

THE USE OF DISEASE-MODIFYING THERAPIES IN MULTIPLE SCLEROSIS:

Principles and Current Evidence

A Consensus Paper by the
Multiple Sclerosis Coalition



Updated September 2018
Original July 2014



DISCLOSURES

2018 Revision -Writing Team

Kathleen Costello, MS, ANP-BC, MSCN – Nothing to disclose

Rosalind Kalb, PhD – Consultant: Sanofi-Genzyme and Novartis Pharmaceuticals

Reviewers

Jack Antel, MD^a – Advisory and/or data safety monitoring board: Biogen, Medday Laboratory support through McGill University: Mallinckrodt, Revalesio, Medday, Roche (Canada); Multiple Sclerosis Journal: Co-Editor for the Americas.

Brenda Banwell, MD^a – Non-remunerated consultant: Biogen, Novartis Pharmaceuticals, Sanofi US; Central MRI reviewer for prior trial for Novartis; Grant Support: National Multiple Sclerosis Society, Canadian Multiple Sclerosis Scientific Research Foundation.

Aliza Ben-Zacharia, DrNP, ANP, MSCN^a – Consultant: Biogen, EMD Serono, Novartis Pharmaceuticals, Genentech, Genzyme Corporation; Grant support: Biogen, Novartis Pharmaceuticals.

James Bowen, MD^a – Consultant: Biogen IDEC, EMD Serono, Genentech, Novartis; Speaker: Acorda Therapeutics, Biogen IDEC, EMD Serono, Genentech, Novartis, Teva Neuroscience; Grant support: Alexion, Alkermes, Biogen IDEC, Celgene, Genzyme, Genentech, Novartis, TG Therapeutics; Shareholder: Amgen.

Bruce Cohen, MD^a – Consultant: Biogen-Idec, EMD Serono, Celgene; Funded Institutional Research through Northwestern University, Novartis Pharmaceuticals, Genentech / Hoffman La Roche, MedDay.

Bruce Cree, MD, PhD^b – Consultant: Abbvie, Biogen, EMD Serono, Genzyme Corporation, Aventis, MedImmune, Novartis Pharmaceuticals, Teva Pharmaceuticals; Grant/research support (including clinical trials): Acorda Therapeutics, Avanir Pharmaceuticals, Biogen, EMD Serono, Hoffman La Roche, Novartis Pharmaceuticals.

Suhayl Dhib-Jalbut, MD^a – Grant support: Teva Pharmaceuticals, Biogen, Bayer.

David E. Jones, MD^c – Past consultant: Biogen, Genzyme Corporation, Novartis Pharmaceuticals; Past grant support: National Multiple Sclerosis Society, Biogen.

Daniel Kantor, MD^d – Consultant: Actelion Pharmaceuticals, Avanir Pharmaceuticals, Biogen, Celgene Corporation, Genzyme Corporation, Mylan, Novartis Pharmaceuticals, Osmotica Pharmaceutical; Speaker: Avanir Pharmaceuticals, Biogen, Genzyme Corporation, Novartis Pharmaceuticals; Grant support: Actelion Pharmaceuticals, Biogen, Genzyme Corporation, Novartis Pharmaceuticals.

Flavia Nelson, MD^b – Consultant for Advisory Boards or Speaker: Biogen, Novartis Pharmaceuticals, Teva Pharmaceuticals, Bayer HealthCare, Mallinckrodt, Genzyme Corporation; Grant support: National Institutes of Health.

Nancy Sicotte, MD^a – Grant support: National Multiple Sclerosis Society, Guthy-Jackson Charitable Foundation, Race to Erase MS, Patient-Centered Outcomes Research Institute (PCORI).

^aReviewed original, March 2015, July 2016, March 2017, September 2018 updates

^bReviewed original only

^cReviewed March 2015, July 2016, March 2017 updates

^dReviewed original, March 2015, July 2016, September 2018 updates

Original Writing and Development Team

Kathleen Costello, MS, ANP-BC, MSCN – Nothing to disclose

June Halper, MSN, APN-C, MSCN, FAAN – Nothing to disclose

Rosalind Kalb, PhD – Nothing to disclose

Lisa Skutnik, PT, MA, MA – Consultant: Biogen, Sanofi-Genzyme

Robert Rapp, MPA* – Nothing to disclose

*deceased

Principles and Current Evidence

A Consensus Paper by the Multiple Sclerosis Coalition

ABSTRACT

Purpose: The purpose of this paper, which was developed by the member organizations of the Multiple Sclerosis Coalition*, is to summarize current evidence about disease modification in multiple sclerosis (MS) and provide support for broad and sustained access to MS disease-modifying therapies for people with MS in the United States.

Development Process: The original writing and development team comprised of professional staff representing the Coalition organizations (Rosalind Kalb, Kathleen Costello, June Halper, Lisa Skutnik and Robert Rapp) developed a draft for review and input by nine external reviewers (Brenda Banwell, Aliza Ben-Zacharia, James Bowen, Bruce Cohen, Bruce Cree, Suhayl Dhib-Jalbut, Daniel Kantor, Flavia Nelson and Nancy Sicotte). The reviewers, selected for their experience and expertise in MS clinical care and research, were charged with ensuring the accuracy, completeness and fair balance of the content. The revised paper was then submitted for review by the medical advisors of the Coalition member [organizations](#).

The final paper, incorporating feedback from these advisors, was endorsed by all Coalition members, and subsequently by Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS), and published in November 2014.

Updates with Reviews by External Reviewers and ACTRIMS for their Endorsement:

March 2015
July 2016
March 2017
September 2018

Conclusions: Based on a comprehensive review of the current evidence, the Multiple Sclerosis Coalition* states the following:

Treatment Considerations:

- Initiation of treatment with an FDA-approved disease-modifying therapy is recommended:
 - As soon as possible following a diagnosis of relapsing multiple sclerosis, regardless of the person's age
 - For individuals with primary progressive multiple sclerosis, with an agent approved for this phenotype
 - For individuals with a first clinical event and MRI features consistent with MS in whom other possible causes have been excluded
 - For individuals with progressive MS who continue to demonstrate clinical relapses and/or demonstrate inflammatory activity
- Clinicians should consider prescribing a high efficacy medication such as alemtuzumab, fingolimod, ocrelizumab or natalizumab for newly-diagnosed individuals with highly active MS.

*The Multiple Sclerosis Coalition was founded in 2005 to increase opportunities for cooperation and provide greater opportunity to leverage the effective use of resources for the benefit of the MS community. Member organizations include Accelerated Cure, Can Do Multiple Sclerosis, Consortium of Multiple Sclerosis Centers, International Organization of Multiple Sclerosis Nurses, Multiple Sclerosis Association of America, Multiple Sclerosis Foundation, National Multiple Sclerosis Society and United Spinal Association. MS Views and News serves as an affiliate member (since 2015).

- Clinicians should also consider prescribing a high efficacy medication for individuals who have breakthrough activity on another disease-modifying therapy, regardless of the number of previously used agents.
- Treatment with a given disease-modifying medication should be continued indefinitely unless any of the following occur – in which case an alternative disease-modifying therapy should be considered:
 - Sub-optimal treatment response as determined by the individual and his or her treating clinician
 - Intolerable side effects, including significant laboratory abnormalities
 - Inadequate adherence to the treatment regimen
 - Availability of a more appropriate treatment option
 - The healthcare provider and patient determine that the benefits no longer outweigh the risks
- Movement from one disease-modifying therapy to another should occur only for medically appropriate reasons as determined by the treating clinician and patient.
- When evidence of additional clinical or MRI activity while on consistent treatment suggests a sub-optimal response, an alternative regimen (e.g., different mechanism of action) should be considered to optimize therapeutic benefit.
- The factors affecting choice of therapy at any point in the disease course are complex and most appropriately analyzed and addressed through a shared decision-making process between the individual and his or her treating clinician. Neither an arbitrary restriction of choice nor a mandatory escalation therapy approach is supported by data.

Access Considerations:

- Due to significant variability in the MS population, people with MS and their treating clinicians require access to the full range of treatment options for several reasons:
 - Different mechanisms of action allow for treatment change in the event of a sub-optimal response.
 - Potential contraindications limit options for some individuals.
 - Risk tolerance varies among people with MS and their treating clinicians.
 - Route of delivery, frequency of dosing and side effects may affect adherence and quality of life.
 - Individual differences related to tolerability and adherence may necessitate access to different medications within the same class.
 - Pregnancy and breastfeeding limit the available options.
- Individuals' access to treatment should not be limited by their frequency of relapses, level of disability, or personal characteristics such as age, sex or ethnicity.
- Absence of relapses while on treatment is a characteristic of treatment effectiveness and should not be considered a justification for discontinuation of treatment.
- Treatment should not be withheld during determination of coverage by payers as this puts the patient at risk for recurrent disease activity.

Contents

ABSTRACT	3
INTRODUCTION	6
Epidemiology, Demographics, Disease Course	6
Inflammation and CNS Damage	7
OVERVIEW OF FDA-APPROVED DISEASE-MODIFYING AGENTS IN MS.....	9
DISEASE-MODIFYING THERAPY CONSIDERATIONS	13
Disease Factors Highlighting the Importance of Early Treatment	13
Evidence Demonstrating the Impact of Treatment Following a First Clinical Event.....	16
Evidence Demonstrating the Impact of Treatment on Relapsing MS.....	17
Head-to-head comparison data in relapsing MS.....	23
Evidence Demonstrating the Impact of Treatment on Progressive MS.....	24
Evidence Supporting the Need for Treatment to be Ongoing	27
Use of Disease-Modifying Therapies in Pediatric MS	28
Treatment Considerations in Women and Men in Their Reproductive Years	29
Rationale for Access to the Full Range of Treatment Options.....	30
CONCLUSIONS REGARDING THE NEEDS OF PEOPLE WITH MS	36
Treatment Considerations	36
Access Considerations.....	36
REFERENCES	37
APPENDICES	56
APPENDIX A: Multiple Sclerosis Disease Courses 2013 Revisions ¹	56
Appendix B: 2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis	59
APPENDIX C: Treatments Used Off-Label for Multiple Sclerosis.....	61
THE MULTIPLE SCLEROSIS COALITION	70

INTRODUCTION

Multiple sclerosis (MS) is a disorder of the central nervous system (CNS) characterized by inflammation, demyelination and degenerative changes. Most people with MS experience relapses and remissions of neurological symptoms, particularly early in the disease, and clinical events are usually associated with areas of CNS inflammation.¹⁻⁴ Gradual worsening or progression, with or without subsequent acute attacks of inflammation or radiological activity, may take place early, but usually becomes more prominent over time.⁵ While traditionally viewed as a disease of only CNS white matter, more advanced imaging techniques have demonstrated significant early and ongoing CNS gray matter damage as well.⁶⁻⁹

Those diagnosed with MS may have many fluctuating and disabling symptoms (including, but not limited to, fatigue, impaired mobility, mood and cognitive changes, pain and other sensory problems, visual disturbances and elimination dysfunction), resulting in a significant impact on quality of life for patients and their families. As the most common non-traumatic, disabling neurologic disorder of young adults – a group not typically faced with a chronic disease – MS threatens personal autonomy, independence, dignity and life planning,¹⁰ potentially limiting the achievement of life goals. The free-spirit spontaneity so highly valued by young adults needs to shift to purposeful planning considering the challenges posed by fluctuations in function and an uncertain future. The patient's self-definition, roles and relationships may be co-opted by the need to adapt to an unpredictable disease requiring frequent healthcare visits, periodic testing and costly medications.

Compared to patients with other chronic diseases, those diagnosed with MS have diminished ratings in health, vitality and physical functions, and experience limitations in social roles.¹¹ Productivity and participation are affected for many, including early departure from the workforce and inability to fulfill household responsibilities.¹² In a study of disease burden, based on data from the Medical Expenditure Panel Survey (MEPS) – a public access, large-scale database that links direct cost information with information on productivity and health-related quality of life – Campbell and colleagues found that annual direct healthcare costs for people with MS were \$24,327 higher than for the general population. In addition, people with MS had a significantly higher risk of being unemployed, spent significantly more time in bed, and lost on average 10.04 quality-adjusted life years compared to the general population. In a systematic review of 48 cost-of-illness studies, medications were the main expense for those with milder disease while loss of income combined with informal care needs contributed the biggest costs for those with more advanced disease.^{13,14} Furthermore, registry studies specific to MS and large population cohort studies of individuals untreated with a disease-modifying therapy have demonstrated a reduced life expectancy of 8-12 years.¹⁵

Epidemiology, Demographics, Disease Course

It is estimated that there are more than two million people with MS worldwide¹⁶ with the number approaching 1,000,000 in the United States.¹⁷ Women are affected at least three times more than men¹⁸ and Caucasians are affected more than other racial groups.¹⁹ However, a recent study²⁰ suggested that African-American women have a higher than previously reported risk of developing MS and several studies have suggested that African-Americans²¹⁻²⁵ and Hispanics²⁶⁻³⁰ may have a more active, rapidly progressive disease course. MS is typically diagnosed in early adulthood, but the age range for disease onset is wide with both pediatric cases and new onset in older adults. Historically, a geographic gradient has been observed with a higher incidence of MS with increased distance from the equator.^{31,32} However, some recent studies have not demonstrated the same latitudinal gradient,^{33,34} suggesting either a change in regional risk determinants for MS or a broadening of the prevalence and recognition of MS worldwide.

The course of MS varies. However, 85-90 percent of individuals demonstrate a relapsing pattern at onset, which transitions over time in most untreated patients to a pattern of progressive worsening with few or no relapses or MRI activity (secondary progressive MS). Approximately 10-15 percent present with a relatively steady progression of symptoms over time (primary progressive MS), of which some will subsequently experience inflammatory activity by clinical or MRI criteria.^{1,2} This primary progressive

course is generally diagnosed at an older age, is typically spinal cord-predominant, and is distributed more equally in men and women. The 2013 revisions to the MS clinical course descriptions¹ further characterize relapsing and progressive MS as active (new relapses and/or new MRI activity) or not active, and worsening (disability progression) or stable based on clinical and MRI criteria. (See Appendix A for a full description of the revised disease courses).

Prior to the era of disease modifying treatments, approximately half of patients diagnosed with relapsing MS would progress to secondary progressive MS by 10 years, and 80-90 percent would do so by 25 years.³⁵⁻³⁷ Approximately half of patients would no longer be able to walk unaided by 15 years.³⁶ More recent data in the era of disease-modifying therapy demonstrate that the percentage of patients with relapsing MS who develop secondary-progressive MS may now be 15-30 percent.³⁸

Inflammation and CNS Damage

At present, much of the CNS damage in MS is believed to result from an immune-mediated process. Although the cause of the immunological changes is not completely understood, Vitamin-D deficiency, which is commonly present in MS, is thought to enhance inflammation. Gut dysbiosis is also thought to contribute to MS pathogenesis through mechanisms that have yet to be defined.³⁹

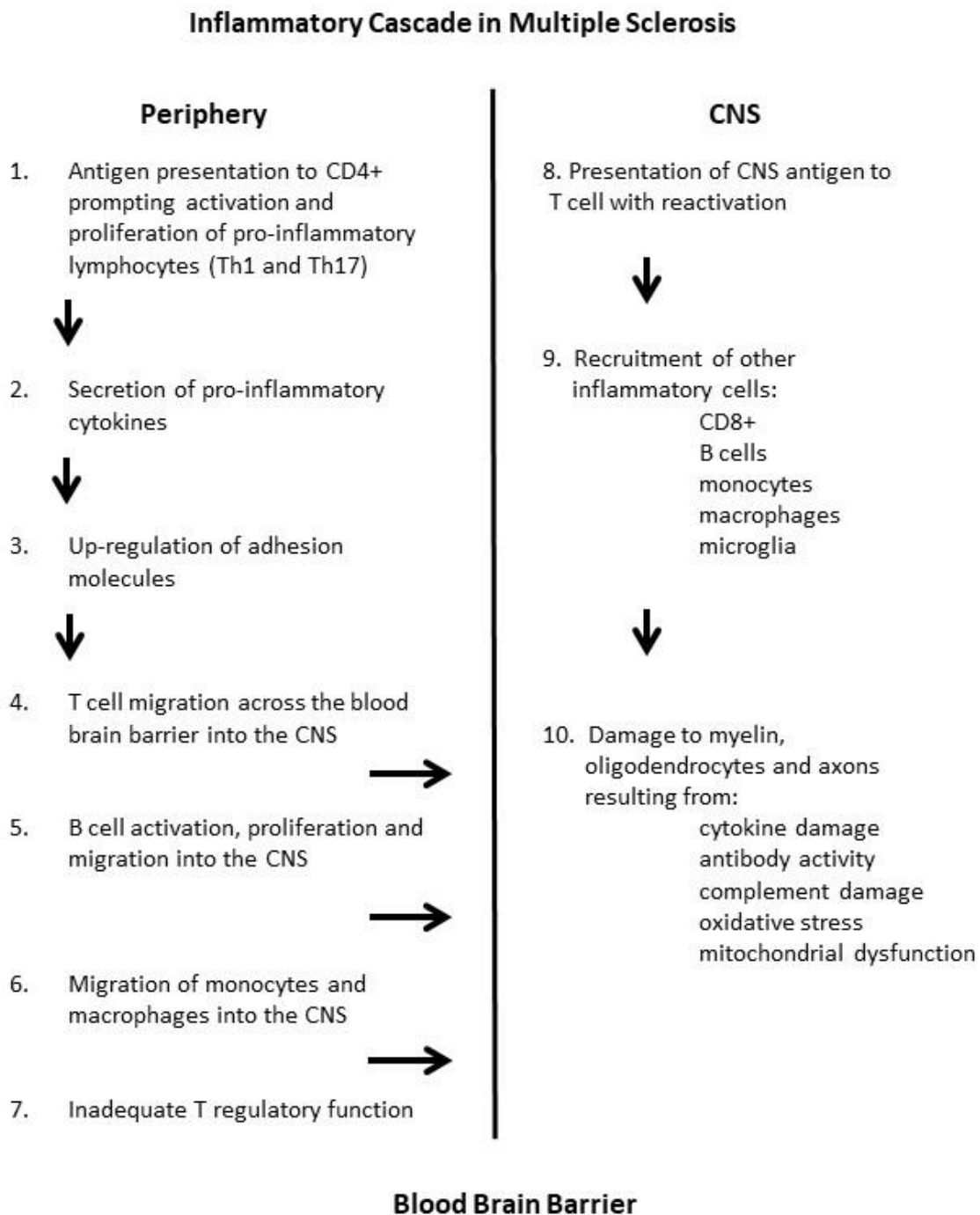
This immune-mediated process includes components of the innate immune system (including macrophages, natural killer cells and others) as well as adaptive immune system activation of certain lymphocyte populations in peripheral lymphoid organs.⁴⁰ CD4+ lymphocytes, CD8+ lymphocytes and B lymphocytes are activated in the peripheral lymph tissues. Antigen presentation to naïve CD4+ lymphocytes causes differentiation into various T lymphocyte cell populations, depending on the antigen presented, the cytokine environment and the presence of co-stimulatory molecules. The T lymphocyte cell populations include Th1 and Th17 lymphocytes (which are associated with a variety of inflammatory cytokines that activate macrophages and opsonizing antibodies) and Th2 lymphocytes and T regulatory cells (which drive humoral immunity or secrete anti-inflammatory cytokines).⁴⁰⁻⁴² In people with MS, there is a bias towards a Th1 and Th17 environment with T regulatory dysfunction that allows inflammation to predominate.⁴³ Secreted cytokines and matrix metalloproteinases disrupt the blood-brain barrier.⁴⁴ This disruption, along with up-regulation of adhesion molecules on blood vessel endothelium and activation of T cells, allows T cells to gain entry into the CNS, where additional activation takes place that initiates a damaging inflammatory cascade of events within the CNS. Multiple inflammatory cells become involved, including microglial cells and macrophages. In addition to CD4+ activation, CD8+ T lymphocytes have also been identified as important contributors to damaging CNS inflammation, and in fact have been identified by numerous researchers as the predominant T cell present in active MS lesions.⁴⁵ Mechanisms of remission and recovery are not fully understood but are believed to be mediated by the expansion of regulatory cells that downregulate inflammation such as Foxp3 positive cells, Tr1 (IL-10 secreting), Th3 (TGF-β secreting) and CD56bright NK cells. Proliferation of progenitor oligodendroglia and remyelination contribute to recovery at least in the early stages of the disease.⁴⁶

Further contributions to CNS damage in MS are associated with B cell activation. B cells function as antigen presenting cells and also produce antibodies and pro-inflammatory cytokines that have damaging effects on myelin, oligodendrocytes and other neuronal structures.⁴⁷ The importance of B cells in MS immunopathogenesis is supported by the consistent finding of oligoclonal immunoglobulins in the CSF; the successful clinical trials with B cell depleting monoclonal antibodies (rituximab and more recently ocrelizumab) that showed efficacy in RRMS and a subset of patients with primary progressive disease; and the presence of B-cell enriched meningeal follicles in progressive patients.⁴⁸

Recent studies have also revealed that mitochondrial damage, possibly as a result of free radical, reactive oxygen species and nitrous oxide (NO) activity associated with activated microglia, and iron deposition occur in MS, and make a significant contribution to demyelination and oligodendrocyte damage.⁴⁹⁻⁵¹

Immune-mediated responses leading to inflammation, with secretion of inflammatory cytokines, activation of microglia, T and B cell activity, mitochondrial damage and inadequate regulatory function, are believed to be at least partially responsible for demyelination, oligodendrocyte loss and axonal damage – all of which occur in acute inflammatory lesions.^{51,52} Axons that survive acute attacks may require increased energy to compensate for damage leading to later death from metabolic stress.⁵¹ Axonal loss, which correlates best with disability, begins early in the disease process as evidenced by identified pathological changes as well as imaging studies.^{52,53}

Figure 1: Inflammatory cascade in multiple sclerosis



OVERVIEW OF FDA-APPROVED DISEASE-MODIFYING AGENTS IN MS

Currently, 15 disease-modifying agents are approved by the U.S. Food and Drug Administration (FDA).

Note: Zinbryta (daclizumab) was approved to treat relapsing forms of MS in 2016 and voluntarily withdrawn from the market in 2018.

Table 1: FDA-approved disease-modifying agents in MS (in alphabetical order by route of administration).

Refer to the full FDA prescribing information for each medication for contraindications and additional details about side effects, warnings and precautions, and pre-treatment recommendations and procedures.

FDA pregnancy categories were replaced by [pregnancy guidelines](#) in June 2015 to make them more meaningful for patients and providers, and to allow for patient-specific counseling and informed decision-making (see p. 29).

Agent - Self-Injected	Proposed MoA	Side Effects	Warnings/Precautions
<p>glatiramer acetate^{54,55} (Copaxone®; Glatopa®- therapeutic equivalent; Glatiramer acetate injection)</p> <p>20mg SC daily or 40mg SC three times weekly</p> <p>Indication: relapsing forms of MS</p> <p>Pregnancy Cat: B</p>	<p>Mechanism of action in MS is not fully understood. Subsequent research suggests:</p> <ul style="list-style-type: none"> -Promotes differentiation in Th2 and T-reg cells leading to bystander suppression in CNS.⁵⁶ -Increases release of neurotrophic factors from immune cells.⁵⁶ -Deletion of myelin-reactive T cells.⁵⁶ 	<ul style="list-style-type: none"> -Injection-site reactions -Lipoatrophy -Vasodilation, rash, dyspnea -Chest pain -Lymphadenopathy⁵⁴ 	<ul style="list-style-type: none"> -Immediate transient post-injection reaction (flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and/or urticaria) -Lipoatrophy and skin necrosis -Potential effects on immune response
<p>interferon beta-1a⁵⁷ (Avonex®)</p> <p>30mcg IM weekly</p> <p>Indication: relapsing forms of MS</p> <p>Pregnancy Cat: C</p>	<p>Mechanism of action in MS is unknown. Subsequent research suggests:</p> <ul style="list-style-type: none"> -Promotes shift from Th1-Th2. -Reduces trafficking across BBB.^{58,59} -Restores T-reg cells.⁵⁶ -Inhibits antigen presentation.⁵⁶ -Enhances apoptosis of autoreactive T-cells.⁵⁶ 	<ul style="list-style-type: none"> -Flu-like symptoms -Depression -Elevated hepatic transaminases 	<ul style="list-style-type: none"> -Depression, suicide and/or psychosis -Hepatic injury -Anaphylaxis and other allergic reactions -CHF -Lower peripheral blood counts -Seizures -Other autoimmune disorders -Thrombotic microangiopathy
<p>interferon beta-1a⁶⁰ (Rebif®)</p> <p>22mcg or 44mcg SC three times weekly</p> <p>Indication: relapsing forms of MS</p> <p>Pregnancy Cat: C</p>	<p>Same as above</p>	<ul style="list-style-type: none"> -Injection-site reactions -Flu-like symptoms -Abdominal pain -Depression -Elevated hepatic transaminases -hematologic abnormalities 	<ul style="list-style-type: none"> -Depression and/or suicide -Hepatic injury -Anaphylaxis and other allergic reactions -Injection-site reactions including necrosis -Lower peripheral blood counts -Seizures -Thrombotic microangiopathy
<p>interferon beta-1b^{61,62} (Betaseron®) (Extavia®)</p> <p>0.25mg SC every other day</p> <p>Indication: relapsing forms of MS</p> <p>Pregnancy Cat: C</p>	<p>Same as above</p>	<ul style="list-style-type: none"> -Flu-like symptoms -Injection-site reactions -Elevated hepatic transaminases -Low WBC -See warnings^{61,62} 	<ul style="list-style-type: none"> -Hepatic injury -Anaphylaxis and other allergic reactions -Depression and/or suicide -CHF -Injection-site necrosis -Low WBC -Flu-like symptoms -Seizures -Thrombotic microangiopathy

Agent - Self-Injected	Proposed MoA	Side Effects	Warnings/Precautions
<p>peginterferon beta-1a⁶³⁻⁶⁵ (Plegridy®)</p> <p>125mcg SC every two weeks</p> <p>Indication: relapsing forms of MS</p> <p>Pregnancy Cat: C</p>	Same as above	<ul style="list-style-type: none"> -Flu-like symptoms -Injection-site reactions -Elevated hepatic transaminases -Low WBC -See warnings⁶³ 	<ul style="list-style-type: none"> -Depression and/or suicide -Hepatic injury -Anaphylaxis and other allergic reactions -CHF -Low peripheral blood counts -Seizures -Other autoimmune disorders -Thrombotic microangiopathy

