# Relapsing–Remitting Multiple Sclerosis—
# Current Treatment Options and Perspectives for the Future

Alex Rae-Grant, MD, FRCP(C)[1] and Daniel Ontaneda, MD[2]

1. Neurologist; 2. Neurology Resident, Mellen Center for Multiple Sclerosis, Neurological Institute, Cleveland Clinic

## Abstract

Multiple sclerosis (MS) is the most prevalent demyelinating condition of the central nervous system and produces significant disability over time. For many years it was considered to be an untreatable disease, but great advances have been made in the treatment of MS in the last 20 years. There are currently six US Food and Drug Administration (FDA)-approved disease-modifying agents for the relapsing form of the disease. We review in detail these medications and the pivotal trials leading to their approval. We will briefly review non-FDA-approved medications already used in MS. We will also discuss some of the medications currently being studied in phase II and III trials that are not yet approved for use in MS.

## Basic Concepts of Multiple Sclerosis

Multiple sclerosis (MS) is a relapsing inflammatory disease of the central nervous system. It is marked pathologically by discrete areas of demyelinated brain tissue in the white matter with accompanying inflammation.[1] It is now evident that axonal loss accompanies demyelination early on in the disease process.[2] Cortical pathology may be as important as white-matter changes in MS.[3]

MS has been modeled as an autoimmune disorder mediated by T-cell responses.[4,5] A chemokine response by T cells mediates activation of macrophages and microglial cells, which in turn are the main effectors of myelin destruction.[6,7] B-cell activity has also been implicated in the pathogenesis of MS. B cells may sustain T-cell activation.[8] Neurodegeneration also occurs, especially in the progressive phase of the disease.[9] Different inflammatory and neurodegenerative processes govern tissue injury in MS.[10,11] Multiple pharmacologic pathways can be targeted to potentially treat MS. It is possible that differing pathologic processes in different lesion types explain the variability in clinical response to medications.[12]

The occurrence of new MS symptoms is thought to be the result of new lesion formation, which has been documented in several serial imaging studies.[13] However, there is a discrepancy between the clinical and radiologic picture in MS. New magnetic resonance imaging (MRI) lesions form five to 10 times as often as there are new clinical events.[14] It is for this reason that MRI has been used as a surrogate marker of efficacy in MS trials.

## Clinical Symptoms and Diagnosis of Relapsing–Remitting Multiple Sclerosis

MS can occur in both relapsing and progressive forms. The most common presentation of MS includes an initial relapsing illness followed by a later progressive course.[15] Eighty percent of patients initially diagnosed with MS have a relapsing form.[16] Currently, clinical criteria for establishing a diagnosis of relapsing MS require the presence of two episodes of demyelination separated in time and in space.[17] Clinical information alone is sufficient to establish a diagnosis; however, when criteria for dissemination in time and space cannot be met on clinical grounds alone, MRI and cerebrospinal fluid (CSF) studies may be used to diagnose MS.

Imaging criteria for dissemination in time and space have been extensively studied and form part of the diagnostic criteria for MS.[18,19] In progressive MS, criteria for dissemination in time and space are provided by a combination of MRI, CSF, and visual evoked potentials. A European group has suggested changing these criteria to include patients with one clinical demyelinating event who, on MRI, have both new enhancing lesions and evidence of older lesions, but this has not yet been widely adopted.[20]

Patients who have experienced a single clinical episode but do not meet criteria for dissemination in time and space have been proposed to have a clinically isolated syndrome (CIS) of demyelination.[21] Patients with a CIS are felt to be at risk for developing MS, especially if MRI of the brain shows lesions consistent with MS.[22]

**Table 1: US Food and Drug Administration-approved Therapies in Multiple Sclerosis**

| | Dosage | Route | Approved Uses | | |
| --- | --- | --- | --- | --- | --- |
| | | | RRMS | CIS | SPMS with Relapses |
| Interferon-beta-1b | 250mcg every other day | SC | Yes | Yes | Yes |
| Interferon-beta-1a | 30mcg weekly | IM | Yes | Yes | No |
| Interferon-beta-1a | 22 or 44mcg 3 times per week | SC | Yes | Yes | No |
| Glatiramer acetate | 20mg daily | SC | Yes | Yes | No |
| Natalizumab | 300mg every 4 weeks | IV infusion | Yes | No | No |
| Mitoxantrone | 12mg/m$^2$ every 3 months | IV infusion | Yes (worsening) | No | Yes |

*CIS = clinically isolated syndrome; IM = intramuscular; IV = intravenous; RRMS = relapsing–remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary progressive multiple sclerosis.*

