with RRMS [74]. Significantly more patients receiving IFNβ-1b remained relapse-free (51% *vs.* 36%) and remained free from new MRI lesions (55% *vs.* 26%). It, however, was associated with high level of neutralizing antibodies (22% *vs.* 6%; $p < 0.01$) [75]. Headache and injection site reactions occurred more frequently in the IFNβ-1b treated patients [76]. An open-label Danish study showed no differences in relapses, disease progression or adverse effects between IFNβ-1b and IFNβ-1a SC formulation after one year of therapy [77].

A small, single-blinded, randomized, 2-year trial suggested that IFNβ-1b and both IFNβ-1a formulations provided statistically significant efficacy in RRMS patients [78]. Subcutaneous products, but not intramuscular product, were associated with significant reductions in EDSS. An open label study (n = 58) has suggested that IFNβ-1b was equally effective and tolerated as glatiramer 20 mg daily or every other day [79]. All treatments provided comparable benefits in relapses and EDSS scores. IFNβ-1b was associated with a slower progression in disability but glatiramer was better tolerated. Another open label study suggested that INFβ-1b and glatiramer, but not INFβ-1a (Avenex®) significantly reduced relapse rate [80].

A retrospective, open-label study also suggested glatiramer reduced relapses more than interferons [81]. An open label study showed that delaying therapy with glatiramer increases the risk of neurologic disability in patients with RRMS [81]. When compared to IFNβ-1b in an open label study involving RRMS patients, glatiramer was associated with better side effect profile, whereas INFβ-1b slowed the progression of disability more significantly [82]. The combination therapy with INFβ-1b and glatiramer in the treatment of MS is being explored [83].

### DRUGS UNDER DEVELOPMENT

Cladribine is a purine nucleoside anti-neoplastic agent that is postulated to modulate the T-cell mediated processes in MS [84]. To date, cladribine has been studied in one phase III trial in patients with chronic progressive MS. In the double-blind, randomized, placebo controlled trial, patients started with a 4-week screening phase, followed by one year of a double-blind phase, and then entered into a 6 year extension study. In group 1, patients were given cladribine 0.07 mg/kg/day SC for 5 consecutive days for 6 months, followed by 2 months of placebo; in group 2, patients were given cladribine SC 0.07 mg/kg/day for 5 consecutive days for 2 months, followed by placebo for 6 months; in group 3, patients were given placebo for 8 months. At the end of the treatment phase, the cladribine groups did not differ from the placebo group in terms of disability scores, but did show fewer gadolinium-enhancing lesions on MRI. At the end of the study, the proportion of patients with gadolinium-enhancing lesions decreased by 70% in the group 1, and by 83% in group 2, as compared to 18% in the placebo group. Treatment-related adverse events included muscle weakness, hypertonia, purpura, rhinitis, ataxia, and upper respiratory tract infection.

Fingolimod is a sphingosine-1-phosphate (S1P) receptor agonist which causes down-regulation of the S1P receptor, leading to sequestration of T-cells in the thymus and secondary lymphoid organs [85]. Suppressing the migration of T-cells can help reduce the autoimmune activity in MS. Fingolimod has been evaluated in the treatment of RRMS in one phase II trial [86]. In the double-blind, placebo-controlled study, 281 patients received oral regimens of either fingolimod 1.25mg, 5mg or placebo once daily for 6 months. In the extension phase of the study, patients receiving placebo were crossed over to receive fingolimod at 1.25 mg or 5 mg daily for 6 months. Patients initially receiving fingolimod continued the drug at the same dose for another 6 months. At the end of the first 6 months, the number of gadolinium-enhanced lesions was lower in the fingolimod 1.25 mg and 5 mg groups than in the placebo group (8.4, 5.7, and 14.8 lesions, respectively; p<0.001). At the end of 12 months, the number of gadolinium-enhanced lesions was similar in patients who received placebo followed by fingolimod as in patients who had received fingolimod for the entire 12 months. Adverse event occurring commonly in the fingolimod patients included nasopharyngitis, dyspepsia, headache, somnolence, diarrhea, and nausea. Elevations in alanine transaminase were seen in the fingolimod 1.25 mg and 5 mg group. A phase III study is currently underway [87].

### CONCLUSION

MS continues to be a complex and devastating disease. Many questions still exist regarding its etiology and pathophysiology, making an appropriate approach to treatment challenging. A few disease modifying agents are available. While interferon beta 1a and 1b have relatively long-term clinical experience in patients with RRMS, the beta 1b formulation recently demonstrated its effect in delaying the time to diagnosis of definite MS. Glatiramer and natalizumab have both established efficacy in relapsing forms of multiple sclerosis; whereas mitoxantrone is more commonly used in patients with advanced disease. Although all disease modifying agents reduce MS relapses by interacting with the immunologic system, each of them have side effects that requires specific clinical monitoring. More data on comparative efficacy and long term information on safety are eagerly awaited. The effects of investigational compounds are also greatly anticipated, and may provide hopes of addressing the

challenges in reducing or delaying the distressing MS-related health concerns.

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