Agent – Oral	Proposed MoA	Side Effects	Warnings/Precautions
<p>dimethyl fumarate⁶⁶ (Tecfidera®)</p> <p>240mg PO twice daily</p> <p>Indication: relapsing forms of MS</p> <p>Pregnancy Cat: C</p>	Mechanism of action in MS is unknown. It has been shown to promote anti-inflammatory and cytoprotective activities mediated by Nrf2 pathway. ⁵⁹	<ul style="list-style-type: none"> -Anaphylaxis and angioedema - Progressive multifocal leukoencephalopathy (PML) -Lymphopenia -Elevated AST -Liver injury -Flushing -GI symptoms -Pruritis -Rash⁶⁵ 	<ul style="list-style-type: none"> -Anaphylaxis and angioedema -PML -Lymphopenia (consider discontinuing treatment in patients with persistent lymphopenia (<500) lasting over 6 months) -Flushing -Liver injury
<p>fingolimod⁶⁷ (Gilenya®)</p> <p>0.5mg PO daily for patients weighing >40kg 0.25mg PO daily for patients weighing <40kg</p> <p>Indication: relapsing forms of MS in patients 10 years of age and older</p> <p>Pregnancy Cat: C</p>	Mechanism of action in MS most likely involves blocking of S1P receptor on lymphocytes thus preventing their egress from secondary lymph organs. ⁶⁷	<ul style="list-style-type: none"> -Headache -Influenza -Diarrhea -Back pain -Elevated hepatic enzymes -Cough -Bradycardia following first dose -Macular edema -Lymphopenia -Bronchitis/pneumonia 	<ul style="list-style-type: none"> -Bradycardia and/or atrioventricular block following first dose -Risk of infections including serious infections – monitor for infection during treatment and for 2 months after d/c -Avoid live attenuated vaccines during treatment and for 2 months after d/c -PML -Cryptococcal infections -Macular edema -Posterior reversible encephalopathy syndrome (PRES) -Low pulmonary function tests (FEV1) -Hepatic injury -Increased BP -Basal cell carcinoma -Fetal risk: women should avoid conception for two months after treatment d/c -Decreased lymphocyte counts for 2 months after drug d/c -Severe increase in disability after stopping treatment

Agent – Oral	Proposed MoA	Side Effects	Warnings/Precautions
<p>teriflunomide⁶⁸ (Aubagio®)</p> <p>7mg or 14mg PO daily</p> <p>Indication: relapsing forms of MS</p> <p>Pregnancy Cat: X</p>	<p>Mechanism of action in MS is unknown.^{68,69} It has been shown to:</p> <ul style="list-style-type: none"> -Have a cytostatic effect on rapidly dividing T- and B-lymphocytes in the periphery. -Inhibit de novo pyrimidine synthesis. <p>It is a metabolite of leflunomide (used in rheumatoid arthritis (RA)).</p>	<ul style="list-style-type: none"> -ALT elevation -Alopecia -Diarrhea -Influenza -Nausea -Paresthesia⁶⁸ 	<ul style="list-style-type: none"> -Hepatotoxicity -Risk of teratogenicity -Elimination of teriflunomide can be accelerated by administration of cholestyramine or activated charcoal for 11 days (confirm undetectable drug level before conception) -Decreased neutrophils, lymphocytes and platelets -Risk of infection, including tuberculosis (TB screen prior to treatment) -No live virus vaccines -Potential increased risk of malignancy -Peripheral neuropathy (consider discontinuation of treatment) -Acute renal failure -Treatment-emergent hyperkalemia -Increased renal uric acid clearance -Interstitial lung disease -Stevens-Johnson syndrome and toxic epidermal necrolysis (stop treatment) -Increased BP -May decrease WBC: recent CBC prior to initiation; monitor for infections; consider suspension for serious infections; do not start in presence of infection -Concomitant use with immunosuppressants has not been evaluated <p>Note: Some of these were carried over from leflunomide use in RA</p> <p>Boxed Warning Hepatotoxicity and risk of teratogenicity</p>

Agent - Intravenous	Proposed MoA	Side Effects	Warnings/Precautions
<p>alemtuzumab⁷⁰⁻⁷² (Lemtrada®)</p> <p>12mg/day IV on five consecutive days followed 12 months later by 12mg/day on three consecutive days</p> <p>Indication: relapsing forms of MS – generally for patients who have had an inadequate response to two or more MS therapies</p> <p>Pregnancy Cat: C</p>	<p>Mechanism of action in MS is presumed to involve binding to CD52, a cell surface molecule present on T and B lymphocytes, and on natural killer cells, monocytes and macrophages. This results in antibody-dependent cellular cytotoxicity and complement-mediated lysis.^{70,73}</p>	<ul style="list-style-type: none"> -More than 90% of patients in clinical trials experienced infusion reactions: skin rash, fever, headache, muscle aches and/or temporary reoccurrence of previous neurologic symptoms. More serious but uncommon infusion reactions include anaphylaxis and/or heart rhythm abnormalities. -Serious adverse reactions include autoimmunity, infusion reactions, malignancies, immune thrombocytopenia (ITP), glomerular nephropathies, thyroid disorder, other autoimmune cytopenias, infections, pneumonitis -Immediate and significant depletion of lymphocytes; herpes simplex and zoster 	<ul style="list-style-type: none"> -Infusion reactions -Autoimmunity (thyroid disorders, immune thrombocytopenia (ITP), glomerular nephropathies and/or other cytopenias) -Infections -No live virus vaccinations following infusion -Malignancies (thyroid, melanoma or lymphoproliferative) -Pneumonitis -Stroke, cervicocephalic arterial dissection <p>Boxed Warning Because of the risk of autoimmunity, life threatening infusion reactions and malignancies, alemtuzumab is available only through restricted distribution under a Risk Evaluation Mitigation Strategy (REMS) program.</p>

Agent - Intravenous	Proposed MoA	Side Effects	Warnings/Precautions
		infections more common in patients who received alemtuzumab in the clinical trials, especially soon after the infusions. Prophylaxis with anti-viral agent is recommended for at least two months or until CD4 count is >200.	
<p>mitoxantrone⁷⁴ (Novantrone®)</p> <p>12mg/m² IV every three months; maximum cumulative dose: 140mg/m²</p> <p>Indication: worsening relapsing-remitting, progressive-relapsing or secondary progressive MS</p> <p>Pregnancy Cat: D</p>	<p>-Disrupts DNA synthesis and repair</p> <p>-Inhibits B cell, T cell, and macrophage proliferation</p> <p>-Impairs antigen presentation</p> <p>-Impairs secretion of interferon gamma, TNFα and IL-2</p>	<p>-Temporary blue discoloration of sclera and urine</p> <p>-Nausea</p> <p>-Alopecia</p> <p>-Menstrual disorders including amenorrhea and infertility</p> <p>-Infections (URI, UTI, stomatitis)</p> <p>-Cardiac toxicity (arrhythmia, abnormal EKG and/or congestive heart failure)</p>	<p>-Severe local tissue damage if there is extravasation</p> <p>-Cardiotoxicity</p> <p>-Acute myelogenous leukemia</p> <p>-Myelosuppression</p> <p>Boxed Warning Cardiotoxicity and secondary leukemia (monitoring required long-term following discontinuation).</p>
<p>natalizumab⁷⁵ (Tysabri®)</p> <p>300mg IV every 28 days</p> <p>Indication: relapsing forms of MS</p> <p>Pregnancy Cat: C</p>	<p>The mechanism of action in MS has not been fully defined. It has been shown to:</p> <p>-Block α4integrin on lymphocytes, thus reducing trafficking of lymphocytes into the CNS.⁵⁹</p>	<p>-Headache</p> <p>-Fatigue</p> <p>-Urinary tract infection</p> <p>-Lower respiratory tract infection</p> <p>-Arthralgia</p> <p>-Urticaria</p> <p>-Gastroenteritis</p> <p>-Vaginitis</p> <p>-Depression</p> <p>-Diarrhea⁷⁵</p>	<p>-PML</p> <p>-Hepatotoxicity</p> <p>-Herpes encephalitis and meningitis caused by herpes simplex and varicella zoster viruses</p> <p>-Acute retinal necrosis</p> <p>-Hypersensitivities</p> <p>-Immunosuppression/infections</p> <p>Boxed Warning Because of the risk of PML, natalizumab is available only through a restricted distribution program called the TOUCH® Prescribing Program.</p>
<p>ocrelizumab⁷⁶ (Ocrevus™)</p> <p>600mg IV every 6 months</p> <p>Indication: relapsing or primary progressive forms of MS</p> <p>Pregnancy Cat: No category assigned due to changes to FDA labeling procedures for pregnancy and lactation. No human data. In monkeys, administration during organogenesis and continuing through the neonatal period resulted in perinatal deaths, renal toxicity, lymphoid follicle formation in the bone marrow and severe decreases in circulating B-lymphocytes in neonates.</p>	<p>The precise mechanism of action is not known but is presumed to involve binding to CD20, a cell surface antigen on pre-B and mature B lymphocytes, causing antibody-dependent and complement-mediated cytotoxicity.</p>	<p>-Infusion reactions (potentially life-threatening)</p> <p>-Infections</p> <p>-Possible increased risk of malignancies (including breast cancer, which occurred in 6 of 781 treated patients and no placebo patients)</p>	<p>-Infusion reactions that can include: pruritis, rash, urticaria, erythema, bronchospasm, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia. Premedication and observation period recommended.</p> <p>-Infections, including respiratory tract infections, herpes and potentially PML</p> <p>-Hepatitis B reactivation</p> <p>-Possible increased immunosuppressive effect if immunosuppressant used prior to or after ocrelizumab</p> <p>-Malignancies</p> <p>-Administer all vaccinations at least 6 weeks prior to administration of ocrelizumab; no live-attenuated or live vaccines during treatment and until B-cell repletion</p>

BBB= Blood Brain Barrier

Adapted from Oh J and Calabresi P in Multiple Sclerosis and Related Disorders Clinical Guide to Diagnosis, Medical Management and Rehabilitation (2013),⁵⁹ with supplemental data from the Full Prescribing Information for each agent: [Copaxone](#) (2018), [Glatopa](#) (2018), [Avonex](#) (2016), [Plegridy](#) (2015), [Rebif](#) (2015), [Betaseron](#) (2018), [Extavia](#) (2016), [Gilenya](#) (2018), [Aubagio](#) (2016), [Tecfidera](#) (2017), [Lemtrada](#) (2016), [Novantrone](#) (2008), [Tysabri](#) (2018), [Ocrevus](#) (2017); Graber et al, 2010.^{54-57,60-63,66-68,70,74-76}

DISEASE-MODIFYING THERAPY CONSIDERATIONS

Several important themes emerge from the growing body of evidence in MS therapeutics:

1) Early successful control of disease activity – including the reduction of clinical and sub-clinical attacks and the delay of the progressive phase of the disease – appears to play a key role in preventing accumulation of disability, prolonging the ability of people with MS to remain active and engaged, and protecting quality of life.

2) Physical impairments comprise only one aspect of disability that results from early disease activity and disease progression. Cognitive impairment and fatigue are common early in the disease process and cause disability independent of physical function. In addition, common physical comorbidities in MS are associated with persistent fatigue, and depression at baseline is associated with worsening fatigue over time.⁷⁷

3) Prognosis at the individual level remains highly variable and unpredictable.

4) Adherence to treatment is important to efficacy and may be impacted by a wide range of factors requiring early identification and intervention.

In 2018, the American Academy of Neurology published the Practice Guideline: Disease-Modifying Therapies for Adults with Multiple Sclerosis. The Guideline provides evidence-based recommendations for starting, switching and stopping disease-modifying agents. These recommendations consider the patient's perspective in the complex decision-making process in order to enhance shared decision-making. Refer to the full Guideline at AAN.com/guidelines.⁷⁸ In the same year,ECTRIMS and the EAN (European Academy of Neurology) published theECTRIMS/EAN Guideline on the Pharmacological Treatment of People with Multiple Sclerosis.⁷⁹ Refer to this guideline for additional expert recommendations for the adult MS population.

Disease Factors Highlighting the Importance of Early Treatment

The goal of disease-modifying treatment is to reduce the early clinical and sub-clinical disease activity that is thought to contribute to long-term disability.^{80,81}

The following points highlight the importance of early treatment:

- **Neuroinflammation and neurodegeneration occur simultaneously throughout the disease course**

It had long been thought that MS was characterized by early inflammatory damage followed by later neurodegeneration. However, a growing body of evidence demonstrates that inflammation and degeneration occur simultaneously, that clinical recovery reflects reserve capacity, and that subclinical damage ultimately leads to permanent clinical deficits. Evidence also indicates that inflammation contributes to worsening progression, even if not the sole cause. Hence, inflammation and degeneration are inter-related rather than independent.^{82,83} Additional evidence to support neuroinflammatory and neurodegenerative changes throughout the disease process includes:

- Early in MS, new MRI activity, evidenced by gadolinium enhancement, occurs approximately 7-10 times more frequently than clinical activity.⁸⁴
- Early in the disease process, advanced MRI techniques demonstrate abnormalities in normal appearing white matter as well as gray matter in the absence of focal lesions seen on conventional imaging.⁷
- Brain atrophy has been identified in early MS, even at the time of the first clinical attack.⁸⁵
- Atrophy has been seen in radiologically isolated syndrome (RIS – the incidental finding of MS-like lesions in the absence of known clinical relapses⁸⁶).⁸⁷
- Inflammatory activity has been observed in patients with both relapsing and progressive forms of the disease.³

Given the evidence that inflammation and neurodegeneration are interrelated and occur throughout the disease process, prompt initiation and optimization of treatment help to minimize early inflammation and axonal damage.

- **Individuals with a first clinical event accompanied by MRI findings consistent with MS have a high probability of experiencing further clinical disease activity**

The term “clinically-isolated syndrome” (CIS) has been used to describe a first episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation and demyelination in one or more sites in the CNS.

Eighty percent of the placebo-treated patients in the four published phase III CIS trials with injectable medications had subsequent clinical events, which was defined at the time as conversion to clinically-definite MS (CDMS).⁸⁸⁻⁹¹ Follow-up data for these patients indicated a variable disease course, with approximately one-third having minimal clinical relapses and physical disability after 15-20 years, but 42-50 percent converting to secondary progressive (SPMS) with increasing disability.^{92,93} Furthermore, baseline MRI findings in CIS predicted the development of definite MS as defined at the time. Lesion volume and the rate of lesion development earlier in the disease course were found to correlate with disability after 20 years.⁹³

The importance of delaying and limiting additional relapses early in the disease process was further supported by a CIS trial with teriflunomide⁹⁴ published in 2014.

The 2017 revision of the McDonald diagnostic criteria (See Appendix B) facilitated an earlier diagnosis of MS based on a first clinical event, and MRI findings demonstrating dissemination in space and time.⁹⁵ Using these newer criteria, many individuals in the early CIS trials would already have been diagnosed with MS. Although the term “CIS” may be nearly obsolete today, the importance of delaying and limiting additional relapses early in the disease process remains clear.

Based on data from the published CIS trials, prompt identification of early relapsing patients with little or no disability is essential in order to achieve the best possible short- and long-term outcomes.⁸¹

- **Individuals with RIS are at significant risk for subsequent clinical disease activity**

Although RIS is not currently recognized as a separate MS phenotype (see Appendix A), emerging data^{96,97} suggest that within five years, 30 percent of patients with an RIS presentation develop a symptomatic clinical event and two-thirds demonstrate new lesions on MRI.⁹⁸⁻¹⁰¹ In these studies, younger individuals with RIS and spinal cord lesions, CSF inflammatory markers, abnormal visual evoked potentials, and/or contrast enhancing MRI lesions were more likely to have a subsequent symptomatic CNS demyelinating event. Notably, nearly 10 percent of people with RIS were found to have a progressive course, thereby fulfilling criteria for PPMS.^{101,102} And, 20-30 percent of RIS patients demonstrate cognitive changes similar to those seen in patients with RRMS.¹⁰³⁻¹⁰⁵ In their

review of these data, Lebrun and colleagues⁹⁶ as well as Labiano-Fontcuberta and Benito-Leon⁹⁷ recommended further study of RIS before a general recommendation for treatment can be made.

- **Early disease activity and disease course appear to impact long-term disability**

Debate is ongoing about the ways and extent to which early disease activity impacts long-term disability.

- Some evidence suggests that early disability progression as measured by the Expanded Disability Status Scale (EDSS)¹⁰⁶ is the result of residual impairments from partially-resolved relapses.^{80,107-109} Natural history studies suggest that relapses in the first two years of disease impact early progression,¹¹⁰ with the impact of early relapses diminishing later in the disease course.¹¹¹ However, Jokubaitis and colleagues found the effect of relapses on disability accrual in a treated cohort of patients to be significant, even for relapses that occurred ≥ 14 years after disease onset, although earlier relapses had the greatest impact.¹¹²
- The onset and evolution of secondary progressive MS (SPMS) – in which inflammatory attacks decrease – also appear to have an important association with long-term disability.¹¹³ From this perspective, earlier SPMS onset is a primary predictor of disability, which means that a person's prognosis is essentially determined before progressive symptoms become predominant.
- Data from both early and late in the disease course highlight the impact of early disease activity on long-term outcomes. In patients identified as having CIS, Brex and colleagues¹¹⁴ found that increases in lesion volume on MRI in the first five years of the disease correlate with the degree of long-term disability. Data from the 16-year follow-up cohort study of the pivotal trial of interferon beta-1b suggest that long-term physical and cognitive outcomes may be determined early in the disease.¹¹⁵

Given the medications that are currently available – all of which primarily target inflammation – the optimal window for impacting long-term disability is during the early relapsing phase of the disease, with the goal being to slow the accumulation of lesion volume, decrease the number of relapses, and prevent disability from both unresolved relapses and disease progression.⁸⁰

- **Cognitive changes, depression and fatigue occur very early in the disease process**

It is currently recognized that approximately 60-65 percent of people with MS will experience cognitive impairment;¹¹⁶ 36-54 percent will experience a major depressive disorder;¹¹⁷ and up to 92 percent will experience significant fatigue,¹¹⁸ contributing to increased disability and reduction in quality of life.

- Evidence is accumulating that approximately 20-30 percent of people with a first clinical event have already experienced cognitive changes.¹¹⁹⁻¹²⁵ In fact, cognitive deficits similar to those seen in RRMS have been found in 20-30 percent of individuals with RIS.¹⁰³⁻¹⁰⁵
- Some studies suggest that cognitive deficits may precede the onset of MS by as much as 1.2 years.¹¹⁹ More specifically, verbal deficits have been shown to occur early and may predict the presence of cognitive impairment in people with a first clinical event.¹²¹
- Early cognitive changes are also known to progress, even in people with little or no physical changes,¹²⁴ and deterioration can be expected over a three-year period in approximately one-third of people with short disease duration.¹²⁶
- Cognitive deficits are detected in approximately 30 percent of pediatric MS patients.¹²⁷⁻¹²⁹
- Depression and fatigue have been found along with cognitive deficits in early MS, with each having a significant impact on quality of life, employment and other important activities of daily life^{130,131} – findings that highlight the importance of early treatment to help preserve people's ability to remain optimally engaged in everyday activities, including employment and social interactions.^{81,124}

- **So-called “benign MS” may not be benign for many people**

The most common working definition of “benign MS” – an Expanded Disability Status Score (EDSS) ≤ 3 at 10 years¹³² – is highly weighted for patients’ motor abilities and fails to capture non-motor components of the disease, particularly mood, cognition and fatigue.

- In one cohort of individuals meeting the criteria for “benign MS,” 45 percent were found to be cognitively impaired, 49 percent had significant fatigue, and 54 percent were found to be depressed.¹³³
- In another cohort of people with “benign MS” followed for 10.9 additional years, 81 percent (35/43) developed higher EDSS scores, cognitive impairment, pain and/or depression, as well as a significant increase in new or enlarging T2 lesions and gadolinium (Gd)-enhancing lesions over time.¹³⁴
- Sayao and colleagues evaluated disease status in a “benign MS” cohort after 20 years and found that while 51 percent remained benign, 21 percent had progressed to EDSS ≥ 6 and 23 percent had converted to SPMS. The authors concluded that appropriate criteria for determining which individuals will have a truly benign course of the disease have not yet been identified.¹³⁵

Based on these findings, benign MS can only be diagnosed retrospectively, after a minimum of 20 years. Therefore, the term should only be applied – if at all – in retrospect, and any decision to delay treatment for a given individual needs to take into account non-motor as well as motor variables.¹³⁶

Evidence Demonstrating the Impact of Treatment Following a First Clinical Event

Although none of the available treatments are fully effective in stopping MS disease activity or disease progression, evidence points to the favorable impact of treatment following a first clinical event:

Delaying conversion to clinically-definite MS (CDMS)

Each of four published placebo-controlled phase III trials of injectable medications⁸⁸⁻⁹¹ in patients with clinically-isolated syndrome (CIS),⁸⁸⁻⁹¹ as well as the CIS trial with teriflunomide,⁹⁴ demonstrated that early treatment successfully delayed conversion to CDMS (as defined at the time of these trials) by 37-45 percent at two to three years compared with placebo.

The eight-year, open-label follow-up of the early intervention study with interferon beta-1b, which compared the immediate treatment group with the delayed treatment (placebo) group, further demonstrated a reduced risk of CDMS and longer median time to CDMS in the early treatment group,¹³⁷ although the greatest differences occurred in the first year of treatment. A follow-up open-label phase of the early intervention study with glatiramer acetate demonstrated a reduced risk of CDMS and a delay in conversion to CDMS in the immediate treatment group as compared with the delayed treatment (placebo) group.¹³⁸

Reducing brain atrophy and disability worsening

In meta-analyses of CIS treatment trials, each of two years duration (ETOMS, PreCISe, TOPIC),^{88,94,139} the rate of brain atrophy was attenuated after one year of treatment.¹⁴⁰

In a large cohort of CIS patients, disease-modifying treatments reduced 3-month confirmed and 12-month sustained disability worsening.¹⁴¹

Evidence Demonstrating the Impact of Treatment on Relapsing MS

Each of the approved disease-modifying therapies has been shown to provide significant benefits in relapsing forms of MS. *Due to differences in patient cohorts, trial designs and outcome measures, as well as changes in diagnostic criteria, these data should not be used to compare efficacy between specific agents except where they are compared in the same trial.*

Impact on clinical outcomes (relapse rates and disability progression)

Table 2: Disease-modifying therapies: pivotal trial data on relapse rate and disability progression (in alphabetical order within route of administration). * Primary outcomes are identified with a ⁺.

Agent - Self-Injected	Effect on Relapse Rate Compared to Placebo or Active Comparator*	Effect on Disability Progression Compared to Placebo or Active Comparator
glatiramer acetate ¹⁴² 20mg qd 40mg tiw ¹⁴³	29% reduction in relapse rate over 24 months ⁺ : 1.68 placebo; 1.19 treated (p=0.007) 34% reduction in annualized relapse rate at 12 months ⁺ : 0.505 placebo; 0.331 treated (p<0.0001)	Progression free at 24 months: 75.4% placebo; 78.4% treated (N.S.)
interferon beta-1a subcutaneous ¹⁴⁴	33.2% reduction (44mcg tiw vs. placebo) Mean number of relapses per person (24 months) ⁺ : 2.56 placebo; 1.73 treated (p<0.005)	30% decrease in proportion of patients with sustained disability progression at 12 weeks ⁺ : 11.9 months placebo; 21.3 months treated (p<0.05)
interferon beta-1a intramuscular ¹⁴⁵	18% reduction ⁵⁹ Mean number of relapses per patient year: 0.82 placebo; 0.67 treated (p=0.04)	37% decrease in time to disability progression sustained for at least 6 months ⁺ : 34.9% placebo; 21.9% treated (p=0.04)
interferon beta-1b ¹⁴⁶	34% reduction annualized relapse rate over two years ⁺ : 1.31 placebo; 0.9 treated (p=0.0001)	29% decrease (N.S.) in significant change from baseline EDSS: 28% placebo; 20% treated
peginterferon beta-1a ^{64,65}	36% reduction annualized relapse rate at 48 weeks ⁺ : 0.397 placebo; 0.256 treated (p=0.0007) ⁶⁴ Proportion of exacerbation-free patients ⁺ : 16% placebo; 25% treated (N.S.) ⁶⁴ Efficacy maintained beyond one year with dosing every two weeks providing greater efficacy than every four weeks ⁶⁵	38% relative risk reduction in disability progression at 48 weeks: 10.5% placebo; 6.8% treated (p=0.0383) ⁶⁴

Agent – Oral	Effect on Relapse Rate Compared to Placebo or Active Comparator*	Effect on Disability Progression Compared to Placebo or Active Comparator
dimethyl fumarate ^{147,148}	Study 1: 49% reduction in proportion relapsing within two years ⁺ : 46% placebo; 27% treated (p<0.001) ¹⁴⁷ Study 2: 44% reduction in annualized relapse rate at two years ⁺ : 40% placebo; 22% DMF bid (p<0.001) ¹⁴⁸	Study 1: 38% decrease in risk of disability progression at 12 weeks ⁺ : 27% placebo; 16% treated (p=0.005) ¹⁴⁷ Study 2: Estimated proportion of patients with progression at 2 years: 17% placebo; 13% DMF bid (N.S.) ¹⁴⁸

<p>fingolimod^{149,150} (compared to IFN beta-1a)¹⁵¹</p>	<p>Study 1: 54% reduction in annualized relapse rate over two years⁺: 0.40 placebo; 0.18 0.5mg dose (p<0.001)¹⁴⁹</p> <p>Study 2: 48% reduction in annualized relapse rate over two years⁺: 0.40 placebo; 0.21 0.5mg dose (p<0.0001)¹⁵⁰</p> <p>Study 3: Annualized relapse rate over 12 months⁺: 0.33 IFN; 0.16 0.5mg dose (p<0.001)¹⁵¹</p>	<p>Study 1: 30% decrease in risk of disability progression (p=0.03 0.5mg dose)¹⁴⁹ Percent with absence of disability progression at three months: 75.9% placebo; 82.3% 0.5mg dose (p=0.03)¹⁴⁹</p> <p>Study 2: Percent with absence of disability progression at three months: 71.0% placebo; 74.7% 0.5mg dose (N.S.)¹⁵⁰</p> <p>Study 3: Percent with absence of disability progression at three months: 92.1% IFN; 94.1% 0.5mg dose (p=0.25)¹⁵¹</p>
<p>teriflunomide^{152,153}</p>	<p>Study 1: 31% reduction in annualized relapse rate over two years⁺: 0.54 placebo; 0.37 for 7mg and 14mg doses (p<0.001)¹⁵²</p> <p>Study 2: Annualized relapse rate over two years⁺: 0.50 placebo; 0.39 for 7mg dose (p<0.0183) and 0.32 for 14 mg dose (p<0.0001)¹⁵³</p>	<p>Study 1: Proportion with confirmed disability progression at 12 weeks: 27.3% placebo; 21.7% 7mg dose (N.S.); 20.2% 14mg dose (p=0.03)¹⁵²</p> <p>Study 2: Risk of sustained accumulation of disability compared to placebo: 7mg dose (N.S.); 31.5% 14mg dose (p=0.04)¹⁵³</p>