## Therapies for Relapsing Multiple Sclerosis

Historically, MS was considered to be an untreatable and incurable disease. Disease-modifying therapy for MS was first approved by the US Food and Drug Adminstration (FDA) in 1993.[23] Since then, five additional medications have been approved and all are currently used to treat MS patients (see *Table 1*). Beta interferon (IFN) was the first approved medication used to treat MS. IFN-γ was known to induce animal models of demyelination and hence IFN-β was studied due to its antagonistic effects on IFN-γ. It was in 1993 that the first results of a large randomized trial of IFN-β1-b were published, leading to FDA approval of medications for treatment of MS. This was followed by phase II and phase III trials studying IFN-β1-a and glatiramer acetate (GA), which subsequently led to FDA approval of these medications. A second brand of IFN-β1-b was recently approved for the US market without additional testing. A single chemotherapeutic agent, mitoxantrone, has been approved for use in worsening relapsing–remitting multiple sclerosis (RRMS) and secondary progressive MS (SPMS). Natalizumab was the first monoclonal antibody used to treat RRMS and was approved in 2004. No known therapy has proved effective for primary progressive MS (PPMS) despite multiple negative trials.

### IFN-β1-b

IFN-β1-b is FDA-approved to treat RRMS, CIS, and relapsing SPMS. IFN-β1-b is composed of 165 amino acids arranged in five paired alpha helices and is produced in *Escherichia coli* with a molecular weight of 18.5kDa.[24,25] The medication is administered subcutaneously at a dose of 250mcg 8 million units [MUI]) every other day. The medication is available in two different commercial forms. IFN-β1-b binds to receptors on the cell surface and induces transcription and signal activation within the cell.[26] The exact mechanism of action of IFN-β1-b is not fully understood; however, it is felt to exert its effects by inhibiting T-cell activation,[27] inducing T-cell apoptosis,[28] and decreasing the permeability of the blood–brain barrier.[29]

IFN-β1-b has been studied in phase III clinical trials in RRMS, SPMS, and CIS. The efficacy of the medication in RRMS was demonstrated in the pivotal 1993 trial.[30] This trial was double-blinded and placebo-controlled and studied a total of 372 subjects. Placebo was compared with two different IFN-β1-b doses. Primary end-points for the trial included exacerbation rates and proportion of exacerbation-free patients. The results demonstrated that patients on both doses of study medication had a significantly lower exacerbation rate compared with controls. The higher-dose group (8MIU) was more effective at reducing the exacerbation rate than the low-dose group (1.6MIU). MRI data from these patients also

demonstrated a decrease in active scans and number of new lesions that was statistically significant.[31] IFN-β1-b was well tolerated in most patients. Adverse effects leading to study drop-out included liver enzyme abnormalities, injection-site pain, fatigue, cardiac arrhythmia, allergic reaction, nausea, headache, and flu-like syndrome. Five-year follow-up data showed that the effects on relapse and MRI data were sustained.[32] Depression and suicide were identified as adverse effects during years three and four of the trial.

The BEtaferon© in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) trial studied the efficacy of IFN-β1-b in CIS.[33] The trial was a double-blind, placebo-controlled phase III study that examined a total of 468 patients who had a single clinical event and at least two silent brain MRI lesions. The results showed that IFN-β1-b delayed the conversion from CIS to RRMS compared with placebo. Follow-up data at three years showed that patients with early treatment had less confirmed Expanded Disability Status Scale (EDSS) progression during the study time.[34]

The effect of IFN-β1-b in SPMS has been studied in two large phase III trials in Europe and North America. The North American trial studied 939 subjects and did not meet its primary end-point (time to EDSS progression). However, there were fewer relapses and MRI burden was lower in the treatment groups. The European trial met its primary end-point of time to confirmed progression of disability.[35] This study additionally found that IFN-β1-b delayed progression from a time of nine to 12 months over the two- to three-year study period. Adverse effects were similar to those described above for both these trials. These populations differed in that patients were younger and had more relapses in the European group.