Agent – Intravenous	Effect on Relapse Rate Compared to Placebo or Active Comparator*	Effect on Disability Progression Compared to Placebo or Active Comparator
<p>alemtuzumab^{71,72} (compared to IFN beta-1a 44mcg tiw)</p>	<p>Study 1: 55% reduction in annualized relapse rate over two years⁺: 0.39 IFN; 0.18 alemtuzumab (p<0.0001)⁷¹</p> <p>Study 2: 49% reduction in annualized relapse rate over two years⁺: 0.52 IFN; 0.26 alemtuzumab (p<0.0001)⁷²</p>	<p>Study 1: 30% relative risk reduction at year two sustained disability accumulation confirmed over six months⁺: 11% IFN; 8% alemtuzumab (N.S.)⁷¹</p> <p>Study 2: 42% relative risk reduction at year 2 Sustained disability accumulation confirmed over six months⁺: 20% IFN; 13% alemtuzumab (p=0.0084)⁷²</p>
<p>mitoxantrone¹⁵⁴</p>	<p>66% reduction in annualized relapse rate over two years: 1.02 placebo; 0.35 treated (p=0.001)</p>	<p>3 months confirmed EDSS change during study: 22% placebo; 8% treated (p=0.036)</p> <p>Increased 0.23 EDSS over 24 months placebo; Decreased 0.13 EDSS over 24 months 12mg/m² dose [absolute and relative risks not reported]</p>
<p>natalizumab¹⁵⁵</p>	<p>68% reduction in annualized relapse rate over two years⁺: 1 year: 0.78 placebo; 0.27 treated (p<0.001) 2 year: 0.73 placebo; 0.23 treated (p<0.001)</p>	<p>42% decrease in risk of confirmed disability progression</p> <p>Cumulative probability of sustained progression at 2yrs⁺: 29% placebo; 17% treated (p<0.001)</p>

Agent – Intravenous	Effect on Relapse Rate Compared to Placebo or Active Comparator*	Effect on Disability Progression Compared to Placebo or Active Comparator
ocrelizumab ^{156,157} <i>(Relapsing MS: comparison with IFN beta-1a 44mcg tiw)</i> <i>(Primary progressive MS: comparison with placebo)</i>	Relapsing MS: Annualized relapse rate [†] : Study 1: IFN 0.292; ocrelizumab 0.156: 46% relative reduction (p<0.0001) ¹⁵⁶ Study 2: IFN 0.290; ocrelizumab 0.155: 47% relative reduction (p<0.0001) ¹⁵⁶	Relapsing MS: Proportion of patients with 12-week confirmed disability progression: 9.8% ocrelizumab; 15.2% IFN (p<0.0001) risk reduction (Studies 1 and 2 - pooled analysis): 40% (p=0.0006) ¹⁵⁶ Primary progressive MS: Study 3: Proportion of patients with 12-week confirmed disability progression [†] : 39.3% placebo; 32.9% treated: relative risk reduction 24% (p=0.0321) ¹⁵⁷ Proportion of patients with 24-week confirmed disability progression: 35.7 placebo; 29.6% treated: relative risk reduction 25% (p=0.04) Study 3: Mean change [improved performance] in 25-foot walk performance baseline to week 120: 55.1% placebo; 38.9% treated: relative reduction 29.3% (p=0.04)

N.S.= Not Significant;

Adapted from Oh & Calabresi in Rae-Grant, et al, 2013;⁵⁹ Calabresi et al, 2014;⁶⁴ Kieseier et al, 2015;⁶⁵ Cohen et al, 2012;⁷¹ Coles et al, 2012;⁷² Johnson et al, 1995;¹⁴² Khan et al, 2013;¹⁴³ PRISMS Study Group 1998;¹⁴⁴ Jacobs et al, 1996;¹⁴⁵ IFNB MS Study Group, 1993;¹⁴⁶ Gold et al, 2012;¹⁴⁷ Fox et al, 2012;¹⁴⁸ Kappos et al, 2010;¹⁴⁹ Calabresi et al, 2014;¹⁵⁰ Cohen et al, 2010;¹⁵¹ O'Connor et al, 2011;¹⁵² Confavreux et al, 2014;¹⁵³ Hartung et al, 2002;¹⁵⁴ Polman et al, 2006;¹⁵⁵ Hauser et al, 2017;¹⁵⁶ Montalban et al, 2017.¹⁵⁷

*** Comparison across clinical trials is impossible due to differences in patient populations, diagnostic definitions, primary and secondary endpoints and outcome metrics.**

MS relapses produce a measurable and sustained impact on disability.^{109,112} While it remains unclear the extent to which reducing relapses impacts long-term disability levels, it is evident that relapse reduction translates into increased comfort and quality of life, fewer days lost from work and other essential activities of daily life, and reduces the risk of residual deficits.^{109,158}

Impact on MRI parameters

MRI is a sensitive indicator of disease activity in relapsing forms of MS that can detect new lesions and predict risk of future clinical changes. Brain MRI is now recommended at least annually for patients with relapsing MS to more accurately measure disease activity and inform therapeutic decision-making – and more often as needed to address specific clinical questions.^{1,159} The [2018 Revised Guidelines of the Consortium of MS Centers MRI Protocol for the Diagnosis and Follow-up of MS](#) provides detailed recommendations for the use of MRI in CIS, diagnosis, and ongoing MS management.¹⁶⁰

Table 3: Disease-modifying therapies: pivotal trial data on MRI parameters (listed alphabetically within route of administration)*

Agent - Self-Injected	Effect on Gd+ Lesions*	Effect on New or Enlarging T2 Lesions*
glatiramer acetate 20mg qd ¹⁶¹ (non-pivotal trial data) 40mg tiw ¹⁴³	29% reduction in mean total # of new contrast enhancing lesions: 36.8 placebo; 25.96 GA 20mg cumulative number of Gd lesions at nine months: 17 placebo; 11 GA 20mg (p=0.003) Cumulative number of Gd lesions at months 6 and 12: 1.639 placebo; 0.905 GA 40mg (p<0.0001) ^{54,143}	Mean number of total new T2: 13.7 placebo; 9.4 GA 20mg (p<0.003) ¹⁶¹ not reported in PI Cumulative new or enlarging T2 at months 6 and 12: 5.59 placebo; 3.65 GA 40mg (p<0.0001) ^{54,143}
interferon beta-1a subcutaneous ^{60,144}	Median number of active lesions per patient per scan: 2.25 placebo; 0.5 44mcg dose (p<0.0001) ⁶⁰	Median percent change of MRI PD-T2 lesion area at two years: 11% placebo; -3.8% 44mcg dose (p<0.0001) ¹⁴⁴
interferon beta-1a intramuscular ¹⁴⁵	Mean number of contrast-enhancing lesions at two years: 1.65 placebo; 0.80 treated (p=0.05)	Median percent change T2 lesion volume from study entry to year 2: -6.55% placebo; -13.2% treated (N.S.)
interferon beta-1b ⁶¹	No Gd outcomes from phase III pivotal trial	Median percent change in MRI area (n=52, scans q 6wks): 16.5% placebo; -1.1% 0.25mg dose (p<0.0001)
peginterferon beta-1a ⁶⁴	Mean number of contrast enhancing lesions at 48 wks: 1.4 placebo; 0.2 treated (p<0.0001)	Mean number of new or newly enlarging T2 lesions at 48 wks: 10.9 placebo; 3.6 treated (p<0.0001)
Agent – Oral	Effect on Gd Lesions*	Effect on New or Enlarging T2 Lesions*
dimethyl fumarate ^{147,148}	Study 1: Mean number of Gd+ lesions at two years: 1.8 placebo; 0.1 240mg bid dose (p<0.0001) ¹⁴⁷ Study 2: Mean number of Gd+ lesions at two years: 2.0 placebo; 0.5 240mg bid dose (p<0.0001) ¹⁴⁸	Study 1: Mean number of new or enlarging T2 lesions at two years: 17 placebo; 2.6 240mg bid dose (p<0.0001) ¹⁴⁷ Study 2: Mean number of new or enlarging T2 lesions at two years: 17.4 placebo; 5.1 240mg bid dose (p<0.0001) ¹⁴⁸
fingolimod ^{149,150}	Study 1: Mean number of T1 Gd+ lesions at month 24: 1.1 placebo; 0.2 0.5mg dose (p<0.001) ¹⁴⁹ Study 2: Mean number of T1 Gd+ lesions at month 24: 1.2 placebo; 0.4 0.5mg dose (p<0.0001) ¹⁵⁰	Study 1: Mean number of new or newly enlarging T2 lesions over 24 months: 9.8 placebo; 2.5 0.5mg dose (p<0.001) ¹⁴⁹ Study 2: Mean number of new or newly enlarging T2 lesions over 24 months: 8.9 placebo; 2.3 0.5mg dose (p<0.0001) ¹⁵⁰
teriflunomide ¹⁵²	Mean number of Gd+ lesions per scan: 1.331 placebo; 0.261 14mg dose (p<0.0001) ¹⁵²	Median change from baseline in total lesion volume (mL) (T1 +T2) at week 108: 1.127 placebo; 0.345 14mg dose (p=0.0003)
Agent – Intravenous	Effect on GD+ Lesions*	Effect on New or Enlarging T2 Lesions*
alemtuzumab ^{71,72} (compared to interferon beta-1a 44mcg tiw)	Percent of patients with Gd+ lesions at 24 months (tertiary outcome): Study 1: 19% IFN; 7% alemtuzumab (p<0.0001) ⁷¹ Study 2: 23% IFN; 9% alemtuzumab (p<0.0001) ⁷²	Patients with new or enlarging T2 lesions (tertiary outcome): Study 1: 58% IFN; 48% alemtuzumab (p=0.04) ⁷¹ Study 2: 68% IFN; 46% alemtuzumab (p<0.0001) ⁷²
mitoxantrone ¹⁵⁴	Number of patients with new Gd+ lesions: 5/32 (16%) placebo; 4/37 (11%) 5mg/m ² dose; 0/31 12mg/m ² dose (p=0.022)	Change in number of T2 lesions, mean (month 24 minus baseline): 1.94 placebo; 0.68 5mg/m ² dose; 0.29 12mg/m ² dose (p<0.001)

<p>natalizumab¹⁵⁵</p>	<p>Median number Gd+ lesions at two years: 0 placebo; 0 treated</p> <p>Percent with two or more enhancing lesions: 16% placebo; 1% treated (p<0.001)</p> <p>Mean number Gd+ lesions at two years: placebo 1.2; treated 0.1 (p<0.001)¹⁵⁵</p>	<p>Median number new or enlarging T2 lesions at two years: 5 placebo; 0 treated (p<0.001)</p> <p>Mean number new or enlarging T2 lesions at two years: 11.0 placebo; 1.9 treated (p<0.001)¹⁵⁵</p>
<p>ocrelizumab^{156,157}</p> <p>(Relapsing MS: comparison with IFN beta-1a 44mcg tiw)</p> <p>(Primary progressive MS: comparison with placebo)</p>	<p>Relapsing MS:</p> <p>Mean number of T1 Gd+ lesions per scan:</p> <p>Study 1: IFN 0.286; ocrelizumab 0.016: 94% relative reduction (p<0.0001)¹⁵⁶</p> <p>Study 2: IFN 0.416; ocrelizumab 0.021: 95% relative reduction (p<0.0001)¹⁵⁶</p>	<p>Relapsing MS:</p> <p>Mean number of new and/or enlarging T2 lesions per scan:</p> <p>Study 1: 1.413 IFN; 0.323 ocrelizumab: 77% relative reduction (p<0.0001)¹⁵⁶</p> <p>Study 2: 1.904 IFN; 0.325 ocrelizumab: 83% relative reduction (p<0.0001)¹⁵⁶</p> <p>Primary progressive MS:</p> <p>Study 3: Mean change in volume (cm³) of T2 lesions from baseline to week 120: 0.79 placebo; -0.39 treated (p<0.0001)⁷⁶</p> <p>Mean percent change in brain volume from week 24 to 120: -1.09 placebo; -0.90 treated (p=0.02)¹⁵⁷</p>

Full Prescribing Information for each agent: [Copaxone](#) (2018), [Glatopa](#) (2018), [Avonex](#) (2016), [Plegridy](#) (2015), [Rebif](#) (2015), [Betaseron](#) (2018), [Extavia](#) (2016), [Gilenya](#) (2018), [Aubagio](#) (2016), [Tecfidera](#) (2017), [Lemtrada](#) (2016), [Novantrone](#) (2008), [Tysabri](#) (2019), [Ocrevus](#) (2017).^{54,55,57,60-63,66-68,70,74-76}

***Comparison across clinical trials is unreliable due to differences in patient populations, diagnostic definitions, primary and secondary endpoints, and outcome metrics.**

After the pivotal trials, several investigations have demonstrated an impact of treatment on the evolution of persistent T1 hypointensities (known as “black holes”) – which are associated with disability as measured by EDSS and considered to be indicative of tissue damage – and on changes in brain volume:

- In a placebo-controlled trial with monthly cerebral MRI, glatiramer acetate was shown to limit the evolution of newly formed lesions into chronic black holes.¹⁶²
- In a phase III trial comparing BG-12 with placebo, which also included glatiramer acetate as an active reference arm, BG-12 and glatiramer acetate significantly reduced the numbers of new T1 hypointense lesions as compared with placebo.¹⁴⁸
- Data analysis from phase III clinical trials and subsequent studies demonstrate a variable effect on brain atrophy.^{71,72,149,150,163-169} Table 4 summarizes the impact of disease-modifying therapies on brain volume loss (BVL) in relapsing-remitting patients in phase III clinical trials – with the following caveats: comparisons across studies cannot be made due to differences in assessment measures and study design; and current methods of MRI brain atrophy quantification provide sufficient precision for cohort studies but are not adequate for assessing changes in individual patients over months or a few years.

Of note, in a two-year, placebo-controlled trial, brain atrophy was greater in year one and less in year two in natalizumab-treated patients,¹⁴² leading some researchers to suggest that the brain atrophy seen in year one may have been “pseudoatrophy” – a reduction in sub-clinical inflammation in response to treatment. However, De Stefano and Arnold¹⁷⁰ assert that a complete understanding of pseudoatrophy requires further study to clarify the possible underlying pathology.

Table 4: The effect of DMTs on BVL in RRMS patients in phase III trials.

Agent	Changes in Brain Volume Loss		
	Year 0-1	Year 1-2	Year 0-2
interferon beta-1a IM ¹⁷¹	×	✓ 55% reduction vs. placebo	×
interferon beta-1a SC ¹⁷²	—	—	×
interferon beta-1b SC ^{173,174}	—	—	—
glatiramer acetate ^{163,175–177}	×	✓	×
	(Eur/Canadian GA trial)	40% reduction vs. placebo (Eur/Canadian GA trial)	(Eur/Canadian GA trial)
	8% reduction vs. SC IFN-β-1a (REGARD) ⁺	22% reduction vs. SC IFN-β-1a (REGARD) ⁺	13% reduction vs. IFN-β-1a (REGARD)
	No sig. difference with GA +/- SC IFN-β-1b (BEYOND)	No sig. difference with GA +/- SC IFN-β-1b (BEYOND)	No sig. difference with GA +/- SC IFN-β-1b (BEYOND)
	No sig. difference with GA +/- SC IFN-β-1a (CombiRx)	No sig. difference with GA +/- SC IFN-β-1a (CombiRx)	No sig. difference with GA +/- SC IFN-β-1a (CombiRx)
natalizumab ^{165,169}		✓	×
	40% increase vs. placebo (AFFIRM)	44% reduction vs. placebo (AFFIRM)	(AFFIRM)
	19% increase vs. placebo (SENTINEL)	×	×
		23% reduction with natalizumab+ IM IFN-β-1a vs. IM IFN-β-1a + placebo (SENTINEL)	(SENTINEL)
teriflunomide ¹⁵²	37% reduction vs. placebo (TEMSO)	31% reduction vs. placebo (TEMSO)	×
dimethyl fumarate ^{178,179}	—	21% reduction vs. placebo (DEFINE)	✓21% reduction vs. placebo (DEFINE) ‡
		Significant effect (DEFINE)	×‡ (CONFIRM)
		×‡ (CONFIRM)	
alemtuzumab ^{71,72}		—	✓ 24-42% reduction vs. IFN-β-1a
laquinimod ^{180,181}	—	—	✓ (ALLEGRO) 33% reduction vs. placebo (BRAVO) 28-34% reduction vs. placebo
fingolimod ^{149–151}	✓	✓	✓
	23-40% reduction vs. placebo	28-45% reduction vs. placebo	33-35% reduction vs. placebo
	✓§ 45% reduction vs. IM IFN-β-1a (TRANSFORMS)	—	—

Table 4 Abbreviations: AFFIRM: Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis; ALLEGRO: Assessment of Oral Laquinimod in preventing progression in Multiple Sclerosis; BEYOND: Betaferon Efficacy Yielding Outcomes of a New Dose; BID: Twice daily; BRAVO: Benefit-Risk Assessment of Avonex and Laquinimod; BVL: Brain Volume Loss; CombiRx: Combination Therapy in Patients with Relapsing-Remitting Multiple Sclerosis; CONFIRM: Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis; DEFINE: Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting Multiple Sclerosis; DMTs: Disease Modifying Therapies; GA: Glatiramer Acetate; IFN: Interferon; IM: Intramuscular; REGARD: The Rebif vs Glatiramer Acetate in Relapsing MS Disease; RRMS: Relapsing-Remitting Multiple Sclerosis; SC: Subcutaneous; SENTINEL: The Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing Remitting Multiple Sclerosis; TEMSO: Teriflunomide Multiple Sclerosis Oral; TID: Three Times Daily; TRANSFORMS: Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis.

Table 4 Symbols:

– Data not reported/available.

× No significant effect or not statistically significant.

✓ Significant effect.

* Not all approved therapies have significant effects on BVL and effects can be delayed until the second year of therapy.

+ No P value reported.

†Significant effect at 9–18 months.

‡Significant effect at 6–24 months in DEFINE (only BID, not TID dose arm), but not in CONFIRM study.

§Significant effect also seen at 0–6 months.

Table 4 was adapted from the following source: Alroughani et al.¹⁸² Copyright: Alroughani R, Deleu D, El Salem K, Al-Hashel J, Alexander KJ, Abdelrazek MA, Aljishi A, Alkhaboori J, Al Azri F, Al Zadjali N, Hbahbih M, Sokrab TE, Said M, Rovira A. 2016. BMC Neurology. Reproduced via Open Access under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>).

Head-to-head comparison data in relapsing MS

In addition to the active comparator registration trial data reported in Table 2, the following comparison trials have been reported:

- **IFNB-1a 44mcg tiw vs. IFNB1a weekly (EVIDENCE):** A prospective, 24-week, randomized, controlled, multi-center trial of 677 RRMS patients demonstrated superior efficacy in favor of IFNB-1a tiw in the number of relapse-free patients ($p=0.0005$) and active MRI lesions ($p<0.001$).¹⁸³
- **IFNB-1a IM weekly + GA 20 mg SC daily vs. IFNB-1a IM weekly or GA 20 mg SC daily (CombiRx):** A double-blind, randomized, controlled study that followed patients for a minimum of three years found: the combination to be significantly better than IFN alone in reducing the risk of relapse and superior to either agent alone in reducing new lesion activity and accumulation of total lesion volume; GA to be significantly better than IFN in reducing the risk of relapse; the combination to be no better than either agent alone in reducing progression.¹⁸⁴
- **IFNB-1b vs. GA (BECOME):** A prospective, randomized, single-blind (MRI rater), one-year study of 75 RRMS patients demonstrated no difference in MRI outcomes.¹⁸⁵
- **IFNB-1b 250 mcg or 500 mcg vs. GA (BEYOND):** A prospective, randomized, multi-center study of 2244 RRMS patients over 2–3.5 years demonstrated no difference in relapse rate, EDSS progression and MRI outcomes.¹⁶³
- **Oral BG12 (dimethyl fumarate) (240 mg bid and tid) vs. GA (reference comparator) (CONFIRM):** A prospective placebo-controlled phase III, randomized trial of 1417 RRMS patients with GA as a reference comparator demonstrated the superiority of all three agents relative to placebo on risk of relapse (BG12 bid $p=0.002$; BG12 tid $p<0.001$; GA $p=0.01$); no significant reduction in disability progression for any of the agents; all agents superior to placebo on MRI outcomes $p<0.001$.¹⁴⁸
- **IFNB-1b vs. IFNB-1a weekly (INCOMIN):** A prospective, 2-year, randomized, multi-center trial of 188 RRMS patients demonstrated superior efficacy in favor of IFNB-1b on risk of relapse ($p=0.003$) and MRI outcomes ($p<0.0003$).¹⁸⁶

- **IFNB-1a tiw vs. GA (REGARD):** A prospective, randomized, comparative, parallel-group, open-label study of 764 RRMS patients demonstrated no difference between groups in time to first relapse and no significant differences for MRI outcomes except IFNB-1a patients had significantly fewer enhancing lesions ($p=0.0002$).¹⁷⁷
- **Teriflunomide vs. IFNB-1a tiw (TENERE):** A prospective, randomized, controlled, phase III, multi-center rater-blinded trial of 324 RRMS patients demonstrated: no difference in the primary outcome of time to failure (first appearance of confirmed relapse or permanent treatment discontinuation for any cause); and no difference in ARR (secondary outcome) between teriflunomide 14 mg and IFNB-1a, but ARR was higher with teriflunomide 7mg vs. IFB-1a ($p=0.03$).¹⁸⁷
- **Fingolimod vs. IFNB-1a weekly (TRANSFORMS):** A prospective, 12-month, double-blind, randomized trial of 1153 RRMS patients demonstrated superior efficacy in favor of fingolimod with respect to relapse rate ($p<0.001$) and MRI outcomes ($p<0.001$).¹⁵¹
- **Ocrelizumab vs. IFNB-1a tiw (OPERA I and II)** demonstrated the superiority of ocrelizumab in annualized relapse rate and MRI outcomes, as well as disability progression (pooled analysis) (see Tables 2 and 3).¹⁵⁶

Additional studies comparing various agents provide important information for healthcare providers and patients who are making complex treatment decisions:

- A large international, observational, prospectively acquired cohort study looking at relapse and disability outcomes in 792 RRMS patients who had disease activity while on IFN beta or GA and switched to either natalizumab or fingolimod, demonstrated a post-switch difference in relapse hazard ($p=0.002$) in favor of natalizumab and a significant sustained disability regression ($p<0.001$) also in favor of natalizumab.¹⁸⁸
- In the MSBase cohort study, Lizak and colleagues used longitudinal data from 4295 patients to evaluate time from baseline to EDSS epochs 3-6, 4-6 and 6-6.5. They found that disease progression in patients with moderately advanced and advanced MS occurs irrespective of prior disease activity and that lower relapse rates and greater time on higher efficacy disease-modifying agents (natalizumab, fingolimod, alemtuzumab, dimethyl fumarate, rituximab, mitoxantrone, cladribine) is associated with a decreased risk of further disability progression.¹⁸⁹
- A retrospective cohort study of 84 RRMS patients treated with natalizumab or IFNB-1a 44 mcg tiw for at least 12 consecutive months demonstrated that both agents reduced ARR, but the effect was stronger in the natalizumab-treated group ($p=0.0125$). EDSS reduction favored natalizumab ($p=0.0018$). MRI outcomes were decreased with both agents. In the second year, ARR and EDSS progression were similar to year one; however, Gd-enhancing lesions decreased more significantly with natalizumab ($p=0.008$).¹⁹⁰
- Nixon and colleagues used a statistical modeling approach to account for differences in baseline characteristics and predict indirect relative risk of achieving NEDA (No Evidence of Disease Activity) status for fingolimod vs. dimethyl fumarate or teriflunomide in an average patient from their respective phase III trials. Results estimated that the relative risk of achieving NEDA status was greater with fingolimod than with the other therapies vs. placebo in each respective trial population.¹⁹¹

Evidence Demonstrating the Impact of Treatment on Progressive MS

Many agents have been investigated for use in secondary progressive or primary progressive MS.^{192,193} Sub-group analyses from some of these clinical trials indicated benefits in patients of younger age with more recent progression, recent relapse and/or MRI activity.¹⁹³ Only mitoxantrone, which is seldom used in the United States because of its high risk profile, has an FDA indication for secondary progressive MS.⁷⁴ Only ocrelizumab has FDA approval for primary progressive MS.⁷⁶ The remaining medications are approved for relapsing forms of MS, which include progressive MS in those patients who experience relapses.

Impact on long-term clinical outcomes

In addition to being expensive and difficult, it is unethical in the current treatment era to carry out long-term randomized controlled studies to assess the value of disease-modifying treatment compared to placebo on the course of MS. Hence, alternate methods for studying natural history in the treatment era need to be employed. Following an observational cohort of people over an extended period has limitations, including non-randomized design, difficulty accounting for drop-outs and, in some studies, retrospective assessments conducted on individuals seen at divergent time periods. However, important data have emerged demonstrating that early and ongoing treatment has a significant impact on long-term clinical outcomes:

- In a cohort observational study of 3,060 patients, disease-modifying therapies delayed long-term disability, as measured by the EDSS, in patients treated either early or, to a lesser extent, in the later phase of the disease compared to untreated patients.⁸²
- In a longitudinal prospective study of newly-diagnosed MS patients at Karolinska Hospital between 2001-2005, early treatment was correlated with longer time from diagnosis to EDSS ≥ 4 .¹⁹⁴
- The 10-year follow-up of the early intervention trial with interferon beta-1a (intramuscular) found a delayed conversion to clinically definite MS and reduced relapse rates in the early treated group compared to the delayed treatment group, but no difference in disability outcomes, most likely because both groups received treatment relatively early in the disease course.¹⁹⁵
- In a nine-year follow-up of the pivotal phase III teriflunomide trial (TEMSO), a positive effect on disease activity persisted in the original treatment group as well as in the placebo patients who switched to active treatment in the open-label extension.¹⁹⁶
- A long-term follow-up (greater than seven years) of a phase II fingolimod study demonstrated a persistent positive effect on relapse and MRI activity.¹⁹⁷
- Approximately 90 percent of untreated RRMS patients will have SPMS after 15-26 years.^{198,199} Evidence from several studies now indicates that disease-modifying therapies have an impact on the conversion from relapsing to progressive MS:
 - In a study comparing the time interval from disease onset to secondary progression in relapsing-remitting patients treated with disease-modifying therapy and patients receiving no treatment, a significantly longer time to secondary progression was seen in the treated group.²⁰⁰
 - A study comparing treated and untreated patients over a 10-year period prior to the endpoint of conversion to secondary progressive MS found that treatment with a disease-modifying therapy significantly reduced the risk of disease progression in patients considered high- or low-risk at disease onset.²⁰¹
 - In a study comparing patients treated with interferon beta for up to seven years with untreated patients, the treated group had a significant reduction in the incidence of secondary progression as well as in the incidence of EDSS progression.²⁰²
 - In a single center prospective observational study of 517 actively treated relapsing MS and CIS patients at a median time point of 16.8 years after disease onset, only 10.7 percent reached an EDSS ≥ 6.0 , and 18.1 percent evolved to secondary progressive MS.²⁰³
- The impact of early treatment on other clinical outcomes is also important. Extension study data from the early treatment trial with interferon beta-1b suggest that early treatment helps to preserve cognitive function compared to delayed treatment,^{204,205} with evidence suggesting that long-term (physical *and* cognitive) outcomes may be largely determined early in the disease course.¹¹⁵ Another study demonstrated decreased mortality in patients treated early in the course of their disease compared with those treated later,¹⁵ a finding that needs to be confirmed with the newer agents in long-term studies.
- Most of the extension studies from the pivotal trials indicated a positive impact on time to a second attack or new lesions, relapse rates and disease progression,^{115,137,175,204} although much of the impact has been thought to take place early in the disease course.¹¹⁵ In a more recent study, using data extracted from the global MSBase Registry, Jokubaitis and colleagues¹¹² examined median EDSS score changes in 2,466 relapse-onset patients initially treated with either interferon-beta or glatiramer

acetate. The patients (including those who stayed on their initial treatment, those who switched to other therapies and those who stopped treatment altogether) were treated an average of 83 percent of the follow-up period. The cumulative time on treatment was independently associated with a lower EDSS score at 10 years, demonstrating that increased exposure to treatment predicts better disability outcomes in the long-term. The authors also found that annualized relapse rate was the strongest predictor of increases in median EDSS scores, with on-therapy relapses being more predictive than off-therapy relapses – and concluded that persistent relapse activity on a first-line therapy is prognostic of increasing disability.

Impact on NEDA (no evidence of disease activity)

NEDA is a term used to describe disease stability, including no new relapses, no disability progression and no new or enlarging MRI lesions.^{206,207} In addition, some researchers have proposed adding no additional brain volume loss to this definition (NEDA-4).^{208,209} Post-hoc analysis of several MS treatment trials has suggested that the goal of NEDA may be achievable for some individuals.^{206,207,210} The evidence to date suggests that NEDA is difficult to sustain over the long term even with treatment. On the basis of their seven-year longitudinal study, Rotstein and colleagues conclude that NEDA status at two years may be a good predictor of long-term disease stability and may be useful as a treatment outcome in investigations of new treatments for MS.²⁰⁷

However, in a prospective single center observational study of 517 actively treated relapsing MS patients, NEDA at two years was not associated with better long term measures of disability by EDSS.²⁰³ In the 16- and 21-year follow-up from the pivotal trial of interferon beta-1b study patients, NEDA based on clinical features predicted long-term disability outcome; however adding MRI changes to the NEDA criteria did not increase predictive validity.²¹¹

Although NEDA is a compelling concept and shared goal among people with MS and their healthcare providers, no consensus has yet emerged for the role of NEDA in making clinical decisions.

Impact on quality of life

Clinical and MRI outcomes do not fully capture the impact of MS disease-modifying therapies for people with MS. Unfortunately, efforts to assess the impact of treatment on quality of life have been limited. In one study of newly-diagnosed patients beginning treatment with an interferon medication, quality of life scores on the MSQoL-54 showed overall improvement at 12 months.²¹²

Not being on a disease-modifying therapy was one of the factors identified as contributing to a decrease in health-related quality of life in the NARCOMS database, although quality of life generally remained fairly stable for most people over the five years of the study.²¹³ Health-related quality of life scores on physical and mental components of the Short Form (36) Health Survey (SF-36 – a patient-reported survey of health outcomes) improved in the pivotal trials of natalizumab.²¹⁴ In the pivotal trial of dimethyl fumarate, patients on treatment evidenced a significant improvement in SF-36 physical component summary scores compared with placebo-treated patients whose scores worsened, and similar benefits were seen in other measures of functioning and general well-being as early as week 24.²¹⁵

Early treatment to reduce loss of mobility has been shown to help preserve people's ability to carry out instrumental activities of daily living,²¹⁶ and the ability to work was found to improve after one year of treatment with natalizumab.²¹⁷

In a review of existing data on the relationship between inflammation, patterns of CNS lesions and the effects of immunotherapeutics on MS fatigue, the disease-modifying therapies were observed to “effectively and sustainably stabilize and ameliorate fatigue in parallel to their dampening effects on the neuroinflammatory process.”²¹⁸

Benefits gained through early treatment may never be equaled in those whose treatment is delayed

Data suggest that benefits gained through early treatment, including delay of a second clinical event or MRI activity in CIS patients, reduced relapse rates and disability, may not be equaled in those who start treatment later in the disease course,^{88,90,112,195,219–222} suggesting that people who start treatment later may not “catch up” with those who start treatment immediately.

As stated earlier however, the 10-year follow-up to the early intervention trial with interferon beta-1a (intramuscular) found no difference in disability outcomes between the early- and delayed-treatment groups, indicating that the delayed treatment group did appear to experience a “catch up” in this particular outcome.¹⁹⁵ It remains to be determined the extent to which the older medications – and the newer medications for which we have limited long-term data – impact longer-term disability outcomes for people with MS. Similarly, 11-year follow-up data on the CIS cohort treated with interferon beta-1b or placebo for up to two years prior to open label active therapy demonstrated no significant difference in EDSS outcome between groups.²²³

Evidence Supporting the Need for Treatment to be Ongoing

Once a disease-modifying treatment is initiated, evidence suggests that treatment needs to be ongoing for benefits to persist. Cessation of treatment has been shown to negatively impact clinical and MRI outcomes.

- Non-adherence and gaps in treatment are associated with an increased rate of relapses and progression of disability.^{224,225}
- In a review of studies looking at treatment discontinuation, Tobin and Weinschenker concluded that discontinuation of treatment early in MS could lead to re-emergence of disease activity. The impact of treatment discontinuation in patients over the age of 60 with long-term progressive disease is less clear.²²⁶
- In a review of the adherence results, relapse rate and progression were greater in those who stopped injectable disease-modifying treatment, and several reviewed trials showed an increase in emergency department utilization by patients who had stopped treatment.²²⁷
- In one study, relapses and MRI activity returned to baseline following cessation of interferon therapy, although there was a several month refractory period before activity resumed.²²⁸ In another study, active patients treated with interferon beta promptly returned to pre-treatment levels of disease activity following discontinuation of treatment,²²⁹ leading the authors to recommend that treatment not be stopped in patients who are responding to treatment. A similar return to baseline disease activity in interferon-treated patients was observed in secondary progressive MS, with an increase in EDSS scores and MRI activity in the year after discontinuation of treatment.²³⁰
- Relapse rates returned to baseline following interruption of natalizumab treatment in three large studies,²³¹ and in a partially placebo-controlled exploratory study of disease activity during an interruption of natalizumab therapy, patients whose treatment was interrupted had an increased risk of disease and MRI activity compared with those on continuous treatment.²³² In a retrospective study of patients refractory to interferon or glatiramer who had been switched to natalizumab and then stopped it, some patients had significant relapses – indicating that simple withdrawal of this medication without early implementation of an alternative treatment strategy may risk return of disease activity or rebound, typically within the first six months.^{220,233–235} In a study of 32 patients with MS who stopped natalizumab treatment, rebound was identified with an increase in relapses and high MRI activity compared to baseline.²³⁶
- Cessation of fingolimod after a period of stability was followed by clinical relapse and multiple enhancing lesions on MRI in two patients,²³⁷ and both patients had a significant worsening in EDSS scores associated with their clinical activity. In another report of six cases of fingolimod discontinuation, five patients returned to pre-treatment disease activity within three months, and one patient had both clinical and MRI rebound activity.²³⁸ A recent review reported five individuals experiencing increased disease activity within 4-16 weeks following discontinuation of fingolimod therapy (10.9 percent of 46 patients discontinuing the drug during the two-year observation period) and identified 11 other reported cases of rebound disease activity.²³⁹

These studies and case reports illustrate the need for ongoing disease-modifying treatment in MS. Regardless of the reason for the discontinuation of treatment – a decision by the treating clinician, patient non-adherence, cost or insurance coverage issues – these findings indicate that discontinuation or interruption of treatment will provoke a return of disease activity in many people.

Situations in which discontinuation of treatment might be considered

While there is ample evidence to support the benefits of ongoing treatment for the majority of people with MS, there may be some situations in which clinicians and their patients might consider stopping treatment.⁷⁸ In a 2015 review of relevant studies, Tobin and Weinshenker²²⁶ conclude that although freedom from subsequent relapse is impossible to guarantee, treatment cessation may be considered in patients who:

- Are over 60 years of age
- Have experienced a progressive disease course for five years or longer
- Have no accumulating T2 lesions or gadolinium enhancing lesions on MRI of the brain or spinal cord after a period of observation over several years

Earlier discontinuation, particularly in patients with active disease, may lead to increased disease activity. Clinical and MRI monitoring for recurrent disease activity is clearly warranted in those patients.

Use of Disease-Modifying Therapies in Pediatric MS

Studies have estimated the incidence of pediatric MS to be between 0.18 and 0.51/100,000 children per year.^{240,241} Three to 10 percent of adult patients retrospectively report a possible first attack prior to age 18.²⁴² More than 97 percent of children and adolescents experience a relapsing-remitting disease course,²⁴⁰ with annualized relapse rates 2-3 times that of adults with MS during the first three years of disease.²⁴³ In addition to motor and other physical symptoms that occur during relapse (and often resolve with relapse therapy), 30-40 percent of children with MS demonstrate cognitive impairment early in the disease course.¹²⁷⁻¹²⁹

The interferon beta medications and glatiramer acetate have traditionally served as the initial treatment options for children with MS.^{240,244} The recently completed PARADIGMS trial, a double-dummy randomized trial comparing fingolimod to interferon beta-1a by subcutaneous injection demonstrated a clear superiority of fingolimod over interferon (82 percent reduction in relapse rate). Superiority of fingolimod was also demonstrated by MRI endpoints. The FDA has now approved fingolimod for pediatric MS, the first FDA approval for any MS therapy in this age group. While data regarding how the PARADIGMS results will alter clinical practice have yet to be accrued, the option of oral therapy will appeal to many children. Safety considerations, however, must be carefully considered. Structured screening protocols, such as ensuring up to date vaccination status (notably confirmation of vaccination against varicella zoster), ophthalmological and dermatological evaluations, and monitoring for first-dose effect bradycardia are critical. Pediatric centers may need to partner with adult MS centers to ensure consistent care programs for fingolimod use.

As in adults, however, evidence of ongoing relapses, MRI activity, and increasing disability (which is less common in pediatric MS patients) indicate the need to escalate to higher potency therapies. Considerations include switching from interferon or glatiramer acetate to oral or infused medications.²⁴⁴ In one study involving 258 children over a mean observation period of 3.9 years, a little more than half were successfully managed on the first medication they were given, while 25.2 percent were switched once, 11.2 percent were switched twice, and 7.8 percent required three changes in medication. While some were switched from one injectable medication to another, others required more aggressive treatment in order to control their disease.²⁴⁴ Several retrospective analyses regarding safety and tolerability of natalizumab support the use of natalizumab in pediatric MS patients with active or aggressive disease.²⁴⁵⁻²⁴⁸ Case report and case series data have advocated use of rituximab for patients

requiring escalation of therapy,^{249–251} while future study of ocrelizumab in pediatric MS patients is awaited.

The importance of high quality data regarding therapeutic safety and efficacy has been emphasized²⁴⁰ and pediatric clinical trials of all new agents are mandated by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).^{252–254} The PARADIGMS trial not only informed on the impact of fingolimod vs. interferon beta-1a on clinical and MRI disease activity in pediatric MS patients, it also provided new insight into the challenges of pediatric MS clinical trials. Enrollment took longer than anticipated, a multinational site study was required owing to the rarity of pediatric MS, and the burden of rigorous clinical trial monitoring and visits challenged patients, parents and providers. Nonetheless, it is imperative to determine how best to ensure that all trials produce informative data on therapeutic safety and efficacy, and the International Pediatric Multiple Sclerosis Study Group is preparing a working group manuscript that addresses these key considerations.

It is noteworthy that access to certain medications for pediatric MS patients in some world regions may be limited by regulation. It is hoped that clinical trial data will enhance regulatory approval and access.

Treatment Considerations in Women and Men in Their Reproductive Years

None of the FDA-approved disease-modifying therapies are approved for use during pregnancy or breastfeeding (see Table 1). Several observational studies, including pregnancy registries, have been done to identify potential risks of the disease-modifying therapies for fetal development and breastfeeding.^{255–257}

- Glatiramer acetate does not cross the placenta and is likely safe for use during breastfeeding.²⁵⁵ Confirming earlier findings in small studies,²⁵⁸ a prospective cohort study of 246 pregnancies (from the German Multiple Sclerosis and Pregnancy Registry), in which 151 women were exposed to glatiramer acetate (pregnancy category B) and 95 were taking no disease-modifying therapy, found no impact on several major pregnancy outcomes (risk for congenital anomaly, lower birth weight, pre-term birth or spontaneous abortion).²⁵⁹
- Beta-interferon crosses the placenta in minimal quantities; it is unknown whether it is excreted in breast milk.²⁶⁰ Using the same German Multiple Sclerosis and Pregnancy Registry database, a prospective study of 445 pregnancies, in which 251 women were exposed to interferon-beta and 194 were taking no disease-modifying therapy, found no differences in mean birth weight and length, pre-term birth, spontaneous abortion or congenital anomalies.²⁶¹
- Teriflunomide carries a boxed warning about the risk of teratogenicity (see Table 1). This medication crosses the placenta; it is unknown whether it is excreted in human milk.⁶⁸ A study of 105 pregnancy exposures (83 female and 22 male) to teriflunomide for varying lengths of time found no increase in spontaneous abortion rate or fetal abnormalities.²⁶² A rapid elimination program using oral cholestyramine over several days is recommended for women to lower teriflunomide levels to less than 0.02 µg/ml. Men taking teriflunomide should stop the medication before trying to conceive and discuss rapid elimination with their healthcare providers. The 2018 AAN Practice Guideline includes a Level B recommendation that clinicians should counsel men with MS regarding the implications of their treatment decisions for their reproductive plans before initiating treatment with a chemotherapeutic agent such as teriflunomide or cyclophosphamide. Refer to AAN.com/guidelines.⁷⁸
- Fingolimod crosses the placenta and is excreted in breastmilk. A pregnancy registry is ongoing and patients are advised to use effective contraception and wait at least two months before attempting conception.⁶⁷
- It is unknown whether dimethyl fumarate crosses the placenta or enters breastmilk.⁶⁶ Animal studies of teratogenicity have shown conflicting results.²⁵⁶ Because of its short half-life (approximately one hour), no washout may be necessary.^{66,257}
- Natalizumab crosses the placenta and is excreted in breast milk.^{75,255} Compared with historical controls, no significant difference has been found in the rate of fetal malformations in MS and Crohn's clinical trial programs or the Tysabri Pregnancy Exposure Registry.²⁶³

- Mitoxantrone crosses the placenta in limited amounts and is excreted in breast milk.⁷⁴ Patients should be instructed not to become pregnant while taking mitoxantrone and for at least six months after discontinuation.²⁵⁵
- Alemtuzumab crosses the placenta; it is not known whether it is excreted in breast milk. Because alemtuzumab has the potential for serious adverse reactions in infants, women should be advised not to breastfeed while on this medication.⁷⁰ There are no adequate and well-controlled studies in pregnant women.⁷⁰
- Ocrelizumab is a humanized monoclonal antibody of an immunoglobulin G1 subtype and immunoglobulins are known to cross the placental barrier. Following administration to pregnant monkeys, at doses 2-10 times the approved human dose by weight, increased perinatal mortality, depletion of B-cell populations, renal, bone marrow and testicular toxicity were observed in the offspring. Women of childbearing age should use contraception while receiving ocrelizumab and for six months after the last dose. There are no data on the presence of ocrelizumab in human milk; it is excreted in the milk of ocrelizumab-treated monkeys. Human IgG is excreted in human milk, and the potential for absorption of ocrelizumab to result in B-cell depletion in infants is unknown.⁷⁶

The current standard of care is to avoid the use of disease-modifying therapies during pregnancy and breastfeeding.^{256–258,264–267} Based on exponential decay, the commonly accepted timeframe for drug discontinuation before conception is five maximal half-lives – approximately two to six weeks,²⁶⁶ with two months recommended for fingolimod and at least three months for natalizumab.²⁶⁴ However, there is increasing evidence that glatiramer acetate and interferon-beta may be continued safely during conception and pregnancy in a woman with very active disease.^{264,265,268–270} The risks and benefits of continuing therapy during pregnancy require careful discussion, taking into account the level of disease activity, personal preferences and the patient’s and doctor’s risk tolerance. Similarly, a discussion about the risks and benefits of postponing resumption of treatment in order to breastfeed is important, particularly for women who had active disease in the year prior to conception.²⁵⁷ In a recent study, natalizumab started within eight days of delivery successfully prevented post-partum relapses in five of six women with very active disease.²⁷¹

Rationale for Access to the Full Range of Treatment Options

At present, 15 medications are FDA-approved to treat MS (See Table 1), with ten different mechanisms of action that are thought to address distinct components of the immune-mediated disease process. These medications also differ in their route and frequency of administration as well as their side effects and risk profiles. *None of these medications are curative and the efficacy of any given medication varies considerably from one individual to another and for any given individual at different points in time.* In addition, people with MS differ in their tolerance for different routes of administration and side effects, and clinicians and patients vary in their tolerance for risk, with risk tolerance likely undergoing shifts as the disease progresses. Access to the full range of options is essential to optimal management, for the following nine reasons.

1. Non-responders need access to other options

The goal of treatment is to control disease activity and prevent irreversible damage as quickly and effectively as possible. When a person’s medication does not provide sufficient suppression of disease activity or provides initial benefit and then ceases to do so – as determined by the individual and his or her clinician in light of continued clinical and/or MRI disease activity – the reasons for lack of efficacy need to be explored²⁷² and alternative options need to be considered.⁸⁰ It is known, for example, that disease activity which occurs in spite of treatment with IFN beta or GA is associated with unfavorable long-term outcomes.^{112,273,274} Furthermore, MRI activity as well as relapses are key indicators of progression^{275,276} and the presence of Gd-enhancing lesions has been shown to correlate with worsening disability after 15 years.²⁷³

2. The effort to achieve NEDA requires access to the full range of treatment options

To achieve NEDA or the lowest possible level of subclinical disease activity, the authors of “Brain Health: Time Matters in Multiple Sclerosis” (endorsed by the MS Coalition) recommend swift action in the face of disease activity, including consideration of switching to another disease-modifying therapy with a different mechanism of action.²⁷⁷

3. Treatment with interferon beta and natalizumab is associated with the development of neutralizing antibodies (NAbs)

Although comparisons are challenged by lack of standardization in assays and lack of consensus concerning the relevant threshold of NAb concentration,²⁷⁸ the phase III trials of the interferon beta medications,^{144–146} as well as subsequent direct comparison studies,^{279,280} have demonstrated that NAbs are a common occurrence with these medications and that there is significant variability between the medications in terms of their occurrence. Furthermore, the studies suggest that the presence of NAbs reduces the clinical efficacy of interferon beta – although the impact may not be clear for some time.²⁷⁸ Determining the impact of NAbs for any given individual is further complicated by the fact that NAb-positive patients may revert to NAb-negative status or fluctuate between positive and negative NAb status.²⁷⁹ However, the fact remains that a person who has persistent disease activity on interferons, regardless of whether or not this is due to NAbs, requires access to non-interferon treatment options.^{281,282}

In two phase III clinical trials of natalizumab,^{155,283} the incidence of persistent antibody positivity associated with the drug was 6 percent. Compared with antibody-negative patients, those with persistent antibody positivity had a significantly higher relapse rate and more activity on MRI in both studies, as well as significantly greater disease progression in one of the studies.²⁸⁴ Persistent antibody positivity was also associated in both studies with a higher incidence of infusion-related adverse events, including hypersensitivity reactions.²⁸⁴

Of the 58 percent of patients in a prospective observational study of 73 consecutive patients²⁸⁵ who developed NAbs, the vast majority reverted to antibody-negative status on follow-up. In this study, the presence of NAbs was inversely correlated with serum natalizumab concentration, and high antibody titers and low serum natalizumab concentrations were associated with an increase in relapses and Gd-enhancing lesions on MRI.

4. Individuals at high-risk for PML need access to other options

People who are or become JC antibody-positive need access to treatments that do not put them at risk for PML.

- The boxed warning for [Tysabri](#) (natalizumab) states that the risk factors for the development of PML include duration of therapy, prior use of immunosuppressants and the presence of anti-JCV antibodies – and that these factors should be taken into account when initiating and continuing treatment with this medication.⁷⁵
- The prescribing information for [Gilenya](#) (fingolimod) states that the medication should be withheld at the first sign or symptom suggestive of PML.⁶⁷ It is not known whether individuals with anti-JCV antibodies taking fingolimod are at higher risk of PML given the limited number of PML cases to date with this agent.
- The prescribing information for [Tecfidera](#) (dimethyl fumarate) states that the medication should be withheld at the first sign or symptom suggestive of PML.⁶⁶ It is not known whether individuals with anti-JCV antibodies taking dimethyl fumarate are at higher risk of PML given the limited number of PML cases to date with this agent.
- The prescribing information for [Ocrevus](#) (ocrelizumab) states that PML is possible with this medication.⁷⁶

A PML risk stratification for disease-modifying therapies is summarized in Table 4.²⁸⁶

TABLE 4: A PML risk stratification table for disease modifying therapies.*

Table 1
A PML risk stratification table for disease modifying therapies.

Therapeutic Agent	Treated condition predisposes to PML?	Latency from time of drug initiation to PML	Frequency/ Incidence of PML	Year drug introduced into U.S. and European markets	Patients/patient-year (PY) exposure#
Class I – high potential risk of PML					
Natalizumab	No MS and Crohn's disease	Yes None < 8 months; > 85% of cases > 24 months	High 1/100–1/1000	U.S.- approved 2004; withdrawn Feb 2005; reintroduced Jun 2006 EUR – Apr 2006	161,300 patients ~527,159 PY (September 30, 2016)
Class II – low potential risk of PML					
Dimethyl fumarate	No MS and psoriasis	Yes 18–54 months	Low/infrequent ~1/50,000	U.S. – Mar 2013 Europe – Feb 2014	224,542 patients 308,732 PY
Fingolimod	MS	18–54 months*	~1/18,000	U.S.- Sep 2010 EUR-Mar 2011	160,000 patients 368,000 PY
Class III – no or very low potential risk of PML					
Alemtuzumab	Yes Hematological malignancies, transplantation	No	Very low or evident only with related drug Unknown; no cases with MS	U.S. – Nov 2014 EUR – Sep 2013	~11,000 patients ~6000 PY
Rituximab	Lymphoproliferative disorders, rheumatoid arthritis, ANCA-associated vasculitis, SLE		1/30,000	MS – unapproved indication	No data
Mitoxantrone	Non-Hodgkins lymphoma and leukemia			U.S.-Oct 2000 EUR-divergent dates	No data
Teriflunomide	No PML observed with teriflunomide but with related leflunomide			U.S.-Sep 2012 EUR-Aug 2013	68,952 patients 96,909 PY
Daclizumab	No PML observed with MS or as nonbivlaxis for renal transplant			U.S.-May 2016 EUR-Jul 2016	1516 patients 3744 PY

Legend PY - Patient year exposure.

U.S. – United States.

EUR - Europe.

- Data on file with respective manufacturer as of submission date.

*This table and the associated paper were published prior to the FDA-approval of ocrelizumab. However, the prescribing information for ocrelizumab states that PML has been seen in patients treated with other anti-CD20 antibodies.

Printed with permission of the publisher

5. Individuals with contraindications need access to suitable options

For a variety of reasons (cited as contraindications in medication labeling),^{54,55,57,60–63,66–68,70,74–76} individuals may not be suitable candidates for one or another of the available disease-modifying therapies:

- Hypersensitivity to glatiramer acetate or mannitol, precluding the use of glatiramer acetate
- Hypersensitivity to natural or recombinant interferon beta, albumin or other component of the formulation, precluding the use of interferon medications Hypersensitivity to dimethyl fumarate or to any of the excipients, precluding the use of dimethyl fumarate
- Cardiac or ocular conditions, or treatment with Class 1a or Class III anti-arrhythmic drugs, precluding the use of fingolimod
- Hypersensitivity to fingolimod or its excipients, precluding the use of fingolimod
- Current use of leflunomide, precluding the use of teriflunomide
- Infection with HIV, precluding the use of alemtuzumab
- Hypersensitivity reaction to natalizumab, precluding the use of natalizumab

- Current or past diagnosis of progressive multifocal leukoencephalopathy (PML), precluding the use of natalizumab
- Severe hepatic impairment, precluding the use of fingolimod, interferons, natalizumab and teriflunomide
- Positive tuberculosis screening requiring standard TB treatment prior to teriflunomide dosing
- Active hepatitis B infection, precluding the use of ocrelizumab
- History of life-threatening infusion reaction to ocrelizumab, precluding its use

In addition to these contraindications, post-marketing data ([Avonex](#); [Rebif](#); [Betaseron](#); [Extavia](#))^{57,60–62} have led many clinicians to avoid the use of interferon beta medications in individuals who are depressed or have a history of significant depression. Although several studies have found no increased frequency of depression in patients taking interferon beta medications compared with those not taking these medications, interferon beta medications may exacerbate or precipitate depression in some patients as warned in the FDA prescribing information.^{287–290}

Other co-morbid conditions may impact use of a particular disease modifying therapeutic agent in individual circumstances compromising safety, efficacy or tolerability and necessitating access to an alternative option.

6. Because severity of disease varies at onset – with some adults experiencing early aggressive disease – patients and their treating clinicians need access to all available options

Although MS remains a highly unpredictable disease, certain clinical and MRI outcomes seem to be associated with a higher risk of disease progression:

- Scalfari and colleagues found that time to Expanded Disability Status Scale (EDSS) 3 highly and independently predicted time to EDSS 6, 8 and 10. The same group found that higher early relapse frequencies and shorter first inter-attack intervals increased the probability of – and hastened conversion to – secondary progression, and that although long-term outcomes were highly variable, some individuals who experienced frequent relapses and/or accumulated a large number of focal lesions on T2 MRI within the first five years were at greater risk of disability.¹¹⁰
- Fisniku and colleagues⁹³ found lesion volume and its change at earlier time points to be correlated with disability after 20 years. In their study, lesion volume increased for at least 20 years in relapse-onset MS and the rate of lesion growth was three times higher in those who developed secondary progression than in those who remained relapsing-remitting.
- A prospective study in British Columbia that utilized three possible criteria for aggressive MS – confirmed Expanded Disability Status Scale (EDSS) ≥ 6 within five years of MS onset; confirmed EDSS ≥ 6 by age 40; and secondary progressive MS within three years of a relapsing-onset course – identified aggressive MS in 4–14 percent of people depending on the definition used.²⁹¹ Although the majority were males and those with PPMS, there were also a significant number of female patients and patients with RRMS.
- In a retrospective database study of aggressive onset MS, defined as two or more relapses in the year after onset and two or more Gd-enhancing lesions on MRI *or* one relapse if resulting in an EDSS of 3 along with two or more Gd-enhancing lesions, those patients who received or were switched to one of the following therapies – natalizumab, rituximab, alemtuzumab or cyclophosphamide – maintained a NEDA status during the 54-month mean duration of follow-up.²⁹²
- Utilizing a different definition of aggressive MS that requires one or more of the following features, Rush and colleagues recommend more aggressive treatment agents to manage this challenging group of patients.²⁹³
 - EDSS of 4 within five years of onset;
 - Multiple (>2) relapses with incomplete resolution within the past year;

- More than two MRI studies showing new or enlarging T2 lesions or Gd-enhancing lesions despite treatment;
- No response to therapy with one or more DMTs for up to one year.