### IFN-β1-a

IFN-β1-a is approved for use in RRMS and CIS. IFN-β1-a is identical to human IFN and is produced in mammalian (hamster) cells. It has a molecular weight of 25.5kDa. IFN-β1-a is available in two forms. The subcutaneous (SC) form is used at a dose of 22 or 44mcg three times weekly and is approved for use in relapsing SPMS. The intramuscular (IM) form is administered at a dose of 30mcg once weekly. The mechanism of action of IFN-β1-a is similar to that of IFN-β1-b, as described above.[36]

#### IFN-β1-a Intramuscular

The IM formulation of IFN-β1-a was studied in RRMS in a placebo-controlled phase III trial involving a total of 301 patients. The treatment group had decreased time to sustained EDSS progression, fewer relapses, and a lower number and volume of gadolinium-enhancing lesions.[37] The

## Table 2: Medications Used for Relapsing–Remitting Multiple Sclerosis Not Currently Approved

| Generic Name | Route |
|---|---|
| Azathioprine | PO |
| Methotrexate | PO |
| Cyclophosphamide | IV |
| Mycophenolate mofetil | PO |

*IV = intravenously; PO = orally.*

## Table 3: Future Prospective Medications for Relapsing–Remitting Multiple Sclerosis

| Generic Name | Route | Mechanism of Action | Adverse Effects |
|---|---|---|---|
| Fingolimod | PO | Sphingosine 1-phosphate modulator, sequesters lymphocytes in secondary lymphoid organs | Herpes encephalitis, disseminated VZV infection |
| Cladribine | PO | Toxic metabolite induces T-cell apoptosis | Localized herpes infection, lymphocytopenia |
| BG-12 | PO | Alters gene expression involved in oxidative stress and immune homeostasis | Flushing, abdominal pain |
| Teriflunomide | PO | Pyrimidine synthesis inhibitor in T cells | Elevated liver enzymes, hepatic dysfunction, infections |
| Rituximab | IV | Targets CD20, B-cell depletion | Infusion reactions, PML (lymphoma patients) |
| Alemtuzumab | IV | Targets CD52, lymphocyte suppression | Immune thrombocytopenic purpura, thyroid dysfunction |
| Daclizumab | IV | Targets CD25, blocks IL-2 binding, T-cell regulation | Cardiac toxicity, infections |

*IL = interleukin; IV = intravenously; PML = progressive multifocal leukoencephalopathy; PO = orally; VZV = varicella zoster virus.*

annual relapse rate was reduced by approximately one-third. No major adverse effects were reported in the study. IM IFN-β1-a was the first agent studied in CIS. The controlled high-risk subjects Avonex© multiple sclerosis prevention study (CHAMPS) trial was a placebo-controlled phase III trial that included 383 patients with a single clinical and exam-documented event and at least two MRI lesions.[38] The results showed that patients on IM IFN-β1-a had a lower cumulative probability of developing clinically definite MS (CDMS) compared with placebo. IFN-β1-a has not shown efficacy in slowing progression of SPMS.[39]

### IFN-β1-a Subcutaneous

The SC formulation of IFN-β1-a has been studied in RRMS, CIS, and SPMS. The Prevention of Relapses and Disability by IFN-β1-a Subcutaneously in Multiple Sclerosis (PRISMS) trial studied 560 patients in a phase III double-blinded, placebo-controlled fashion. It found that patients on SC IFN-β1-a three times a week at high doses (44mcg) and low doses (22mcg) had a significantly lower relapse rate than placebo.[40] Time to first relapse was also increased in both IFN arms. MRI data from

that same cohort of patients showed the medication arms to have a decreased active lesion burden compared with placebo.[41]

The effect of IFN-β1-a SC on CIS was studied in the Early Treatment of Multiple Sclerosis study group (ETOMS) trial.[42] In total, 309 patients were randomized to placebo or 22mcg of IFN-β1-a SC three times weekly. Results showed that time to conversion of CDMS was delayed in the treatment group, and fewer patients in the treatment group converted to CDMS over the two-year follow-up.

IFN-β1-a SC has also been studied in SPMS. The Secondary Progressive Efficacy Clinical Trial of Recombinant IFN-β1-a in MS (SPECTRIMS) trial studied 618 patients with SPMS in a placebo-controlled fashion. Treatment was allocated at 44 and 22mcg doses. No effect on progression was observed in the treatment groups. A reduction in relapse rate was observed in both treatment groups.[43]

### Glatiramer Acetate

GA is approved for use in relapsing forms of MS. GA is a synthetic copolymer that resembles the amino-acid sequence of myelin basic protein (MBP).[44] It is used as a daily subcutaneous 20mg dose. Multiple mechanisms of action have been described for GA. GA competes with MBP at the MHCII molecule. It then forms a MHC/GA complex that competes with the MBP/MHC complex at the T-cell receptor. Additionally, GA induces activation of regulatory TH-2 cells. GA is also felt to act as a ligand and induce tolerance of MBP-specific T cells.