Given these findings, patients with highly inflammatory and potentially aggressive disease may determine with their treating clinician that the benefit-to-risk ratio warrants starting or switching to a therapy with a higher potency and risk profile.²⁹⁴

In fact, the 2018 AAN Guideline⁷⁸ states as a Level B recommendation that “Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with highly active MS.”

Data also support the use of mitoxantrone.^{295–298} However, as noted previously, mitoxantrone is seldom prescribed because of its high risk profile. The 2018 AAN Guideline states as a level B recommendation that “Because of the high frequency of severe AEs, clinicians should not prescribe mitoxantrone to people with MS unless the potential therapeutic benefits greatly outweigh the risks.” Refer to AAN.com/guidelines.⁷⁸

7. Some children experience very active disease from onset

As previously mentioned, some children may experience very active disease that does not respond to the medications generally considered to be first-line treatment options for pediatric-onset MS.

8. African-Americans and Hispanics appear to have more active disease

Several studies have now pointed to a more active disease course in African-Americans and Hispanics with MS.

- In a multicenter study of retinal damage and vision loss, African-Americans with MS were found to have accelerated damage compared to Caucasian MS patients, suggesting a more aggressive inflammatory disease course.²¹
- In a different cohort, primary progressive MS was more common in African-American patients, as was cerebellar dysfunction and a more rapid progression of disability.²²
- Compared to Caucasians, African-American patients have also been found to have a greater likelihood of developing opticospinal MS and transverse myelitis and have a more aggressive course.²³
- More than one study has shown increased lesion volumes in African-Americans,^{24,25} with one also showing more tissue damage.²⁴
- Given that there are also preliminary indications that African-Americans may not respond as well to some of the available disease-modifying therapies,^{299,300} it is essential for African-American patients and their clinicians to have access to the full range of treatment options in the event that one or another does not provide sufficient benefit.
- Hispanics as well as African Americans could be at greater risk of greater disease burden early in the disease course, while also facing greater barriers to care.^{26–29}
- Hispanics, along with African Americans and Asians, are more likely to develop opticospinal MS than Caucasians, often leading to greater ambulatory disability.³⁰

9. People who for one reason or another are not adhering to a treatment regimen need access to other treatment options.

In a retrospective cohort study of people starting treatment with interferon beta or glatiramer acetate, only 3040 percent were adherent to treatment after two years.³⁰¹ People who do not adhere to their treatment regimen are unlikely to receive the full benefit of the treatment.^{302,303}

Factors associated with non-adherence include:

- Perceived lack of efficacy in relation to expectations^{303,304}
- Route of administration^{305,306}
- Perceived risks^{304,307,308}
- Tolerability issues with self-injectable medications, including flu-like symptoms and injection-site reactions^{309–312}
- Length of time on treatment³⁰⁸
- Costs³¹³
- Psychosocial factors, including coping style,³¹⁴ mood,^{315,316} and “forgetting”^{308,311,312}

Addressing adherence issues begins with identifying the non-adherent patient so that the cause(s) can be addressed. In some instances, this may require an alternative treatment option that is likely to enhance the person’s ability to adhere to the treatment plan.

Under certain circumstances, other off-label agents may be needed to modify the disease course

For all the same reasons that clinicians and their patients need access to the full range of approved disease-modifying therapies, they may also need to turn to non-approved options that have demonstrated efficacy in people with MS (see Appendix C for further information about these off-label options).

CONCLUSIONS REGARDING THE NEEDS OF PEOPLE WITH MS

Although there is still much that we do not fully understand about the pathophysiology of MS, the last 20 years have provided a significant number of treatment options that improve prognosis and quality of life for people with MS. Furthermore, the growing body of evidence highlights the importance of early and ongoing access to and treatment with disease-modifying therapies.

Treatment Considerations

- Initiation of treatment with an FDA-approved disease-modifying therapy is recommended:
 - As soon as possible following a diagnosis of relapsing or primary progressive multiple sclerosis, regardless of the person's age.
 - For individuals with a first clinical event and MRI features consistent with MS, in whom other possible causes have been excluded.
 - For individuals with progressive MS who continue to demonstrate clinical relapses and/or demonstrate inflammatory activity.
- Clinicians should consider prescribing a high efficacy medication such as alemtuzumab, fingolimod, ocrelizumab or natalizumab for newly-diagnosed individuals with highly active MS.
- Clinicians should also consider prescribing a high efficacy medication for individuals who have breakthrough activity on another disease-modifying therapy, regardless of the number of previously used agents.
- Treatment with a given disease-modifying medication should be continued indefinitely unless any of the following occur (in which case an alternative disease-modifying therapy should be considered):
 - Sub-optimal treatment response as determined by the individual and his or her treating clinician
 - Intolerable side effects, including significant laboratory abnormalities
 - Inadequate adherence to the treatment regimen
 - Availability of a more appropriate treatment option
 - The healthcare provider and patient determine that the benefits no longer outweigh the risks
- Movement from one disease-modifying therapy to another should occur only for medically appropriate reasons as determined by the treating clinician and patient.
- When evidence of additional clinical or MRI activity while on consistent treatment suggests a sub-optimal response, an alternative regimen (e.g., different mechanism of action) should be considered to optimize therapeutic benefit.
- The factors affecting choice of therapy at any point in the disease course are complex and most appropriately analyzed and addressed through a shared decision-making process between the individual and his or her treating clinician. Neither an arbitrary restriction of choice nor a mandatory escalation therapy approach is supported by data.

Access Considerations

- Due to significant variability in the MS population, people with MS and their treating clinicians require access to the full range of treatment options for several reasons:
 - Different mechanisms of action allow for treatment change in the event of a sub-optimal response
 - Potential contraindications limit options for some individuals
 - Risk tolerance varies among people with MS and their treating clinicians
 - Route of delivery and side effects may affect adherence and quality of life
 - Individual differences related to tolerability and adherence may necessitate access to different medications within the same class
 - Pregnancy and breastfeeding limit the available options
- Individuals' access to treatment should not be limited by their frequency of relapses, level of disability, or personal characteristics such as age, sex or ethnicity
- Absence of relapses while on treatment is a characteristic of treatment effectiveness and should not be considered a justification for discontinuation of treatment

- Treatment should not be withheld to allow for determination of coverage by payers as this puts the patient at risk for recurrent disease activity

REFERENCES

1. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. [Neurology. 2014;83\(3\):278-286.](#)
2. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. [Neurology. 1996;46\(4\):907-911.](#)
3. Frischer JM, Bramow S, Dal-Bianco A, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. [Brain J Neurol. 2009;132\(Pt 5\):1175-1189.](#)
4. Charil A, Filippi M. Inflammatory demyelination and neurodegeneration in early multiple sclerosis. [J Neurol Sci. 2007;259\(1-2\):7-15.](#)
5. Lassmann H, van Horssen J, Mahad D. Progressive multiple sclerosis: pathology and pathogenesis. [Nat Rev Neurol. 2012;8\(11\):647-656.](#)
6. Simon JH. MRI outcomes in the diagnosis and disease course of multiple sclerosis. [Handb Clin Neurol. 2014;122:405-425.](#)
7. Lucchinetti CF, Popescu BFG, Bunyan RF, et al. Inflammatory cortical demyelination in early multiple sclerosis. [N Engl J Med. 2011;365\(23\):2188-2197.](#)
8. Klaver R, De Vries HE, Schenk GJ, Geurts JGG. Grey matter damage in multiple sclerosis: a pathology perspective. [Prion. 2013;7\(1\):66-75.](#)
9. Rocca MA, Preziosa P, Mesaros S, et al. Clinically Isolated Syndrome Suggestive of Multiple Sclerosis: Dynamic Patterns of Gray and White Matter Changes-A 2-year MR Imaging Study. [Radiology. 2016;278\(3\):841-853.](#)
10. Boeije HR, Duijnste MSH, Grypdonck MHF, Pool A. Encountering the downward phase: biographical work in people with multiple sclerosis living at home. [Soc Sci Med 1982. 2002;55\(6\):881-893.](#)
11. Sprangers MA, de Regt EB, Andries F, et al. Which chronic conditions are associated with better or poorer quality of life? [J Clin Epidemiol. 2000;53\(9\):895-907.](#)
12. Julian LJ, Vella L, Vollmer T, Hadjimichael O, Mohr DC. Employment in multiple sclerosis. Exiting and re-entering the work force. [J Neurol. 2008;255\(9\):1354-1360.](#)
13. Ernstsson O, Gyllensten H, Alexanderson K, Tinghög P, Friberg E, Norlund A. Cost of Illness of Multiple Sclerosis - A Systematic Review. [PloS One. 2016;11\(7\):e0159129.](#)
14. Campbell JD, Ghushchyan V, Brett McQueen R, et al. Burden of multiple sclerosis on direct, indirect costs and quality of life: National US estimates. [Mult Scler Relat Disord. 2014;3\(2\):227-236.](#)
15. Goodin DS, Reder AT, Ebers GC, et al. Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFN β -1b trial. [Neurology. 2012;78\(17\):1315-1322.](#)
16. Multiple Sclerosis International Federation. Atlas of MS. 2017. <http://www.msif.org/wp-content/uploads/2014/09/Atlas-of-MS.pdf>b. Accessed September 7, 2018.

17. Wallin M, Culpepper WJ, Campbell J, et al. The Prevalence of Multiple Sclerosis in the United States: A Population-Based Healthcare Database Approach. ECTRIMS Online Library. October 26, 2017. Abstract P344. <https://onlinelibrary.ectrims-congress.eu/ectrims/2017/ACTRIMS-ECTRIMS2017/199999/mitchell.t.wallin.the.prevalence.of.multiple.sclerosis.in.the.united.states.a.html>. Accessed October 2, 2018.
18. Bove R, Chitnis T. The role of gender and sex hormones in determining the onset and outcome of multiple sclerosis. [*Mult Scler Houndmills Basingstoke Engl.* 2014;20\(5\):520-526.](#)
19. Evans C, Beland S-G, Kulaga S, et al. Incidence and prevalence of multiple sclerosis in the Americas: a systematic review. [*Neuroepidemiology.* 2013;40\(3\):195-210b.](#)
20. Langer-Gould A, Brara SM, Beaber BE, Zhang JL. Incidence of multiple sclerosis in multiple racial and ethnic groups. [*Neurology.* 2013;80\(19\):1734-1739bbbbbbbbb.](#)
21. Kimbrough DJ, Sotirchos ES, Wilson JA, et al. Retinal damage and vision loss in African American multiple sclerosis patients. [*Ann Neurol.* 2015;77\(2\):228-236.](#)
22. Naismith RT, Trinkaus K, Cross AH. Phenotype and prognosis in African-Americans with multiple sclerosis: a retrospective chart review. [*Mult Scler Houndmills Basingstoke Engl.* 2006;12\(6\):775-781.](#)
23. Cree B a. C, Khan O, Bourdette D, et al. Clinical characteristics of African Americans vs Caucasian Americans with multiple sclerosis. [*Neurology.* 2004;63\(11\):2039-2045.](#)
24. Weinstock-Guttman B, Ramanathan M, Hashmi K, et al. Increased tissue damage and lesion volumes in African Americans with multiple sclerosis. [*Neurology.* 2010;74\(7\):538-544.](#)
25. Howard J, Battaglini M, Babb JS, et al. MRI correlates of disability in African-Americans with multiple sclerosis. [*PloS One.* 2012;7\(8\):e43061.](#)
26. Rivas-Rodríguez E, Amezcua L. Ethnic Considerations and Multiple Sclerosis Disease Variability in the United States. [*Neurol Clin.* 2018;36\(1\):151-162.](#)
27. Amezcua L, Lund BT, Weiner LP, Islam T. Multiple sclerosis in Hispanics: a study of clinical disease expression. [*Mult Scler Houndmills Basingstoke Engl.* 2011;17\(8\):1010-1016.](#)
28. Langille MM, Islam T, Burnett M, Amezcua L. Clinical Characteristics of Pediatric-Onset and Adult-Onset Multiple Sclerosis in Hispanic Americans. [*J Child Neurol.* 2016;31\(8\):1068-1073.](#)
29. Amezcua L, Conti DV, Liu L, Ledezma K, Langer-Goulda AM. Place of birth, age of immigration, and disability in Hispanics with multiple sclerosis. [*Mult Scler Relat Disord.* 2015;4\(1\):25-30.](#)
30. Amezcua L, Lerner A, Ledezma K, et al. Spinal cord lesions and disability in Hispanics with multiple sclerosis. [*J Neurol.* 2013;260\(11\):2770-2776.](#)
31. Alla S, Mason DF. Multiple sclerosis in New Zealand. [*J Clin Neurosci Off J Neurosurg Soc Australas.* 2014;21\(8\):1288-1291.](#)
32. Simpson S, Blizzard L, Otahal P, Van der Mei I, Taylor B. Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. [*J Neurol Neurosurg Psychiatry.* 2011;82\(10\):1132-1141.](#)
33. Berg-Hansen P, Moen S, Harbo H, Celius E. High prevalence and no latitude gradient of multiple sclerosis in Norway. [*Mult Scler.* 2014;20\(13\):1780-1782.](#)
34. Aguirre-Cruz L, Flores-Rivera J, De La Cruz-Aguilera DL, Rangel-López E, Corona T. Multiple sclerosis in Caucasians and Latino Americans. [*Autoimmunity.* 2011;44\(7\):571-575.](#)

35. Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. [N Engl J Med. 2000;343\(20\):1430-1438.](#)
36. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. [Brain J Neurol. 1989;112 \(Pt 1\):133-146.](#)
37. Runmarker B, Andersen O. Prognostic factors in a multiple sclerosis incidence cohort with twenty-five years of follow-up. [Brain J Neurol. 1993;116 \(Pt 1\):117-134.](#)
38. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. [Lancet Lond Engl. 2018;391\(10130\):1622-1636.](#)
39. Yadav SK, Mindur JE, Ito K, Dhib-Jalbut S. Advances in the immunopathogenesis of multiple sclerosis. [Curr Opin Neurol. 2015;28\(3\):206-219.](#)
40. Koch MW, Metz LM, Agrawal SM, Yong VW. Environmental factors and their regulation of immunity in multiple sclerosis. [J Neurol Sci. 2013;324\(1-2\):10-16.](#)
41. Lubetzki C, Stankoff B. Demyelination in multiple sclerosis. [Handb Clin Neurol. 2014;122:89-99.](#)
42. Durelli L, Conti L, Clerico M, et al. T-helper 17 cells expand in multiple sclerosis and are inhibited by interferon-beta. [Ann Neurol. 2009;65\(5\):499-509.](#)
43. Viglietta V, Baecher-Allan C, Weiner HL, Hafler DA. Loss of functional suppression by CD4+CD25+ regulatory T cells in patients with multiple sclerosis. [J Exp Med. 2004;199\(7\):971-979.](#)
44. Obermeier B, Daneman R, Ransohoff RM. Development, maintenance and disruption of the blood-brain barrier. [Nat Med. 2013;19\(12\):1584-1596.](#)
45. Babbe H, Roers A, Waisman A, et al. Clonal expansions of CD8(+) T cells dominate the T cell infiltrate in active multiple sclerosis lesions as shown by micromanipulation and single cell polymerase chain reaction. [J Exp Med. 2000;192\(3\):393-404.](#)
46. Bhise V, Dhib-Jalbut S. Further understanding of the immunopathology of multiple sclerosis: impact on future treatments. [Expert Rev Clin Immunol. June 2016:1-21.](#)
47. Disanto G, Hall C, Lucas R, et al. Assessing interactions between HLA-DRB1*15 and infectious mononucleosis on the risk of multiple sclerosis. [Mult Scler Houndmills Basingstoke Engl. 2013;19\(10\):1355-1358.](#)
48. Michel L, Touil H, Pikor NB, Gommerman JL, Prat A, Bar-Or A. B Cells in the Multiple Sclerosis Central Nervous System: Trafficking and Contribution to CNS-Compartmentalized Inflammation. [Front Immunol. 2015;6:636.](#)
49. Haider L, Fischer MT, Frischer JM, et al. Oxidative damage in multiple sclerosis lesions. [Brain J Neurol. 2011;134\(Pt 7\):1914-1924.](#)
50. Witte ME, Mahad DJ, Lassmann H, van Horssen J. Mitochondrial dysfunction contributes to neurodegeneration in multiple sclerosis. [Trends Mol Med. 2014;20\(3\):179-187.](#)
51. Trapp BD, Stys PK. Virtual hypoxia and chronic necrosis of demyelinated axons in multiple sclerosis. [Lancet Neurol. 2009;8\(3\):280-291.](#)
52. Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mörk S, Bö L. Axonal transection in the lesions of multiple sclerosis. [N Engl J Med. 1998;338\(5\):278-285.](#)

53. Ellwardt E, Zipp F. Molecular mechanisms linking neuroinflammation and neurodegeneration in MS. [Exp Neurol. 2014;262 Pt A:8-17.](#)
54. Copaxone® (glatiramer acetate) [prescribing information]. Overland Park, KS: Teva Neuroscience, Inc. September 2018. <https://www.copaxone.com/Resources/pdfs/PrescribingInformation.pdf>. Accessed September 24, 2018.
55. Glatopa® (glatiramer acetate injection) [prescribing information]. Princeton, NJ; Sandoz Inc. January 2018. <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=5f01e40a-b6f6-40fb-b37c-3d06f1428e86&type=display>. Accessed September 24, 2018.
56. Graber JJ, McGraw CA, Kimbrough D, Dhib-Jalbut S. Overlapping and distinct mechanisms of action of multiple sclerosis therapies. [Clin Neurol Neurosurg. 2010;112\(7\):583-591.](#)
57. Avonex® (interferon beta-1a) [prescribing information]. Cambridge, MA: Biogen Inc. March 2016. https://www.avonex.com/content/dam/commercial/multiple-sclerosis/avonex/pat/en_us/pdf/Avonex%20US%20%20Prescribing%20Information.pdf. Accessed June 24, 2016.
58. Korporal M, Haas J, Balint B, et al. Interferon beta-induced restoration of regulatory T-cell function in multiple sclerosis is prompted by an increase in newly generated naive regulatory T cells. [Arch Neurol. 2008;65\(11\):1434-1439.](#)
59. Oh, J, Calabresi, PA. Disease Modifying Therapies in Relapsing Multiple Sclerosis. In: *Rae-Grant, Fox & Bethoux Multiple Sclerosis and Related Disorders Clinical Guide to Diagnosis, Medical Management and Rehabilitation*. New York: Demos Health; 2013.
60. Rebif® (interferon beta-1a) [prescribing information]. Rockland, MA: EMD Serono, Inc. November 2015. http://www.emdserono.com/ms.country.us/en/images/Rebif_PI_tcm115_140051.pdf. Accessed April 15, 2016.
61. Betaseron® (interferon beta-1b) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc. August 2018. http://labeling.bayerhealthcare.com/html/products/pi/Betaseron_PI.pdf. Accessed September 24, 2018.
62. Extavia® (interferon beta-1b) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation. May 2016. <http://www.pharma.us.novartis.com/product/pi/pdf/extavia.pdf>. Accessed June 24, 2016.
63. Plegridy® (pegylated interferon beta-1a) [prescribing information]. Cambridge, MA: Biogen Idec, Inc. July 2016. <https://www.plegridy.com/pdfs/plegridy-prescribing-information.pdf>. Accessed January 9, 2018.
64. Calabresi PA, Kieseier BC, Arnold DL, et al. Pegylated interferon β -1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. [Lancet Neurol. 2014;13\(7\):657-665.](#)
65. Kieseier BC, Arnold DL, Balcer LJ, et al. Peginterferon beta-1a in multiple sclerosis: 2-year results from ADVANCE. [Mult Scler. 2015;21\(8\):1025-1035.](#)
66. TECFIDERA® (dimethyl fumarate) [prescribing information]. Cambridge, MA: Biogen Inc. December 2017. <http://www.tecfidera.com/pdfs/full-prescribing-information.pdf>. Accessed January 9, 2018.
67. GILENYA® (fingolimod) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation. May 2018. <http://www.pharma.us.novartis.com/product/pi/pdf/gilenya.pdf>. Accessed September 24, 2018.

68. AUBAGIO® (teriflunomide) [prescribing information]. Cambridge, MA: Genzyme Corporation. November 2016. <http://products.sanofi.us/aubagio/aubagio.pdf>. Accessed March 30, 2017.
69. Bar-Or A, Pachner A, Menguy-Vacheron F, Kaplan J, Wiendl H. Teriflunomide and Its Mechanism of Action in Multiple Sclerosis. *Drugs*. 2014;74(6):659-674.
70. Lemtrada® (alemtuzumab) [package insert]. Cambridge, MA: Genzyme Corporation. December 2017. <http://products.sanofi.us/lemtrada/lemtrada.pdf>. Accessed January 9, 2018.
71. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet*. 2012;380(9856):1819-1828.
72. Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet*. 2012;380(9856):1829-1839.
73. Ruck T, Afzali AM, Lukat K-F, et al. ALAIN01-Alemtuzumab in autoimmune inflammatory neurodegeneration: mechanisms of action and neuroprotective potential. *BMC Neurol*. 2016;16(1):34.
74. Novantrone® (mitoxantrone) [package insert]. Rockland, MA: EMD Serono, Inc. August 2008. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019297s030s0311bl.pdf. Accessed April 21, 2016.
75. Tysabri® (natalizumab) [medication guide]. Cambridge, MA: Biogen Inc. April 2018. https://www.tysabri.com/content/dam/commercial/multiple-sclerosis/tysabri/pat/en_us/pdfs/tysabri_prescribing_information.pdf. Accessed September 24, 2018.
76. Ocrevus(TM) (ocrelizumab) [prescribing information]. South San Francisco, CA: Genentech, Inc. November 2017. https://www.gene.com/download/pdf/ocrevus_prescribing.pdf. Accessed January 9, 2018.
77. Fiest KM, Fisk JD, Patten SB, et al. Fatigue and Comorbidities in Multiple Sclerosis. *Int J MS Care*. 2016;18(2):96-104.
78. Rae-Grant A, Day GS, Marrie RA, et al. *Practice Guideline: Disease-Modifying Therapies for Adults with Multiple Sclerosis*. American Academy of Neurology (AAN); 2018:1-228. https://download.lww.com/wolterskluwer_vitalstream_com/PermaLink/WNL/A/WNL_2018_04_19_RAEGRANT_NEUROLOGY2017835181R1_SDC3.pdf. Accessed September 26, 2018.
79. Montalban X, Gold R, Thompson AJ, et al.ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Eur J Neurol*. 2018;25(2):215-237.
80. Freedman MS, Selchen D, Arnold DL, et al. Treatment optimization in MS: Canadian MS Working Group updated recommendations. *Can J Neurol Sci*. 2013;40(3):307-323.
81. Gold R, Wolinsky JS, Amato MP, Comi G. Evolving expectations around early management of multiple sclerosis. *Ther Adv Neurol Disord*. 2010;3(6):351-367.
82. Cocco E, Sardu C, Spinicci G, et al. Influence of treatments in multiple sclerosis disability: A cohort study. *Mult Scler*. 2015;21(4):433-441.
83. Paz Soldán MM, Novotna M, Abou Zeid N, et al. Relapses and disability accumulation in progressive multiple sclerosis. *Neurology*. 2015;84(1):81-88.