The clinical effects of GA in RRMS have been studied in a placebo-controlled, randomized phase III trial. The trial involved 251 patients and showed that GA reduced the two-year relapse rate compared with placebo.[45] The treatment was well tolerated except for the occurrence of local skin reactions and a systemic self-limited reaction present at least once in 15% of patients over the course of the study. A second placebo-controlled phase III clinical trial (239 patients) showed that patients taking GA had a significantly reduced number of gadolinium-enhancing lesions during a nine-month study period.[46]

The effectiveness of GA in CIS was studied in the Early Glatiramer Acetate Treatment in Delaying Conversion to Clinically Definite Multiple Sclerosis in Subjects Presenting with a Clinically Isolated Syndrome (PreCISe) trial that studied 481 patients with a single neurologic event and two or more brain MRI lesions.[47] Results showed that patients on GA had a 45% reduced risk for developing CDMS over the 36-month study period. Adverse effects were similar to those described in the RR trials above.

### Mitoxantrone

Mitoxantrone is currently FDA-approved for use in worsening RRMS and SPMS. Mitoxantrone is a 517.4Da anthracenedione derivate that has been used for treatment of lymphoma, leukemias, and breast and prostate cancers.[48] Mitoxantrone is delivered by infusion at a dose of 12mg/m$^2$ of body surface every three months. Due to dose-dependent toxicity a therapeutic ceiling is reached at 140mg/m$^2$. Mitoxantrone is a topoisomerase II inhibitor and exerts its beneficial effects in MS by a number of different mechanisms, including inhibiting proliferation of T and B cells, enhancing suppressor T-cell functions, and limiting the secretion of pro-inflammatory chemokines.[49]

Mitoxantrone has been studied in the more advanced stages of MS. A randomized placebo-controlled phase III trial studying 194 patients with worsening RRMS or SPMS showed a benefit of mitoxantrone in a composite clinical outcome.[50] In active RRMS mitoxantrone has been shown to reduce the number of new enhancing lesions compared with methylprednisolone.[51] Adverse events are a major consideration when using this medication. Cardiac toxicity has been well documented[52] and an echocardiogram or multigated acquisition (MUGA) scan is conducted before each dose in the US. This medication has also been related to cases of acute myeloid leukemia (0.15–0.80% incidence).[53]

## Natalizumab

Natalizumab is the first monoclonal antibody approved for use in MS. Currently, natalizumab is FDA-approved for RRMS, but primarily for patients with continued disease activity despite disease-modifying therapy. Natalizumab is a humanized monoclonal antibody directed at $\alpha_4$ integrins.[54] Binding of natalizumab to $\alpha_4\beta_1$ integrin suppresses leukocyte entry into the CNS.[55] Natalizumab is administered by monthly intravenous infusion at a dose of 300mg.

The clinical effects of matalizumab have been studied in two large phase III controlled trials. The Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM) multicenter, placebo-controlled, double-blinded trial studied 942 patients with RRMS. Natalizumab was found to decrease the relapse rate by 68% and additionally decreased sustained progression compared with placebo over the three-year study duration.[56] This study also found 92% fewer gadolinium-enhancing lesions compared with placebo.

The Safety and Efficacy of Natalizumab in Combination with Interferon-β1-a (SENTINEL) trial studied 1,171 patients on IFN-β1-a who had suffered at least one relapse over the 12 months preceding trial enrollment. Patients were randomized to natalizumab or placebo in addition to IFN. The study found a relapse rate reduction and a decrease in enhancing lesions as well as a decrease in the sustained progression rate, all in favor of the natalizumab group.[57]

Natalizumab has been generally well tolerated; however, three cases of progressive multifocal leukoencephalopathy (PML) led to voluntary withdrawal of natalizumab for one year.[58–60] Since being re-introduced in 2006, the total number of PML cases reported with the use of natalizumab has exceeded 28, of which eight have been fatal.[61] The rate of PML is less than one per 1,000 in the first year, and rises to 1.5 per 1,000 between years two and three. Treatment for natalizumab-induced PML includes plasma exchange therapy[62] and high-dose intravenous steroids for the occurrence of the immune reconstitution inflammatory syndrome (IRIS).[63]

## Non-US Food and Drug Administration-approved Medications in Multiple Sclerosis

Non-FDA-approved medications have been used and studied in MS historically. The majority of these are immunosuppressive or chemotherapeutic agents (see *Table 2*). Azathioprine is an oral immunosuppressant, and a recent Cochrane database analysis found that the medication significantly reduced the number of patients who had relapses during one year of treatment.[64] Cyclophosphamide is an intravenous immunosuppressant that has been studied in aggressive MS that has not responded to IFN or copaxone.[65] Methotrexate has also been used orally for MS. Data from a Cochrane review showed a trend for improvement in RRMS; however, this was non-significant.[66] There are limited data for the use of mycophenolate mophetil in MS and further clinical trials are needed to establish the efficacy of this medication.[67]

## US Food and Drug Administration-approved Non-disease-modifying Agents

Extended-release fampridine (Dalfampridine) is a twice-daily oral medication that is FDA-approved for improving speed of walking in MS patients. A placebo-controlled phase II trial found that fampridine improved walking times in treatment responders with all types of MS. The medication was well tolerated, but it carried a significant risk of lowering the seizure threshold in a dose-dependent manner.[68]

## Treatments Currently Under Investigation

Fingolimod is a sphingosine 1-phosphate receptor modulator that sequesters T and B cells in secondary lymphoid organs.[69] It was studied in a recent double-blind parallel phase III study in which 1,153 RRMS patients were treated with fingolimod or IFN-β1-a IM.[70] Fingolimod was found to reduce annualized relapse rate compared with IFN-β1-a IM. Two deaths were reported in the study group from herpes simplex virus (HSV) encephalitis and disseminated varicella zoster infection. FDA approval is currently pending (see *Table 3*).

Cladribine, through its active metabolite 2-chlorodeoxyadenosine triphosphate, induces apoptosis of lymphocytes.[71] It has been studied in a placebo-controlled clinical phase III trial in RRMS that studied 1,326 patients.[72] The study found a decreased relapse rate and there was a higher relapse-free rate in the cladrabine group. Significant adverse effects included lymphocytopenia and localized herpes zoster.

BG-12 (oral dimethyl-fumarate) is a fumaric acid derivative that has a complex mechanism of action involving altered gene expression crucial in oxidative stress and immune homeostasis.[73] BG-12 was studied in a randomized, placebo-controlled phase IIb trial in 257 patients with RRMS where the number of new gadolinium-enhancing lesions was the primary end-point. Subjects treated with BG-12 had a reduction in gadolinium-enhancing lesions of 69% compared with placebo. Adverse effects included abdominal pain and flushing. Phase III trials are under way.

Rituximab is a chimeric monoclonal antibody directed at CD20. It acts in MS by inducing B-cell depletion. It has been studied in a phase II clinical trial compared with placebo and showed reduced numbers of gadolinium-enhancing and new gadolinium-enhancing lesions.[74] A humanized CD20 monoclonal antibody (ocrelizumab) has been developed and is undergoing clinical trials. Teriflunomide is another oral medication that acts by inhibiting pyrimidine synthesis and has met primary end-points in RR phase II trials.[75] Alemtuzumab and daclizumab are monoclonal antibodies directed at CD52 and CD25, respectively; both have been studied in phase II trials.[76,77]

## Conclusion

There are currently seven FDA-approved disease-modifying therapies for relapsing forms of MS. Good level I evidence exists for all these compounds. Natalizumab and novantrone are effective medications but their use may be limited by their adverse effect profile, which includes potentially lethal conditions. Fampridine is an oral medication that improves walking speed in various types of MS and is FDA-approved for that use. Medications that appear to be close to FDA approval after large phase III trials include cladribine and fingolimod. The potential adverse effects of these medications will be weighed against their benefit and ease of use (both are oral medications).

There are currently multiple medications under phase II–III testing that may bring further options for treatment in the future. Treatment of MS in the near future will include multiple agents with diverse mechanisms of action, and clinicians will need to know how to treat and identify the adverse events that result from these agents. ■

Alex Rae-Grant, MD, FRCP(C), is a Neurologist at the Mellen Center for Multiple Sclerosis (MS) and the Neurological Institute at the Cleveland Clinic. His area of expertise is in MS and related diseases. He is also involved in educational activities at the Cleveland Clinic and regionally, and participates in many clinical trials in MS. Dr Rae-Grant has written two textbooks: *Neurology for the House Officer* and *The Five-minute Consult in Neurology*.

Daniel Ontaneda, MD, is a Neurology Resident at the Mellen Center for Multiple Sclerosis (MS) and the Neurological Institute at the Cleveland Clinic, where he is completing his fourth year of post-graduate training. He will be completing a three-year clinical neuro-immunology fellowship at the Mellen Center for MS in conjunction with an MSc in clinical research at Case Western Reserve University. Dr Ontaneda graduated from the Pontifical Catholic University and completed a post-doctoral fellowship at Baylor College of Medicine.

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