84. Kappos L, Moeri D, Radue EW, et al. Predictive value of gadolinium-enhanced magnetic resonance imaging for relapse rate and changes in disability or impairment in multiple sclerosis: a meta-analysis. Gadolinium MRI Meta-analysis Group. [Lancet. 1999;353\(9157\):964-969.](#)
85. Dalton CM, Chard DT, Davies GR, et al. Early development of multiple sclerosis is associated with progressive grey matter atrophy in patients presenting with clinically isolated syndromes. [Brain J Neurol. 2004;127\(Pt 5\):1101-1107.](#)
86. Okuda DT, Siva A, Kantarci O, et al. Radiologically isolated syndrome: 5-year risk for an initial clinical event. [PloS One. 2014;9\(3\):e90509.](#)
87. Stromillo ML, Giorgio A, Rossi F, et al. Brain metabolic changes suggestive of axonal damage in radiologically isolated syndrome. [Neurology. 2013;80\(23\):2090-2094.](#)
88. Comi G, Martinelli V, Rodegher M, et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial. [Lancet. 2009;374\(9700\):1503-1511.](#)
89. Kappos L, Polman CH, Freedman MS, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. [Neurology. 2006;67\(7\):1242-1249.](#)
90. Comi G, Filippi M, Barkhof F, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. [Lancet. 2001;357\(9268\):1576-1582.](#)
91. Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. [N Engl J Med. 2000;343\(13\):898-904.](#)
92. Miller DH, Chard DT, Ciccarelli O. Clinically isolated syndromes. [Lancet Neurol. 2012;11\(2\):157-169.](#)
93. Fisniku LK, Brex PA, Altmann DR, et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. [Brain J Neurol. 2008;131\(Pt 3\):808-817.](#)
94. Miller AE, Wolinsky JS, Kappos L, et al. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. [Lancet Neurol. 2014;13\(10\):977-986.](#)
95. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. [Lancet Neurol. 2018 Feb;17\(2\):162-173.](#)
96. Lebrun C, Kantarci OH, Siva A, Pelletier D, Okuda DT, RISConsortium. Anomalies Characteristic of Central Nervous System Demyelination: Radiologically Isolated Syndrome. [Neurol Clin. 2018;36\(1\):59-68.](#)
97. Labiano-Fontcuberta A, Benito-León J. Radiologically isolated syndrome: An update on a rare entity. [Mult Scler Houndmills Basingstoke Engl. 2016;22\(12\):1514-1521.](#)
98. Lebrun C, Bensa C, Debouverie M, et al. Association between clinical conversion to multiple sclerosis in radiologically isolated syndrome and magnetic resonance imaging, cerebrospinal fluid, and visual evoked potential: follow-up of 70 patients. [Arch Neurol. 2009;66\(7\):841-846.](#)
99. Lebrun C, Bensa C, Debouverie M, et al. Unexpected multiple sclerosis: follow-up of 30 patients with magnetic resonance imaging and clinical conversion profile. [J Neurol Neurosurg Psychiatry. 2008;79\(2\):195-198.](#)

100. Siva A, Saip S, Altintas A, Jacob A, Keegan BM, Kantarci OH. Multiple sclerosis risk in radiologically uncovered asymptomatic possible inflammatory-demyelinating disease. [Mult Scler Houndmills Basingstoke Engl. 2009;15\(8\):918-927.](#)
101. Okuda DT, Siva A, Kantarci O, et al. Radiologically isolated syndrome: 5-year risk for an initial clinical event. [PloS One. 2014;9\(3\):e90509.](#)
102. Kantarci OH, Lebrun C, Siva A, et al. Primary Progressive Multiple Sclerosis Evolving From Radiologically Isolated Syndrome. [Ann Neurol. 2016;79\(2\):288-294.](#)
103. Lebrun C, Blanc F, Brassat D, Zephir H, de Seze J, CFSEP. Cognitive function in radiologically isolated syndrome. [Mult Scler Houndmills Basingstoke Engl. 2010;16\(8\):919-925.](#)
104. Amato MP, Hakiki B, Goretti B, et al. Association of MRI metrics and cognitive impairment in radiologically isolated syndromes. [Neurology. 2012;78\(5\):309-314.](#)
105. Labiano-Fontcuberta A, Martínez-Ginés ML, Aladro Y, et al. A comparison study of cognitive deficits in radiologically and clinically isolated syndromes. [Mult Scler Houndmills Basingstoke Engl. 2016;22\(2\):250-253.](#)
106. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). [Neurology. 1983;33\(11\):1444-1452.](#)
107. Vercellino M, Romagnolo A, Mattioda A, et al. Multiple sclerosis relapses: a multivariable analysis of residual disability determinants. [Acta Neurol Scand. 2009;119\(2\):126-130.](#)
108. Hirst C, Ingram G, Pearson O, Pickersgill T, Scolding N, Robertson N. Contribution of relapses to disability in multiple sclerosis. [J Neurol. 2008;255\(2\):280-287.](#)
109. Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. [Neurology. 2003;61\(11\):1528-1532.](#)
110. Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. [Brain J Neurol. 2010;133\(Pt 7\):1914-1929.](#)
111. Tremlett H, Yousefi M, Devonshire V, Rieckmann P, Zhao Y, UBC Neurologists. Impact of multiple sclerosis relapses on progression diminishes with time. [Neurology. 2009;73\(20\):1616-1623.](#)
112. Jokubaitis VG, Spelman T, Kalincik T, et al. Predictors of long-term disability accrual in relapse-onset multiple sclerosis. [Ann Neurol. 2016;80\(1\):89-100.](#)
113. Scalfari A, Neuhaus A, Daumer M, Deluca GC, Muraro PA, Ebers GC. Early relapses, onset of progression, and late outcome in multiple sclerosis. [JAMA Neurol. 2013;70\(2\):214-222.](#)
114. Brex PA, Ciccarelli O, O'Riordan JI, Sailer M, Thompson AJ, Miller DH. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. [N Engl J Med. 2002;346\(3\):158-164.](#)
115. Goodin DS, Traboulsee A, Knappertz V, et al. Relationship between early clinical characteristics and long term disability outcomes: 16 year cohort study (follow-up) of the pivotal interferon β -1b trial in multiple sclerosis. [J Neurol Neurosurg Psychiatry. 2012;83\(3\):282-287.](#)
116. Langdon DW, Amato MP, Boringa J, et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). [Mult Scler Houndmills Basingstoke Engl. 2012;18\(6\):891-898.](#)

117. Minden S, Turner A, Kalb R, Burke D. Emotional Disorders in Multiple Sclerosis. 2014. <http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Clinical-Bulletin-Emotional-Disorders-5-5-14.pdf>. Accessed June 2, 2014.
118. Minden SL, Frankel D, Hadden L, Perloff J, Srinath KP, Hoaglin DC. The Sonya Slifka Longitudinal Multiple Sclerosis Study: methods and sample characteristics. *Mult Scler Houndmills Basingstoke Engl.* 2006;12(1):24-38.
119. Achiron A, Chapman J, Magalashvili D, et al. Modeling of cognitive impairment by disease duration in multiple sclerosis: a cross-sectional study. *PLoS One.* 2013;8(8):e71058.
120. Anhoque CF, Biccás-Neto L, Domingues SCA, Teixeira AL, Domingues RB. Cognitive impairment and optic nerve axonal loss in patients with clinically isolated syndrome. *Clin Neurol Neurosurg.* 2013;115(7):1032-1035.
121. Viterbo RG, Iaffaldano P, Trojano M. Verbal fluency deficits in clinically isolated syndrome suggestive of multiple sclerosis. *J Neurol Sci.* 2013;330(1-2):56-60.
122. Reuter F, Zaaraoui W, Crespy L, et al. Frequency of cognitive impairment dramatically increases during the first 5 years of multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2011;82(10):1157-1159.
123. Zipoli V, Goretti B, Hakiki B, et al. Cognitive impairment predicts conversion to multiple sclerosis in clinically isolated syndromes. *Mult Scler Houndmills Basingstoke Engl.* 2010;16(1):62-67.
124. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol.* 2008;7(12):1139-1151.
125. Glanz BI, Healy BC, Hviid LE, Chitnis T, Weiner HL. Cognitive deterioration in patients with early multiple sclerosis: a 5-year study. *J Neurol Neurosurg Psychiatry.* 2012;83(1):38-43.
126. Amato MP, Portaccio E, Goretti B, et al. Relevance of cognitive deterioration in early relapsing-remitting MS: a 3-year follow-up study. *Mult Scler Houndmills Basingstoke Engl.* 2010;16(12):1474-1482.
127. Julian L, Serafin D, Charvet L, et al. Cognitive impairment occurs in children and adolescents with multiple sclerosis: results from a United States network. *J Child Neurol.* 2013;28(1):102-107.
128. Till C, Ghassemi R, Aubert-Broche B, et al. MRI correlates of cognitive impairment in childhood-onset multiple sclerosis. *Neuropsychology.* 2011;25(3):319-332.
129. Amato MP, Goretti B, Ghezzi A, et al. Cognitive and psychosocial features of childhood and juvenile MS. *Neurology.* 2008;70(20):1891-1897.
130. Langdon D, Benedict R, Wicklein EM, Fredrikson S. *Report of Cognitive Difficulties by Clinically Isolated Syndrome Patients and Caregivers: The Multiple Sclerosis Neuropsychological Questionnaire Data from the CogniCIS Baseline Cohort; Abstract P406.* Dusseldorf: 25th Congress of the European Committee for the Treatment and Research in Multiple Sclerosis (ECTRIMS); 2009.
131. Langdon D, Benedict R, Wicklein EM, Fredrikson S. *Report of Cognitive Difficulties by Clinically Isolated Syndrome Patients and Caregivers: The Multiple Sclerosis Neuropsychological Questionnaire Data from the CogniCIS Baseline Cohort; Abstract P407.* Dusseldorf: 25th Congress of the European Committee for the Treatment and Research in Multiple Sclerosis (ECTRIMS); 2009.
132. Ramsaransing GSM, De Keyser J. Predictive value of clinical characteristics for “benign” multiple sclerosis. *Eur J Neurol Off J Eur Fed Neurol Soc.* 2007;14(8):885-889.

133. Amato MP, Zipoli V, Goretti B, et al. Benign multiple sclerosis: cognitive, psychological and social aspects in a clinical cohort. [J Neurol. 2006;253\(8\):1054-1059.](#)
134. Correale J, Peirano I, Romano L. Benign multiple sclerosis: a new definition of this entity is needed. [Mult Scler Houndmills Basingstoke Engl. 2012;18\(2\):210-218.](#)
135. Sayao A-L, Devonshire V, Tremlett H. Longitudinal follow-up of “benign” multiple sclerosis at 20 years. [Neurology. 2007;68\(7\):496-500.](#)
136. Sayao A-L, Bueno A-M, Devonshire V, Tremlett H, UBC MS Clinic Neurologists. The psychosocial and cognitive impact of longstanding “benign” multiple sclerosis. [Mult Scler Houndmills Basingstoke Engl. 2011;17\(11\):1375-1383.](#)
137. Edan G, Kappos L, Montalbán X, et al. Long-term impact of interferon beta-1b in patients with CIS: 8-year follow-up of BENEFIT. [J Neurol Neurosurg Psychiatry. 2014;85\(11\):1183-1189.](#)
138. Comi G, Martinelli V, Rodegher M, et al. Effects of early treatment with glatiramer acetate in patients with clinically isolated syndrome. [Mult Scler Houndmills Basingstoke Engl. 2013;19\(8\):1074-1083.](#)
139. Filippi M, Rovaris M, Inglese M, et al. Interferon beta-1a for brain tissue loss in patients at presentation with syndromes suggestive of multiple sclerosis: a randomised, double-blind, placebo-controlled trial. [Lancet Lond Engl. 2004;364\(9444\):1489-1496.](#)
140. Tsivgoulis G, Katsanos AH, Grigoriadis N, et al. The effect of disease-modifying therapies on brain atrophy in patients with clinically isolated syndrome: a systematic review and meta-analysis. [Ther Adv Neurol Disord. 2015;8\(5\):193-202.](#)
141. Jokubaitis VG, Spelman T, Kalincik T, et al. Predictors of disability worsening in clinically isolated syndrome. [Ann Clin Transl Neurol. 2015;2\(5\):479-491.](#)
142. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. [Neurology. 1995;45\(7\):1268-1276.](#)
143. Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R, GALA Study Group. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. [Ann Neurol. 2013;73\(6\):705-713.](#)
144. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. [Lancet. 1998;352\(9139\):1498-1504.](#)
145. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). [Ann Neurol. 1996;39\(3\):285-294.](#)
146. The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. [Neurology. 1993;43\(4\):655-661.](#)
147. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. [N Engl J Med. 2012;367\(12\):1098-1107.](#)
148. 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\(12\):1087-1097.](#)
149. Kappos L, Radue E-W, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. [N Engl J Med. 2010;362\(5\):387-401.](#)

150. Calabresi PA, Radue E-W, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. [Lancet Neurol. 2014;13\(6\):545-556.](#)
151. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. [N Engl J Med. 2010;362\(5\):402-415.](#)
152. O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. [N Engl J Med. 2011;365\(14\):1293-1303.](#)
153. Confavreux C, O'Connor P, Comi G, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. [Lancet Neurol. 2014;13\(3\):247-256.](#)
154. Hartung H-P, Gonsette R, König N, et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. [Lancet. 2002;360\(9350\):2018-2025.](#)
155. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. [N Engl J Med. 2006;354\(9\):899-910.](#)
156. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. [N Engl J Med. 2017;376\(3\):221-234.](#)
157. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. [N Engl J Med. 2017;376\(3\):209-220.](#)
158. Kalb R. The emotional and psychological impact of multiple sclerosis relapses. [J Neurol Sci. 2007;256 Suppl 1:S29-33.](#)
159. Traboulsee A, Simon JH, Stone L, et al. Revised Recommendations of the Consortium of MS Centers Task Force for a Standardized MRI Protocol and Clinical Guidelines for the Diagnosis and Follow-Up of Multiple Sclerosis. [AJNR Am J Neuroradiol. 2016;37\(3\):394-401.](#)
160. Consortium of Multiple Sclerosis Centers. 2018 Revised Guidelines of the Consortium of MS Centers MRI Protocol for the Diagnosis and Follow-up of MS. February 2018. [https://cdn.ymaws.com/mscare.site-ym.com/resource/collection/9C5F19B9-3489-48B0-A54B-623A1ECE07B/2018MRIGuidelines booklet with final changes 0522.pdf](https://cdn.ymaws.com/mscare.site-ym.com/resource/collection/9C5F19B9-3489-48B0-A54B-623A1ECE07B/2018MRIGuidelines%20booklet%20with%20final%20changes%200522.pdf). Accessed September 6, 2018.
161. Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. [Ann Neurol. 2001;49\(3\):290-297.](#)
162. Filippi M, Rovaris M, Rocca MA, et al. Glatiramer acetate reduces the proportion of new MS lesions evolving into "black holes." [Neurology. 2001;57\(4\):731-733.](#)
163. O'Connor P, Filippi M, Arnason B, et al. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. [Lancet Neurol. 2009;8\(10\):889-897.](#)
164. Calabrese M, Bernardi V, Atzori M, et al. Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis. [Mult Scler Houndmills Basingstoke Engl. 2012;18\(4\):418-424.](#)
165. Radue E-W, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1a reduces lesion formation in relapsing multiple sclerosis. [J Neurol Sci. 2010;292\(1-2\):28-35.](#)

166. Zivadinov R, Locatelli L, Cookfair D, et al. Interferon beta-1a slows progression of brain atrophy in relapsing-remitting multiple sclerosis predominantly by reducing gray matter atrophy. [Mult Scler Houndmills Basingstoke Engl. 2007;13\(4\):490-501.](#)
167. Khan O, Bao F, Shah M, et al. Effect of disease-modifying therapies on brain volume in relapsing-remitting multiple sclerosis: results of a five-year brain MRI study. [J Neurol Sci. 2012;312\(1-2\):7-12.](#)
168. Barkhof F, de Jong R, Sfikas N, et al. The influence of patient demographics, disease characteristics and treatment on brain volume loss in Trial Assessing Injectable Interferon vs FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS), a phase 3 study of fingolimod in multiple sclerosis. [Mult Scler. 2014;20\(13\):1704-1713.](#)
169. Miller DH, Soon D, Fernando KT, et al. MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS. [Neurology. 2007;68\(17\):1390-1401.](#)
170. De Stefano N, Arnold DL. Towards a better understanding of pseudoatrophy in the brain of multiple sclerosis patients. [Mult Scler Houndmills Basingstoke Engl. 2015;21\(6\):675-676.](#)
171. Rudick RA, Fisher E, Lee JC, Duda JT, Simon J. Brain atrophy in relapsing multiple sclerosis: relationship to relapses, EDSS, and treatment with interferon beta-1a. [Mult Scler Houndmills Basingstoke Engl. 2000;6\(6\):365-372.](#)
172. Kappos L, Traboulsee A, Constantinescu C, et al. Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS. [Neurology. 2006;67\(6\):944-953.](#)
173. Simon JH. Brain atrophy in multiple sclerosis: what we know and would like to know. [Mult Scler Houndmills Basingstoke Engl. 2006;12\(6\):679-687.](#)
174. Zivadinov R, Reder AT, Filippi M, et al. Mechanisms of action of disease-modifying agents and brain volume changes in multiple sclerosis. [Neurology. 2008;71\(2\):136-144.](#)
175. Rovaris M, Comi G, Rocca MA, et al. Long-term follow-up of patients treated with glatiramer acetate: a multicentre, multinational extension of the European/Canadian double-blind, placebo-controlled, MRI-monitored trial. [Mult Scler Houndmills Basingstoke Engl. 2007;13\(4\):502-508.](#)
176. Comi G, Cohen JA, Arnold DL, Wynn D, Filippi M, FORTE Study Group. Phase III dose-comparison study of glatiramer acetate for multiple sclerosis. [Ann Neurol. 2011;69\(1\):75-82.](#)
177. Mikol DD, Barkhof F, Chang P, et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. [Lancet Neurol. 2008;7\(10\):903-914.](#)
178. Arnold DL, Gold R, Kappos L, et al. Effects of delayed-release dimethyl fumarate on MRI measures in the Phase 3 DEFINE study. [J Neurol. 2014;261\(9\):1794-1802.](#)
179. Miller DH, Fox RJ, Phillips JT, et al. Effects of delayed-release dimethyl fumarate on MRI measures in the phase 3 CONFIRM study. [Neurology. 2015;84\(11\):1145-1152.](#)
180. Comi G, Jeffery D, Kappos L, et al. Placebo-controlled trial of oral laquinimod for multiple sclerosis. [N Engl J Med. 2012;366\(11\):1000-1009.](#)
181. Vollmer TL, Sorensen PS, Selmaj K, et al. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. [J Neurol. 2014;261\(4\):773-783.](#)
182. Alroughani R, Deleu D, El Salem K, et al. A regional consensus recommendation on brain atrophy as an outcome measure in multiple sclerosis. [BMC Neurol. 2016;16\(1\):240.](#)

183. Panitch H, Goodin DS, Francis G, et al. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. *Neurology*. 2002;59(10):1496-1506.
184. Lublin FD, Cofield SS, Cutter GR, et al. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. *Ann Neurol*. 2013;73(3):327-340.
185. Cadavid D, Wolansky LJ, Skurnick J, et al. Efficacy of treatment of MS with IFNbeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study. *Neurology*. 2009;72(23):1976-1983.
186. Durelli L, Verdun E, Barbero P, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). *Lancet Lond Engl*. 2002;359(9316):1453-1460.
187. Vermersch P, Czlonkowska A, Grimaldi LME, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. *Mult Scler Houndmills Basingstoke Engl*. 2014;20(6):705-716.
188. Kalincik T, Horakova D, Spelman T, et al. Switch to natalizumab versus fingolimod in active relapsing-remitting multiple sclerosis. *Ann Neurol*. 2015;77(3):425-435.
189. Lizak N, Lugesia A, Alroughani R, et al. Highly active immunomodulatory therapy ameliorates accumulation of disability in moderately advanced and advanced multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2017;88(3):196-203.
190. Lanzillo R, Quarantelli M, Bonavita S, et al. Natalizumab vs interferon beta 1a in relapsing-remitting multiple sclerosis: a head-to-head retrospective study. *Acta Neurol Scand*. 2012;126(5):306-314.
191. Nixon R, Bergvall N, Tomic D, et al. No evidence of disease activity: indirect comparisons of oral therapies for the treatment of relapsing-remitting multiple sclerosis. *Adv Ther*. 2014;31(11):1134-1154.
192. Hawker K, O'Connor P, Freedman MS, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. *Ann Neurol*. 2009;66(4):460-471.
193. Willis MA, Fox RJ. Progressive Multiple Sclerosis. *Contin Minneap Minn*. 2016;22(3):785-798.
194. Kavaliunas A, Stawiarz L, Hedbom J, et al. The influence of immunomodulatory treatment on the clinical course of multiple sclerosis. *Adv Exp Med Biol*. 2015;822:19-24.
195. Kinkel RP, Dontchev M, Kollman C, et al. Association between immediate initiation of intramuscular interferon beta-1a at the time of a clinically isolated syndrome and long-term outcomes: a 10-year follow-up of the Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance. *Arch Neurol*. 2012;69(2):183-190.
196. O'Connor P, Comi G, Freedman MS, et al. Long-term safety and efficacy of teriflunomide: Nine-year follow-up of the randomized TEMSO study. *Neurology*. 2016;86(10):920-930.
197. Montalban X, Comi G, Antel J, et al. Long-term results from a phase 2 extension study of fingolimod at high and approved dose in relapsing multiple sclerosis. *J Neurol*. 2015;262(12):2627-2634.
198. Trojano M, Paolicelli D, Bellacosa A, Cataldo S. The transition from relapsing-remitting MS to irreversible disability: clinical evaluation. *Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol*. 2003;24 Suppl 5:S268-270.
199. Tedeholm H, Skoog B, Lisovskaja V, et al. The outcome spectrum of multiple sclerosis: disability, mortality, and a cluster of predictors from onset. *J Neurol*. 2015;262(5):1148-1163.

200. Tedeholm H, Lycke J, Skoog B, et al. Time to secondary progression in patients with multiple sclerosis who were treated with first generation immunomodulating drugs. [Mult Scler Houndmills Basingstoke Engl. 2013;19\(6\):765-774.](#)
201. Bergamaschi R, Quaglini S, Tavazzi E, et al. Immunomodulatory therapies delay disease progression in multiple sclerosis. [Mult Scler Houndmills Basingstoke Engl. 2016;12\(13\):1732-1740 \(Epub 2012 May 31\).](#)
202. Trojano M, Pellegrini F, Fuiani A, et al. New natural history of interferon-beta-treated relapsing multiple sclerosis. [Ann Neurol. 2007;61\(4\):300-306.](#)
203. University of California, San Francisco MS-EPIC Team: Cree BAC, Gourraud P-A, et al. Long-term evolution of multiple sclerosis disability in the treatment era. [Ann Neurol. 2016;80\(4\):499-510.](#)
204. Kappos L, Freedman MS, Polman CH, et al. Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial. [Lancet Neurol. 2009;8\(11\):987-997.](#)
205. Penner I-K, Stemper B, Calabrese P, et al. Effects of interferon beta-1b on cognitive performance in patients with a first event suggestive of multiple sclerosis. [Mult Scler Houndmills Basingstoke Engl. 2012;18\(10\):1466-1471.](#)
206. Havrdova E, Galetta S, Hutchinson M, et al. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study. [Lancet Neurol. 2009;8\(3\):254-260.](#)
207. Rotstein DL, Healy BC, Malik MT, et al. Evaluation of no evidence of disease activity in a 7-year longitudinal multiple sclerosis cohort. [JAMA Neurol. 2015;72\(2\):152-158.](#)
208. Kappos L, De Stefano N, Freedman MS, et al. Inclusion of brain volume loss in a revised measure of “no evidence of disease activity” (NEDA-4) in relapsing-remitting multiple sclerosis. [Mult Scler Houndmills Basingstoke Engl. 2016 Sep;22\(10\):1297-305.](#)
209. Duquette P, Giacomini PS, Bhan V, et al. Balancing Early Aggression Against Risk of Progression in Multiple Sclerosis. [Can J Neurol Sci J Can Sci Neurol. 2016;43\(1\):33-43.](#)
210. Arnold DL, Calabresi PA, Kieseier BC, et al. Effect of peginterferon beta-1a on MRI measures and achieving no evidence of disease activity: results from a randomized controlled trial in relapsing-remitting multiple sclerosis. [BMC Neurol. 2014;14:240.](#)
211. Goodin DS, Reder AT, Traboulsee AL, et al. Predictive validity of NEDA in the 16- and 21-year follow-up from the pivotal trial of interferon beta-1b. [Mult Scler Houndmills Basingstoke Engl. May 2018;1352458518773511.](#)
212. Mokhber N, Azarpazhooh A, Orouji E, et al. Therapeutic effect of Avonex, Rebif and Betaferon on quality of life in multiple sclerosis. [Psychiatry Clin Neurosci. 2015;69\(10\):649-657.](#)
213. Janzen W, Turpin KVL, Warren SA, et al. Change in the Health-Related Quality of Life of Multiple Sclerosis Patients over 5 Years. [Int J MS Care. 2013;15\(1\):46-53.](#)
214. Rudick RA, Miller D, Hass S, et al. Health-related quality of life in multiple sclerosis: effects of natalizumab. [Ann Neurol. 2007;62\(4\):335-346.](#)
215. Kappos L, Gold R, Arnold DL, et al. Quality of life outcomes with BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: the DEFINE study. [Mult Scler Houndmills Basingstoke Engl. 2014;20\(2\):243-252.](#)

216. Salter AR, Cutter GR, Tyry T, et al. Impact of loss of mobility on instrumental activities of daily living and socioeconomic status in patients with MS. [Curr Med Res Opin. 2010;26\(2\):493-500.](#)
217. Wickström A, Nyström J, Svenningsson A. Improved ability to work after one year of natalizumab treatment in multiple sclerosis. Analysis of disease-specific and work-related factors that influence the effect of treatment. [Mult Scler Houndmills Basingstoke Engl. 2013;19\(5\):622-630.](#)
218. Patejdl R, Penner IK, Noack TK, Zettl UK. Multiple sclerosis and fatigue: A review on the contribution of inflammation and immune-mediated neurodegeneration. [Autoimmun Rev. 2016;15\(3\):210-220.](#)
219. Comi G, De Stefano N, Freedman MS, et al. Subcutaneous interferon β -1a in the treatment of clinically isolated syndromes: 3-year and 5-year results of the phase III dosing frequency-blind multicentre REFLEXION study. [J Neurol Neurosurg Psychiatry. 2017;88\(4\):285-294.](#)
220. Fragoso YD, Arruda NM, Arruda WO, et al. We know how to prescribe natalizumab for multiple sclerosis, but do we know how to withdraw it? [Expert Rev Neurother. 2014;14\(2\):127-130.](#)
221. PRISMS Study Group and the University of British Columbia MS/MRI Analysis Group. PRISMS-4: Long-term efficacy of interferon-beta-1a in relapsing MS. [Neurology. 2001;56\(12\):1628-1636.](#)
222. Schwid SR, Bever CT. The cost of delaying treatment in multiple sclerosis: what is lost is not regained. [Neurology. 2001;56\(12\):1620.](#)
223. Kappos L, Edan G, Freedman MS, et al. The 11-year long-term follow-up study from the randomized BENEFIT CIS trial. [Neurology. 2016;87\(10\):978-987.](#)
224. Cohen B, Leist T, Coyle P, et al. MS therapy adherence and relapse risk. 2013. http://www.neurology.org/cgi/content/meeting_abstract/80/1_MeetingAbstracts/P01.193. Accessed June 2, 2014.
225. Burks J, Malagone M, Jhaveri S, et al. The clinical outcomes associated with adherence to and discontinuation of disease-modifying treatments. *Mult Scler J.* 18 (Suppl 4):279-508; Poster 716.
226. Tobin WO, Weinshenker BG. Stopping immunomodulatory medications in MS: Frequency, reasons and consequences. [Mult Scler Relat Disord. 2015;4\(5\):437-443.](#)
227. Menzin J, Caon C, Nichols C, et al. Narrative review of the literature on adherence to disease-modifying therapies among patients with multiple sclerosis. [J Manag Care Pharm JMCP. 2013;19\(1 Suppl A\):S24-40.](#)
228. Richert ND, Zierak MC, Bash CN, et al. MRI and clinical activity in MS patients after terminating treatment with interferon beta-1b. [Mult Scler Houndmills Basingstoke Engl. 2000;6\(2\):86-90.](#)
229. Siger M, Durko A, Nicpan A, et al. Discontinuation of interferon beta therapy in multiple sclerosis patients with high pre-treatment disease activity leads to prompt return to previous disease activity. [J Neurol Sci. 2011;303\(1-2\):50-52.](#)
230. Wu X, Dastidar P, Kuusisto H, et al. Increased disability and MRI lesions after discontinuation of IFN-beta-1a in secondary progressive MS. [Acta Neurol Scand. 2005;112\(4\):242-247.](#)
231. O'Connor PW, Goodman A, Kappos L, et al. Disease activity return during natalizumab treatment interruption in patients with multiple sclerosis. [Neurology. 2011;76\(22\):1858-1865.](#)
232. Fox RJ, Cree BAC, De Sèze J, et al. MS disease activity in RESTORE: a randomized 24-week natalizumab treatment interruption study. [Neurology. 2014;82\(17\):1491-1498.](#)

233. Salhofer-Polanyi S, Baumgartner A, Kraus J, et al. What to expect after natalizumab cessation in a real-life setting. [Acta Neurol Scand. 2014;130\(2\):97-102.](#)
234. Sorensen PS, Koch-Henriksen N, Petersen T, et al. Recurrence or rebound of clinical relapses after discontinuation of natalizumab therapy in highly active MS patients. [J Neurol. 2014;261\(6\):1170-1177.](#)
235. West TW, Cree BAC. Natalizumab dosage suspension: are we helping or hurting? [Ann Neurol. 2010;68\(3\):395-399.](#)
236. Gueguen A, Roux P, Deschamps R, et al. Abnormal inflammatory activity returns after natalizumab cessation in multiple sclerosis. [J Neurol Neurosurg Psychiatry. 2014;85\(9\):1038-1040.](#)
237. Ghezzi A, Rocca MA, Baroncini D, et al. Disease reactivation after fingolimod discontinuation in two multiple sclerosis patients. [J Neurol. 2013;260\(1\):327-329.](#)
238. Hakiki B, Portaccio E, Giannini M, et al. Withdrawal of fingolimod treatment for relapsing-remitting multiple sclerosis: report of six cases. [Mult Scler Houndmills Basingstoke Engl. 2012;18\(11\):1636-1639.](#)
239. Hatcher SE, Waubant E, Nourbakhsh B, et al.. Rebound Syndrome in Patients With Multiple Sclerosis After Cessation of Fingolimod Treatment. [JAMA Neurol. 2016;73\(7\):790-794.](#)
240. Chitnis T, Tardieu M, Amato MP, et al. International Pediatric MS Study Group Clinical Trials Summit: meeting report. *Neurology*. 2013;80(12):1161-1168.
241. Absoud M, Lim MJ, Chong WK, et al. Paediatric acquired demyelinating syndromes: incidence, clinical and magnetic resonance imaging features. *Mult Scler Houndmills Basingstoke Engl.* 2013;19(1):76-86.
242. Chitnis T, Glanz B, Jaffin S, Healy B. Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States. [Mult Scler Houndmills Basingstoke Engl. 2009;15\(5\):627-631.](#)
243. Gorman MP, Healy BC, Polgar-Turcsanyi M, Chitnis T. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. [Arch Neurol. 2009;66\(1\):54-59.](#)
244. Yeh EA, Waubant E, Krupp LB, et al. Multiple sclerosis therapies in pediatric patients with refractory multiple sclerosis. [Arch Neurol. 2011;68\(4\):437-444.](#)
245. Ghezzi A, Moiola L, Pozzilli C, et al. Natalizumab in the pediatric MS population: results of the Italian registry. *BMC Neurol.* 2015;15:174.
246. Arnal-Garcia C, García-Montero MR, Málaga I, et al. Natalizumab use in pediatric patients with relapsing-remitting multiple sclerosis. [Eur J Paediatr Neurol EJPN Off J Eur Paediatr Neurol Soc. 2013;17\(1\):50-54.](#)
247. Ghezzi A, Pozzilli C, Grimaldi LME, et al. Natalizumab in pediatric multiple sclerosis: results of a cohort of 55 cases. [Mult Scler Houndmills Basingstoke Engl. 2013;19\(8\):1106-1112.](#)
248. Kornek B, Aboul-Enein F, Rostasy K, et al. Natalizumab therapy for highly active pediatric multiple sclerosis. [JAMA Neurol. 2013;70\(4\):469-475.](#)
249. Dale RC, Brilot F, Duffy LV, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. [Neurology. 2014;83\(2\):142-150.](#)

250. Salzer J, Lycke J, Wickström R, et al. Rituximab in paediatric onset multiple sclerosis: a case series. *J Neurol.* 2016;263(2):322-326.
251. Beres SJ, Graves J, Waubant E. Rituximab use in pediatric central demyelinating disease. [Pediatr Neurol. 2014;51\(1\):114-118.](#)
252. Chitnis T. Pediatric demyelinating diseases. [Continn Minneap Minn. 2013;19\(4 Multiple Sclerosis\):1023-1045.](#)
253. Chitnis T, Tenembaum S, Banwell B, et al. Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis. [Mult Scler Houndmills Basingstoke Engl. 2012;18\(1\):116-127.](#)
254. Penkov D, Tomasi P, Eichler I, et al. Pediatric Medicine Development: An Overview and Comparison of Regulatory Processes in the European Union and United States. [Ther Innov Regul Sci. 2017;51\(3\):360-371.](#)
255. Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk.* Tenth edition. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2015.
256. Cree BAC. Update on reproductive safety of current and emerging disease-modifying therapies for multiple sclerosis. [Mult Scler Houndmills Basingstoke Engl. 2013;19\(7\):835-843.](#)
257. Coyle PK. Management of women with multiple sclerosis through pregnancy and after childbirth. [Ther Adv Neurol Disord. 2016;9\(3\):198-210.](#)
258. Miller AE. Multiple sclerosis disease-modifying therapy and pregnancy. [Mult Scler Houndmills Basingstoke Engl. 2016;22\(6\):715-716.](#)
259. Herbstritt S, Langer-Gould A, Rockhoff M, et al. Glatiramer acetate during early pregnancy: A prospective cohort study. [Mult Scler Houndmills Basingstoke Engl. 2016;22\(6\):810-816.](#)
260. Ferrero S, Pretta S, Ragni N. Multiple sclerosis: management issues during pregnancy. [Eur J Obstet Gynecol Reprod Biol. 2004;115\(1\):3-9.](#)
261. Thiel S, Langer-Gould A, Rockhoff M, et al. Interferon-beta exposure during first trimester is safe in women with multiple sclerosis-A prospective cohort study from the German Multiple Sclerosis and Pregnancy Registry. [Mult Scler Houndmills Basingstoke Engl. 2016;22\(6\):801-809.](#)
262. Kieseier BC, Benamor M. Pregnancy outcomes following maternal and paternal exposure to teriflunomide during treatment for relapsing-remitting multiple sclerosis. [Neurol Ther. 2014;3\(2\):133-138.](#)
263. Friend S, Richman S, Bloomgren G, et al. Evaluation of pregnancy outcomes from the Tysabri® (natalizumab) pregnancy exposure registry: a global, observational, follow-up study. [BMC Neurol. 2016;16\(1\):150.](#)
264. Tsui A, Lee MA. Multiple sclerosis and pregnancy. [Curr Opin Obstet Gynecol. 2011;23\(6\):435-439.](#)
265. Lu E, Wang BW, Guimond C, et al. Safety of disease-modifying drugs for multiple sclerosis in pregnancy: current challenges and future considerations for effective pharmacovigilance. [Expert Rev Neurother. 2013;13\(3\):251-260; quiz 261.](#)
266. Bove R, Alwan S, Friedman JM, et al. Management of multiple sclerosis during pregnancy and the reproductive years: a systematic review. [Obstet Gynecol. 2014;124\(6\):1157-1168.](#)

267. Lu E, Wang BW, Alwan S, et al. A review of safety-related pregnancy data surrounding the oral disease-modifying drugs for multiple sclerosis. [CNS Drugs. 2014;28\(2\):89-94.](#)
268. Fragoso YD, Finkelsztein A, Kaimen-Maciél DR, et al. Long-term use of glatiramer acetate by 11 pregnant women with multiple sclerosis: a retrospective, multicentre case series. [CNS Drugs. 2010;24\(11\):969-976.](#)
269. Salminen HJ, Leggett H, Boggild M. Glatiramer acetate exposure in pregnancy: preliminary safety and birth outcomes. [J Neurol. 2010;257\(12\):2020-2023.](#)
270. Dung AA, Panda AK. Interferon β -1a therapy for multiple sclerosis during pregnancy: an unresolved issue. [BMJ Case Rep. 2014;2014.](#)
271. Vukusic S, Durand-Dubief F, Benoit A, et al. Natalizumab for the prevention of post-partum relapses in women with multiple sclerosis. [Mult Scler Houndmills Basingstoke Engl. 2015;21\(7\):953-955.](#)
272. Freedman MS, Cohen B, Dhib-Jalbut S, et al. Recognizing and treating suboptimally controlled multiple sclerosis: steps toward regaining command. [Curr Med Res Opin. 2009;25\(10\):2459-2470.](#)
273. Bermel RA, You X, Foulds P, et al. Predictors of long-term outcome in multiple sclerosis patients treated with interferon β . [Ann Neurol. 2013;73\(1\):95-103.](#)
274. Prosperini L, Gallo V, Petsas N, et al. One-year MRI scan predicts clinical response to interferon beta in multiple sclerosis. [Eur J Neurol Off J Eur Fed Neurol Soc. 2009;16\(11\):1202-1209.](#)
275. Rudick RA, Lee J-C, Simon J, et al. Defining interferon beta response status in multiple sclerosis patients. [Ann Neurol. 2004;56\(4\):548-555.](#)
276. Sormani MP, Li DK, Bruzzi P, et al. Combined MRI lesions and relapses as a surrogate for disability in multiple sclerosis. [Neurology. 2011;77\(18\):1684-1690.](#)
277. Giovannoni G, Butzkueven H, Dhib-Jalbut S, et al. *Brain Health: Time Matters in Multiple Sclerosis.* [Mult Scler Relat Disord. 2016;9 Suppl 1:S5-S48.](#)
278. O'Connor PW, Oh J. Disease-modifying agents in multiple sclerosis. [Handb Clin Neurol. 2014;122:465-501.](#)
279. Sorensen PS, Koch-Henriksen N, Ross C, et al. Danish Multiple Sclerosis Study Group. Appearance and disappearance of neutralizing antibodies during interferon-beta therapy. [Neurology. 2005;65\(1\):33-39.](#)
280. Sorensen PS, Ross C, Clemmesen KM, et al. Clinical importance of neutralising antibodies against interferon beta in patients with relapsing-remitting multiple sclerosis. [Lancet. 2003;362\(9391\):1184-1191.](#)
281. Bertolotto A, Capobianco M, Amato MP, et al. Guidelines on the clinical use for the detection of neutralizing antibodies (NAbs) to IFN beta in multiple sclerosis therapy: report from the Italian Multiple Sclerosis Study group. [Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2014;35\(2\):307-316.](#)
282. Goodin DS, Frohman EM, Hurwitz B, et al. Neutralizing antibodies to interferon beta: assessment of their clinical and radiographic impact: an evidence report: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. [Neurology. 2007;68\(13\):977-984.](#)
283. Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. [N Engl J Med. 2006;354\(9\):911-923.](#)

284. Calabresi PA, Giovannoni G, Confavreux C, et al. The incidence and significance of anti-natalizumab antibodies: results from AFFIRM and SENTINEL. [Neurology. 2007;69\(14\):1391-1403.](#)
285. Vennegoor A, Rispens T, Strijbis EM, et al. Clinical relevance of serum natalizumab concentration and anti-natalizumab antibodies in multiple sclerosis. [Mult Scler Houndmills Basingstoke Engl. 2013;19\(5\):593-600.](#)
286. Berger JR. Classifying PML risk with disease modifying therapies. [Mult Scler Relat Disord. 2017;12:59-63.](#)
287. Kirzinger SS, Jones J, Siegwald A, Crush AB. Relationship between disease-modifying therapy and depression in multiple sclerosis. [Int J MS Care. 2013;15\(3\):107-112.](#)
288. Kim S, Foley FW, Picone MA, et al. Depression levels and interferon treatment in people with multiple sclerosis. [Int J MS Care. 2012;14\(1\):10-16.](#)
289. Patti F, Amato MP, Trojano M, et al. Quality of life, depression and fatigue in mildly disabled patients with relapsing-remitting multiple sclerosis receiving subcutaneous interferon beta-1a: 3-year results from the COGIMUS (COGNitive Impairment in MULTiple Sclerosis) study. [Mult Scler Houndmills Basingstoke Engl. 2011;17\(8\):991-1001.](#)
290. Patten SB, Williams JVA, Metz LM. Anti-depressant use in association with interferon and glatiramer acetate treatment in multiple sclerosis. [Mult Scler Houndmills Basingstoke Engl. 2008;14\(3\):406-411.](#)
291. Menon S, Shirani A, Zhao Y, et al. Characterising aggressive multiple sclerosis. [J Neurol Neurosurg Psychiatry. 2013;84\(11\):1192-1198.](#)
292. Kaunzner UW, Kumar G, Askin G, et al. A study of patients with aggressive multiple sclerosis at disease onset. [Neuropsychiatr Dis Treat. 2016;12:1907-1912.](#)
293. Rush CA, MacLean HJ, Freedman MS. Aggressive multiple sclerosis: proposed definition and treatment algorithm. [Nat Rev Neurol. 2015;11\(7\):379-389.](#)
294. Cross AH, Naismith RT. Established and novel disease-modifying treatments in multiple sclerosis. [J Intern Med. 2014;275\(4\):350-363.](#)
295. Edan G, Comi G, Le Page E, et al. Mitoxantrone prior to interferon beta-1b in aggressive relapsing multiple sclerosis: a 3-year randomised trial. [J Neurol Neurosurg Psychiatry. 2011;82\(12\):1344-1350.](#)
296. Le Page E, Leray E, Taurin G, et al. Mitoxantrone as induction treatment in aggressive relapsing remitting multiple sclerosis: treatment response factors in a 5 year follow-up observational study of 100 consecutive patients. [J Neurol Neurosurg Psychiatry. 2008;79\(1\):52-56.](#)
297. Vollmer T, Panitch H, Bar-Or A, et al. Glatiramer acetate after induction therapy with mitoxantrone in relapsing multiple sclerosis. [Mult Scler Houndmills Basingstoke Engl. 2008;14\(5\):663-670.](#)
298. Edan G, Miller D, Clanet M, et al. Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicentre study of active disease using MRI and clinical criteria. [J Neurol Neurosurg Psychiatry. 1997;62\(2\):112-118.](#)
299. Klineova S, Nicholas J, Walker A. Response to disease modifying therapies in African Americans with multiple sclerosis. [Ethn Dis. 2012;22\(2\):221-225.](#)
300. Cree BAC, Al-Sabbagh A, Bennett R, Goodin D. Response to interferon beta-1a treatment in African American multiple sclerosis patients. [Arch Neurol. 2005;62\(11\):1681-1683.](#)

301. Hansen K, Schüssel K, Kieble M, et al. Adherence to Disease Modifying Drugs among Patients with Multiple Sclerosis in Germany: A Retrospective Cohort Study. [PloS One. 2015;10\(7\):e0133279.](#)
302. Patti F. Optimizing the benefit of multiple sclerosis therapy: the importance of treatment adherence. [Patient Prefer Adherence. 2010;4:1-9.](#)
303. Tremlett HL, Oger J. Interrupted therapy: stopping and switching of the beta-interferons prescribed for MS. [Neurology. 2003;61\(4\):551-554.](#)
304. Fox RJ, Salter AR, Tyry T, et al. Treatment discontinuation and disease progression with injectable disease-modifying therapies: findings from the north american research committee on multiple sclerosis database. [Int J MS Care. 2013;15\(4\):194-201.](#)
305. Saunders C, Caon C, Smrtka J, Shoemaker J. Factors that influence adherence and strategies to maintain adherence to injected therapies for patients with multiple sclerosis. [J Neurosci Nurs J Am Assoc Neurosci Nurses. 2010;42\(5 Suppl\):S10-18.](#)
306. Mohr DC, Cox D, Merluzzi N. Self-injection anxiety training: a treatment for patients unable to self-inject injectable medications. [Mult Scler Houndmills Basingstoke Engl. 2005;11\(2\):182-185.](#)
307. Clanet MC, Wolinsky JS, Ashton RJ, et al. Risk evaluation and monitoring in multiple sclerosis therapeutics. [Mult Scler Houndmills Basingstoke Engl. 2014;20\(10\):1306-1311.](#)
308. Caon C, Saunders C, Smrtka J, et al. Injectable disease-modifying therapy for relapsing-remitting multiple sclerosis: a review of adherence data. [J Neurosci Nurs J Am Assoc Neurosci Nurses. 2010;42\(5 Suppl\):S5-9.](#)
309. Giovannoni G, Southam E, Waubant E. Systematic review of disease-modifying therapies to assess unmet needs in multiple sclerosis: tolerability and adherence. [Mult Scler Houndmills Basingstoke Engl. 2012;18\(7\):932-946.](#)
310. Beer K, Müller M, Hew-Winzeler AM, et al. The prevalence of injection-site reactions with disease-modifying therapies and their effect on adherence in patients with multiple sclerosis: an observational study. [BMC Neurol. 2011;11:144.](#)
311. Devonshire V, Lapierre Y, Macdonell R, et al. The Global Adherence Project (GAP): a multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis. [Eur J Neurol Off J Eur Fed Neurol Soc. 2011;18\(1\):69-77.](#)
312. Treadaway K, Cutter G, Salter A, et al. Factors that influence adherence with disease-modifying therapy in MS. [J Neurol. 2009;256\(4\):568-576.](#)
313. Dor A, Lage MJ, Tarrants ML, Castelli-Haley J. Cost sharing, benefit design, and adherence: the case of multiple sclerosis. [Adv Health Econ Health Serv Res. 2010;22:175-193.](#)
314. Grytten N, Aarseth JH, Espeset K, et al. Stoppers and non-starters of disease-modifying treatment in multiple sclerosis. [Acta Neurol Scand. 2013;127\(2\):133-140.](#)
315. Fragoso YD, Adoni T, Anacleto A, et al. Recommendations on diagnosis and treatment of depression in patients with multiple sclerosis. [Pract Neurol. 2014;14\(4\):206-209.](#)
316. Tarrants M, Oleen-Burkey M, Castelli-Haley J, Lage MJ. The impact of comorbid depression on adherence to therapy for multiple sclerosis. [Mult Scler Int. 2011;2011:271321.](#)

APPENDICES

APPENDIX A: Multiple Sclerosis Disease Courses 2013 Revisions¹

In 2013, the International Advisory Committee on Clinical Trials of MS updated the disease course descriptions that were first published in 1996 (Lublin & Reingold, 1996), based on advances in the understanding of the disease process in MS and in MRI technology. The updated disease courses are *clinically isolated syndrome (CIS)*, *relapsing-remitting MS (RRMS)*, *primary progressive MS (PPMS)* and *secondary progressive MS*.

Clinically Isolated Syndrome (CIS) – a first episode of inflammatory demyelination in the central nervous system that could become MS if dissemination in time and space are established.

According to the 2017 revisions to the diagnostic criteria for MS,² the diagnosis of MS in a patient with CIS (with evidence of > 2 lesions) can be made when establishing dissemination in time – when there is an additional clinical attack; *or* simultaneous presence of both enhancing and non-enhancing, symptomatic or asymptomatic MS- typical MRI lesions; *or* new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan); *or* CSF-specific (i.e., not in serum) oligoclonal bands.

In a patient with CIS (with objective clinical evidence of 1 lesion), the diagnosis can be made if dissemination in space and dissemination in time are established. Dissemination in space would be established by an additional attack implicating a different CNS site *or* > 1 MS-typical symptomatic or asymptomatic T2 lesions in > 2 areas of the CNS. Dissemination in time would be established by when there is an additional clinical attack; *or* simultaneous presence of both enhancing and non-enhancing, symptomatic or asymptomatic MS- typical MRI lesions; *or* new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan); *or* CSF-specific (i.e., not in serum) oligoclonal bands.

Continue onto the following pages for text and graphics describing the other disease courses

¹Lublin FD, Reingold SC, Cohen JA et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. [Neurology. 2014;83\(3\):278-286.](#)

²Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. [Lancet Neurol. 2018;17\(2\):162-173.](#)

Relapsing-Remitting MS (RRMS) – episodes of acute worsening of neurologic functioning (new symptoms or worsening of existing symptoms) with total or partial recovery and no apparent progression of disease. RRMS can be further characterized as:

Active – showing evidence of new relapses, new gadolinium-enhancing lesions and/or new or enlarging T2 lesions on MRI over a specified time **OR**

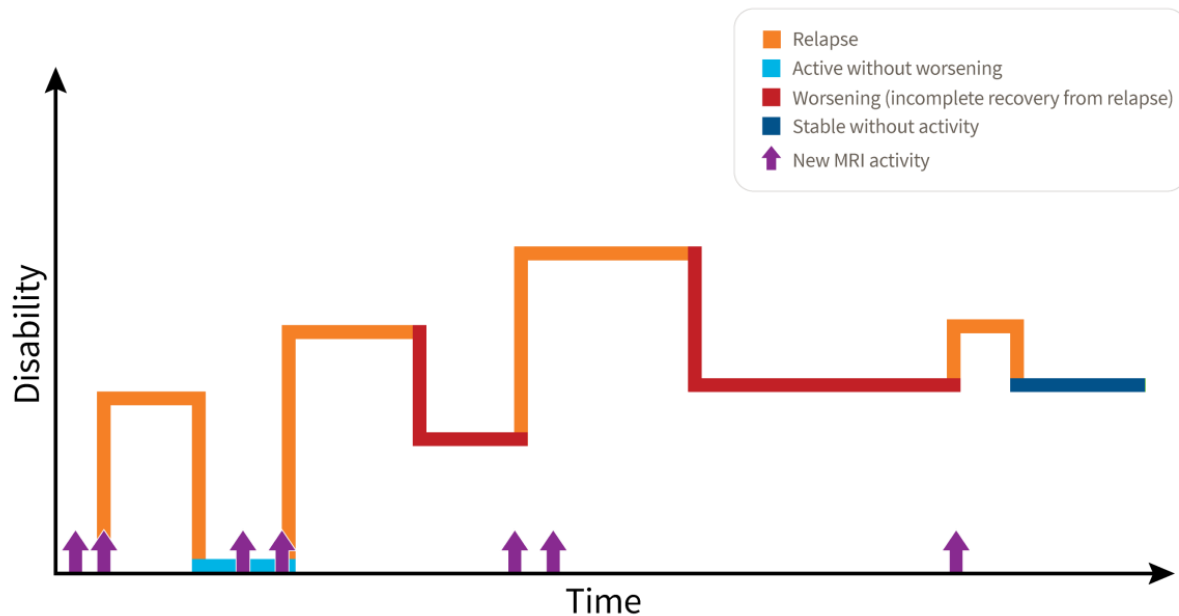
Not active – showing no evidence of disease activity

AND

Worsening – increased disability confirmed over a specified time following a relapse **OR**

Stable – no evidence of increasing disability over a specified time following a relapse

RRMS



Primary Progressive MS (PPMS) – steadily worsening neurologic function (accumulation of disability) from the onset of symptoms without initial relapses or remission. PPMS can be further characterized as:

Active – showing evidence of new relapses, new gadolinium-enhancing lesions and/or new or enlarging T2 lesions on MRI over a specified time **OR**

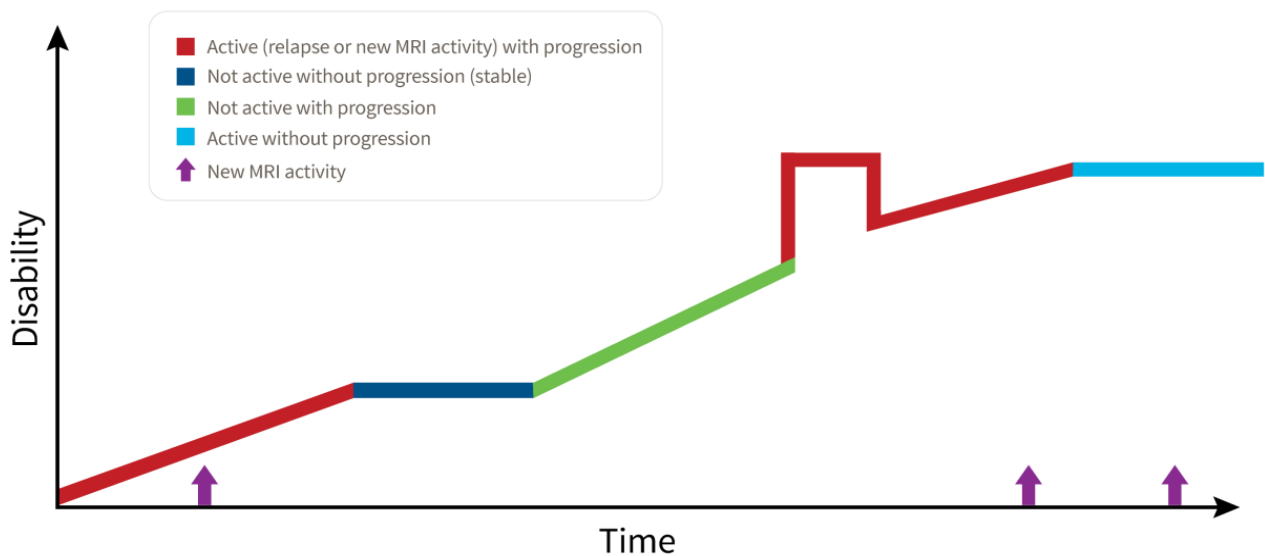
Not active – showing no evidence of disease activity

AND

With progression – evidence of disease worsening on an objective measure of change, confirmed over a specified time, with or without relapses **OR**

Without progression – no evidence of disease worsening on an objective measure of change over a specified time

PPMS



Secondary Progressive MS (SPMS) – following an initial relapsing-remitting course, the disease becomes more steadily progressive, with or without relapses. SPMS can be further characterized as:

Active – showing evidence of new relapses, new gadolinium-enhancing lesions and/or new enlarging T2 lesions on MRI over a specified time **OR**

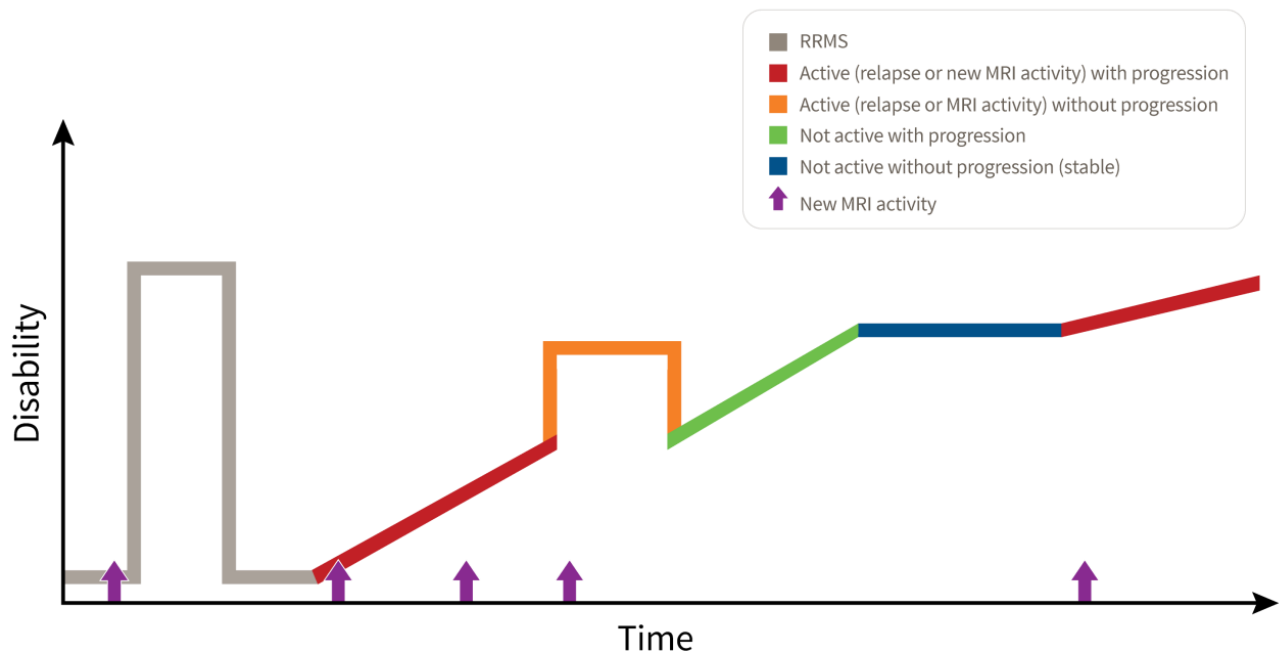
Not active –showing no evidence of disease activity

AND

With progression – evidence of disease worsening on an objective measure of change, confirmed over a specified time, with or without relapses **OR**

Without progression – no evidence of disease worsening on an objective measure of change over a specified time

SPMS



Appendix B: 2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis



2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis



Diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in the CNS in space and time. See [Lancet Neurology](#) paper* for details.

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED TO MAKE MS DIAGNOSIS
...in a person with a typical attack/CIS at onset (see KEY below for definitions)	
<ul style="list-style-type: none"> • ≥2 attacks and objective clinical evidence of ≥2 lesions • ≥2 attacks and objective clinical evidence of 1 lesion with historical evidence of prior attack involving lesion in different location 	None. Dissemination in space (DIS) and dissemination in time (DIT) have been met.
<ul style="list-style-type: none"> • ≥2 attacks and objective clinical evidence of 1 lesion 	One of these criteria: - DIS : additional clinical attack implicating different CNS site - DIS : ≥1 symptomatic or asymptomatic MS-typical T2 lesions in ≥2 areas of CNS: periventricular, juxtacortical/cortical , infratentorial or spinal cord
<ul style="list-style-type: none"> • 1 attack and objective clinical evidence of ≥2 lesions 	One of these criteria: - DIT : additional clinical attack - DIT : simultaneous presence of both enhancing and non-enhancing symptomatic or asymptomatic MS-typical MRI lesions - DIT : new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF-specific (i.e. not in serum) oligoclonal bands

CONTINUED ON REVERSE

Colored text= revisions compared to previous McDonald Criteria

KEY: CIS: clinically isolated syndrome CNS: central nervous system CSF: cerebrospinal fluid DIS: dissemination in space

DIT: dissemination in time **T2 lesion:** hyperintense lesion on T2-weighted MRI

*Thompson AJ, et al. *Lancet Neurol* 2017; online Dec 21. [http://dx.doi.org/10.1016/S1474-4422\(17\)30470-2](http://dx.doi.org/10.1016/S1474-4422(17)30470-2).

2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis (continued)

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED TO MAKE MS DIAGNOSIS
...in a person with a typical attack/CIS at onset (continued) (see KEY on reverse for definitions)	
<ul style="list-style-type: none"> • 1 attack and objective clinical evidence of 1 lesion 	One of these criteria: - DIS : additional attack implicating different CNS site - DIS : ≥1 MS-typical symptomatic or asymptomatic T2 lesions in ≥2 areas of CNS: periventricular, juxtacortical/cortical , infratentorial or spinal cord AND One of these criteria: - DIT : additional clinical attack - DIT : simultaneous presence of both enhancing and non-enhancing symptomatic or asymptomatic MS-typical MRI lesions - DIT : by new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF-specific (i.e. not in serum) oligoclonal bands
...in a person with progression of disability from onset	
<ul style="list-style-type: none"> • progression from onset 	- 1 year of disability progression (retrospective or prospective) AND Two of these criteria: - ≥1 symptomatic or asymptomatic MS-typical T2 lesions (periventricular, juxtacortical/cortical or infratentorial) - ≥2 T2 spinal cord lesions - CSF-specific (i.e. not in serum) oligoclonal bands

The International Panel on Diagnosis of Multiple Sclerosis was convened under the auspices of the International Advisory Committee on Clinical Trials in MS, sponsored by the National MS Society and the European Committee for Treatment and Research in Multiple Sclerosis.

More resources for clinicians: <https://www.nationalmssociety.org/For-Professionals/Physicians>

©2018 National Multiple Sclerosis Society 733 Third Avenue, New York, NY 10017-3288

APPENDIX C: Treatments Used Off-Label for Multiple Sclerosis

The U.S. Food and Drug Administration (FDA) has approved medications for the treatment of relapsing forms of MS, as well as one medication for secondary progressive MS (SPMS) and one for primary progressive MS (PPMS). However, response to these medications is variable and each has contraindications, side effects and risks that restrict their use for some people. In addition, barriers to access may exist for some people with one or another of the approved medications. Over the past few decades, several medications have been prescribed for the treatment of MS that have FDA approval for diagnoses other than MS. For each of these agents, there is some, but often limited clinical trial evidence of efficacy in MS. The available information is summarized here. Information about hematopoietic stem cell transplantation is also provided.

Azathioprine (Imuran®)

[Azathioprine](#)¹ is an oral immunosuppressant drug that targets activation, proliferation, and differentiation of both T and B lymphocytes. Azathioprine is FDA-approved for use in combination with other medications to prevent organ rejection after kidney transplant and for the treatment of active rheumatoid arthritis.

It is used outside of FDA approval for conditions such as Crohn's disease, ulcerative colitis, lupus, autoimmune hepatitis, neuromyelitis optica, myasthenia gravis and multiple sclerosis.

Azathioprine has been used in MS for over 30 years; however, the results of clinical trials with this agent have been mixed.²

- A meta-analysis of placebo-controlled, double-blind, randomized trials in MS³ concluded that azathioprine is probably effective in reducing relapses and may reduce the risk of progression.
- In a study comparing interferon beta-1a used alone vs. interferon beta-1a plus azathioprine or interferon beta-1a plus azathioprine and prednisone, no difference was found between the groups in annualized relapse rate, cumulative probability of sustained disability progression, change in percentage of brain volume loss or T2 lesion volume.⁴ Follow-up after 6 years of treatment yielded similar results.⁵
- Lus and colleagues⁶ evaluated the impact of azathioprine plus interferon beta-1a in three groups of relapsing-remitting patients: 1) a group with no prior treatment; 2) a group with inadequate response to prior treatment with azathioprine; and 3) a group with inadequate response to prior treatment with interferon beta-1a. The combined treatment reduced the mean number of relapses in all three groups and reduced the mean Delta EDSS score in groups 2 and 3. The combined treatment also resulted in significantly reduced MRI activity.
- A small two-year pilot study⁷ of azathioprine combined with interferon beta-1b in patients with secondary progressive MS whose disease had not been adequately controlled with interferon beta-1b alone reported a reduction in annual relapse rate of about 50 percent in year 2, a significant trend for an increase in EDSS, a decrease in lesion load on MRI at 12 and 24 months and a significant improvement in neuropsychological testing after 24 months. The investigators concluded that the combination treatment was safe and generally well tolerated; however, they recommended strict clinical and laboratory monitoring during treatment with this combination.
- In an open-label pilot trial⁸ to evaluate the addition of oral azathioprine to interferon beta-1b in patients who had break-through disease on interferon beta-1b alone, patients had a 65 percent reduction in the number of Gd-enhancing lesions compared to their baseline values. A total WBC count less than 4800/mm³ was the best predictor of MRI response.
- In a single-blind study⁹ comparing azathioprine with interferon beta over one year, the proportion of relapse-free patients was greater in the azathioprine group and the mean EDSS was also improved in this group.

Azathioprine is approved to treat MS in parts of Europe.

Side effects and risks include abdominal pain, severe nausea, vomiting, loss of appetite, mouth sores/ulcers, increased risk of infection, hair loss, change in hair color and texture, and risk of malignancies and blood abnormalities. Azathioprine can cause fetal abnormalities.

Cladribine

Cladribine,¹⁰ a purine nucleoside analogue prodrug, reduces lymphocyte subtypes, specifically CD4+ T cells, CD8+ T cells and B cells, as well as pro-inflammatory chemokine levels.¹¹ A parenteral form of cladribine is approved as a treatment for hairy cell leukemia.

In MS, two early studies of cladribine injected subcutaneously (SC) yielded conflicting results in patients with progressive MS.^{12,13} An 18-month randomized controlled trial of SC cladribine in relapsing-remitting MS demonstrated significant benefits of cladribine vs. placebo in reducing both the frequency and severity of relapses, as well as improvement in MRI variables. However, concerns about the depletion of total lymphocyte count raised safety concerns.¹⁴

The subsequent creation of an oral formulation of cladribine increased interest in cladribine for the treatment of MS:

- In a phase 3 clinical trial of oral cladribine that included 1,326 relapsing-remitting patients randomized to receive one of two doses of cladribine or placebo for 96 weeks, both treatment doses significantly reduced the rate of relapses, disease progression and MRI measures of disease activity.¹⁵
- In a phase 3 trial of oral cladribine in 616 patients with a first demyelinating event randomized to receive one of two doses of cladribine or placebo, both doses of cladribine significantly delayed the diagnosis of MS compared with placebo.¹⁶

The most common adverse event with cladribine is lymphocytopenia, which is sometimes severe. Infections and infestations can also occur, particularly herpes zoster. In the clinical trials, malignant neoplasms were identified in the cladribine treatment groups. Cladribine is a pregnancy category D.

The medication was approved in 2010 in Russia and Australia.

In a meta-analysis of phase III trials of licensed disease-modifying therapies for relapsing MS and a phase III trial of cladribine, no evidence was found of an increased cancer risk for cladribine.¹⁷ Based on these data, the EMA approved Mavenclad in 2018.¹⁸ Merck has also filed for an NDA to the FDA.

Cyclophosphamide (Cytosan®)

Cyclophosphamide¹⁹ is an alkylating agent related to nitrogen mustard that binds to DNA and disrupts cell replication. In MS, the treatment serves as a general immune suppressant impacting cell-mediated and humoral immunity.²⁰ It is given intravenously or orally.

Cyclophosphamide is FDA-approved for the treatment of various types of cancers. It is used off-label to treat autoimmune conditions such as Wegener's granulomatosis, myasthenia gravis, lupus, rheumatoid arthritis and multiple sclerosis.

Placebo-controlled trials in progressive MS populations with different dosing regimens have found no benefit over placebo.^{21,22} However, several trials in people with active relapsing MS have demonstrated a reduction in relapses, fewer new areas of CNS inflammation and a variable effect on disease worsening, highlighting the usefulness of cyclophosphamide in younger, inflammatory and less progressed patients.²

- Monthly intravenous cyclophosphamide led to improvement and neurologic stability within six months, sustained for at least 18 months after treatment onset, in patients with rapidly deteriorating relapsing-remitting MS.²³
- In a combination trial of cyclophosphamide and interferon beta, with follow-up at 12 and 24 months, Reggio and colleagues²⁴ found that the combination treatment halted disease progression in active, deteriorating MS patients who had received insufficient benefits from interferon beta alone.
- In a study of 10 patients with very active disease and severe frequent attacks who had not benefited from interferon beta alone, Patti and colleagues²⁵ used pulsed cyclophosphamide to obtain a chronic lymphocytopenia, resulting in a marked and significant relapse reduction, improvement in disability and reduction of T2 burden of disease. Thirty-six months after discontinuation of cyclophosphamide, clinical and MRI benefits were maintained.²⁶
- In a randomized single-blind, parallel-group, multi-center trial, combination therapy using pulsed cyclophosphamide with methylprednisolone along with interferon beta-1a significantly decreased the number of Gd-enhancing lesions and slowed clinical activity in patients who had experienced active disease on interferon beta alone.²⁷

Side effects and risks include nausea, vomiting, hair thinning/loss, low white blood cell count, risk of infections, risk of cancers, infertility, and inflammation of the bladder with bleeding. Cyclophosphamide causes fetal abnormalities.

Minocycline

Minocycline²⁸ is an oral tetracycline antibiotic that is FDA approved for the treatment of a number of different types of bacterial infection. It is used off-label as a treatment for rheumatoid arthritis. Minocycline has also been studied in conditions such as osteoporosis, schizophrenia, cystic fibrosis and multiple sclerosis.

- In patients with RRMS, interferon beta-1a plus minocycline was found to be no more effective than interferon beta-1a plus placebo in time to first relapse, annualized relapse rate, number of new or enlarging T2 lesions on MRI, or change in brain volume.²⁹
- In patients with RRMS, minocycline plus glatiramer acetate was found to be safe and well-tolerated, and reduced the number of T1 gadolinium-enhanced lesions, the total number of new and enlarging T2 lesions, and the total T2 burden of disease compared to glatiramer acetate plus placebo.³⁰

Side effects and risks include gastrointestinal problems, liver damage, mild to severe skin conditions, respiratory problems, kidney toxicity, muscle and joint pain, blood cell abnormalities and central nervous system disorders. Minocycline is a pregnancy category D medication, indicating potential for fetal abnormalities.

Mycophenolate mofetil (Cellcept®)

Mycophenolate mofetil³¹ is an immunosuppressant given by mouth twice daily that selectively inhibits an enzyme responsible for the de novo synthesis of the DNA nucleotide guanine within T-cells, B-cells and macrophages. It is FDA approved for preventing rejection in patients receiving organ transplants and is used off-label for lupus, certain types of skin diseases and immune system-related diseases, including multiple sclerosis.

- Mycophenolate mofetil has been studied in small, open-label trials as a monotherapy or in combination with interferon beta or glatiramer acetate³²⁻³⁴ and in two blinded, placebo-controlled pilot studies in combination with interferon beta-1a.^{35,36}

- Mycophenolate mofetil has also been compared with interferon beta-1a in a small randomized, blinded, parallel group pilot trial in patients with relapsing-remitting MS.³⁷

The results of these studies suggest that mycophenolate mofetil may reduce the annual number of MS relapses, limit new areas of CNS damage and may slow disease worsening, however additional studies are needed to confirm these benefits.²

Side effects and risks include increased risk of infection (including opportunistic infections such as PML), nausea, diarrhea, stomach pain, weakness, dizziness, difficulty sleeping, increased risk of skin cancer and lymphoma, stomach ulcers and bleeding, elevation in liver enzymes and jaundice. Mycophenolate mofetil can cause fetal death or malformations.

Rituximab (Rituxan®)

Rituximab³⁸ is a chimeric monoclonal antibody that targets CD20 on the surface of B-lymphocytes, which are known to cause inflammation and damage in MS.

Rituximab is FDA approved for the treatment of several conditions including non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis and granulomatosis with polyangiitis, and microscopic polyangiitis. It has been used successfully off-label to treat neuromyelitis optica, multiple sclerosis, myasthenia gravis, autoimmune encephalitis, and autoimmune neuropathies and myopathies.³⁹

Several clinical trials in MS have demonstrated that rituximab is effective in reducing clinical relapses and limiting new inflammation in the central nervous system.⁴⁰

- In a phase 2, double-blind, 48-week trial in relapsing-remitting MS, a single course of rituximab reduced inflammatory brain lesions and clinical relapses for 48 weeks.⁴¹
- A randomized, double-blind, placebo-controlled study of rituximab in primary progressive MS came close to meeting its endpoint, suggesting that selective B-cell depletion may slow disease progression in younger patients with inflammatory lesions.⁴²
- Rituximab was found to be more effective than fingolimod in reducing the risk of clinical relapses and contrast-enhancing lesions in stable relapsing-remitting MS patients who switch from natalizumab after becoming JC virus antibody positive.⁴³
- In a retrospective uncontrolled observational multicenter study that included relapsing-remitting, secondary progressive and primary progressive MS patients receiving different doses of rituximab, the treatment was generally well-tolerated, with a low incidence of serious side effects, and was effective in controlling relapses.⁴⁴

Rituximab is given by intravenous infusion. A common dosing regimen is two intravenous infusions separated by 2 weeks, repeated every 6 months.

Side effects and risks include infusion reactions, infections (including opportunistic infections such as PML), allergic reactions, headache, fatigue and anemia. Rituximab is a pregnancy category C.

Hematopoietic stem cell transplantation (HSCT)

HSCT uses autologous, hematopoietic stem cells, derived from the bone marrow or blood, to repopulate the body's immune cells and stop the inflammatory process that contributes to active relapsing MS. While the procedure varies somewhat depending on the medical center and doctors who are performing it, the essential steps include: outpatient chemotherapy by intravenous infusion for up to 10 days to stimulate the production of bone marrow stem cells and promote their release into the blood; storage of stem cells from the blood for future use; inpatient chemotherapy for up to 11 days to suppress the body's immune cells; infusion of stored stem cells into the bloodstream; administration of antibiotics to combat infection; immune reconstitution completed within three to six months.

- In a multicenter, single-group phase 2 trial⁴⁵ involving 24 patients with aggressive relapsing MS that had not responded to other therapies, investigators reported a 69.6 percent MS activity-free survival rate at three years following transplantation, with no relapses and no Gd-enhancing lesions or new T2 lesions on 314 MRI sequential scans over a median follow-up of 6.7 years (range 3.9-12.7 years). The rate of brain atrophy decreased to the level expected in healthy controls and 35 percent of patients had a sustained improvement in EDSS. One patient died of transplantation-related complications resulting in liver failure; one patient required intensive hospital care for severe liver complications; all participants developed fevers typically associated with infections.
- In a 5-year multi-center study, 25 people with active relapsing MS that had not been controlled by disease-modifying therapies underwent HSCT with high-dose immunosuppressive therapy. After five years, 69 percent of participants remained free of disease activity and required no disease-modifying therapy. Reported side effects included blood cell reductions and infections.⁴⁶
- Other studies using a low-intensity lympho-ablative regimen⁴⁷ or a non-myeloablative regimen designed to reduce toxicity,⁴⁸ demonstrated some improvement in some trial participants, with fewer adverse events, leading investigators to conclude that these techniques may not be optimal for individuals with highly aggressive disease or disease of long-standing.⁴⁹

Scolding and colleagues, on behalf of the attendees at the International Conference on Cell-Based Therapies for Multiple Sclerosis, concluded the following based on their review of I/AHSCT (Immunoablation followed by autologous hematopoietic stem cell transplantation) studies:

- The available evidence suggests substantial efficacy in suppressing inflammatory disease activity; however, the benefit/risk/cost profile is not completely known.
- Patients most likely to benefit include those with active relapsing-remitting MS, ≤ 50 years of age, with ≤ 5 years disease duration, who are ambulatory and have ongoing disease despite disease-modifying therapy.
- Additional study is needed, particularly head-to-head comparisons with high efficacy disease-modifying agents.
- If HSCT is performed in clinical practice, safety and efficacy data should be collected, reported and published. However, the group strongly encouraged enrolling patients in ongoing clinical trials when available.

REFERENCES

1. IMURAN® (azathioprine) [prescribing information]. San Diego, CA: Prometheus Laboratories Inc. 2011. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/016324s034s0351bl.pdf. Accessed March 28, 2017.
2. Stankiewicz JM, Kolb H, Karni A, Weiner HL. Role of immunosuppressive therapy for the treatment of multiple sclerosis. [*Neurother J Am Soc Exp Neurother.* 2013;10\(1\):77-88.](#)
3. Casetta I, Iuliano G, Filippini G. Azathioprine for multiple sclerosis. [*Cochrane Database Syst Rev.* 2007;\(4\):CD003982.](#)
4. Havrdova E, Zivadinov R, Krasensky J, et al. Randomized study of interferon beta-1a, low-dose azathioprine, and low-dose corticosteroids in multiple sclerosis. [*Mult Scler Houndmills Basingstoke Engl.* 2009;15\(8\):965-976.](#)
5. Kalincik T, Horakova D, Dolezal O, et al. Interferon, azathioprine and corticosteroids in multiple sclerosis: 6-year follow-up of the ASA cohort. [*Clin Neurol Neurosurg.* 2012;114\(7\):940-946.](#)
6. Lus G, Romano F, Scuotto A, Accardo C, Cotrufo R. Azathioprine and interferon beta(1a) in relapsing-remitting multiple sclerosis patients: increasing efficacy of combined treatment. [*Eur Neurol.* 2004;51\(1\):15-20.](#)
7. Fernández O, Guerrero M, Mayorga C, et al. Combination therapy with interferon beta-1b and azathioprine in secondary progressive multiple sclerosis. A two-year pilot study. [*J Neurol.* 2002;249\(8\):1058-1062.](#)
8. Pulicken M, Bash CN, Costello K, et al. Optimization of the safety and efficacy of interferon beta 1b and azathioprine combination therapy in multiple sclerosis. [*Mult Scler Houndmills Basingstoke Engl.* 2005;11\(2\):169-174.](#)
9. Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of interferon beta products and azathioprine in the treatment of relapsing-remitting multiple sclerosis. [*J Neurol.* 2007;254\(12\):1723-1728.](#)
10. Leustatin® (cladribine) [prescribing information]. Raritan, NJ: Centocor Ortho Biotech Products, L.P. July 2012. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020229s0341bl.pdf. Accessed March 28, 2017.
11. Fox EJ. Emerging oral agents for multiple sclerosis. [*Am J Manag Care.* 2010;16\(8 Suppl\):S219-226.](#)
12. Beutler E, Sipe JC, Romine JS, Koziol JA, McMillan R, Zyroff J. The treatment of chronic progressive multiple sclerosis with cladribine. [*Proc Natl Acad Sci U S A.* 1996;93\(4\):1716-1720.](#)
13. Rice GP, Filippi M, Comi G. Cladribine and progressive MS: clinical and MRI outcomes of a multicenter controlled trial. Cladribine MRI Study Group. [*Neurology.* 2000;54\(5\):1145-1155.](#)
14. Janiec K, Wajgt A, Kondera-Anasz Z. Effect of immunosuppressive cladribine treatment on serum leucocytes system in two-year clinical trial in patients with chronic progressive multiple sclerosis. [*Med Sci Monit Int Med J Exp Clin Res.* 2001;7\(1\):93-98.](#)
15. Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. [*N Engl J Med.* 2010;362\(5\):416-426.](#)

16. Leist TP, Comi G, Cree BAC, et al. Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial. [Lancet Neurol. 2014;13\(3\):257-267.](#)
17. Pakpoor J, Disanto G, Altmann DR, et al. No evidence for higher risk of cancer in patients with multiple sclerosis taking cladribine. [Neurol Neuroimmunol Neuroinflammation. 2015;2\(6\):e158.](#)
18. European Medicines Agency. Mavenclad (cladribine). August 2018. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004230/human_med_002150.jsp&mid=WC0b01ac058001d124. Accessed October 1, 2018.
19. Cyclophosphamide [prescribing information]. Deerfield, IL: Baxter Healthcare Corporation. May 2013. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/012141s090,012142s112lbl.pdf. Accessed March 28, 2017.
20. Okuda DT. Immunosuppressive treatments in multiple sclerosis. [Handb Clin Neurol. 2014;122:503-511.](#)
21. The Canadian cooperative trial of cyclophosphamide and plasma exchange in progressive multiple sclerosis. The Canadian Cooperative Multiple Sclerosis Study Group. [Lancet Lond Engl. 1991;337\(8739\):441-446.](#)
22. Likosky WH, Fireman B, Elmore R, et al. Intense immunosuppression in chronic progressive multiple sclerosis: the Kaiser study. [J Neurol Neurosurg Psychiatry. 1991;54\(12\):1055-1060.](#)
23. Khan OA, Zvartau-Hind M, Caon C, et al. Effect of monthly intravenous cyclophosphamide in rapidly deteriorating multiple sclerosis patients resistant to conventional therapy. [Mult Scler Houndmills Basingstoke Engl. 2001;7\(3\):185-188.](#)
24. Reggio E, Nicoletti A, Fiorilla T, Politi G, Reggio A, Patti F. The combination of cyclophosphamide plus interferon beta as rescue therapy could be used to treat relapsing-remitting multiple sclerosis patients-- twenty-four months follow-up. [J Neurol. 2005;252\(10\):1255-1261.](#)
25. Patti F, Cataldi ML, Nicoletti F, Reggio E, Nicoletti A, Reggio A. Combination of cyclophosphamide and interferon-beta halts progression in patients with rapidly transitional multiple sclerosis. [J Neurol Neurosurg Psychiatry. 2001;71\(3\):404-407.](#)
26. Patti F, Reggio E, Palermo F, et al. Stabilization of rapidly worsening multiple sclerosis for 36 months in patients treated with interferon beta plus cyclophosphamide followed by interferon beta. [J Neurol. 2004;251\(12\):1502-1506.](#)
27. Smith DR, Weinstock-Guttman B, Cohen JA, et al. A randomized blinded trial of combination therapy with cyclophosphamide in patients-with active multiple sclerosis on interferon beta. [Mult Scler Houndmills Basingstoke Engl. 2005;11\(5\):573-582.](#)
28. Minocycline HCl [prescribing information]. Scottsdale, AZ: Medicis Pharmaceutical Corporation. March 2011. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/050808s014lbl.pdf. Accessed March 28, 2017.
29. Sørensen PS, Sellebjerg F, Lycke J, et al. Minocycline added to subcutaneous interferon β -1a in multiple sclerosis: randomized RECYCLINE study. [Eur J Neurol. 2016;23\(5\):861-870.](#)
30. Metz LM, Li D, Traboulsee A, et al. Glatiramer acetate in combination with minocycline in patients with relapsing--remitting multiple sclerosis: results of a Canadian, multicenter, double-blind, placebo-controlled trial. [Mult Scler Houndmills Basingstoke Engl. 2009;15\(10\):1183-1194.](#)

31. CellCept® (mycophenolate mofetil capsules) [prescribing information]. Nutley, NJ: Roche Pharmaceuticals. 2008 1998. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050722s018lbl.pdf. Accessed March 28, 2017.
32. Ahrens N, Salama A, Haas J. Mycophenolate-mofetil in the treatment of refractory multiple sclerosis. *J Neurol*. 2001;248(8):713-714.
33. Frohman EM, Brannon K, Racke MK, Hawker K. Mycophenolate mofetil in multiple sclerosis. *Clin Neuropharmacol*. 2004;27(2):80-83.
34. Vermersch P, Waucquier N, Michelin E, et al. Combination of IFN beta-1a (Avonex) and mycophenolate mofetil (Cellcept) in multiple sclerosis. *Eur J Neurol*. 2007;14(1):85-89.
35. Remington GM, Treadaway K, Frohman T, et al. A one-year prospective, randomized, placebo-controlled, quadruple-blinded, phase II safety pilot trial of combination therapy with interferon beta-1a and mycophenolate mofetil in early relapsing-remitting multiple sclerosis (TIME MS). *Ther Adv Neurol Disord*. 2010;3(1):3-13.
36. Etemadifar M, Kazemi M, Chitsaz A, et al. Mycophenolate mofetil in combination with interferon beta-1a in the treatment of relapsing-remitting multiple sclerosis: A preliminary study. *J Res Med Sci Off J Isfahan Univ Med Sci*. 2011;16(1):1-5.
37. Frohman EM, Cutter G, Remington G, et al. A randomized, blinded, parallel-group, pilot trial of mycophenolate mofetil (CellCept) compared with interferon beta-1a (Avonex) in patients with relapsing-remitting multiple sclerosis. *Ther Adv Neurol Disord*. 2010;3(1):15-28.
38. Rituxan® (rituximab) [prescribing information]. South San Francisco, CA: Genentech, Inc. February 2010. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103705s5311lbl.pdf. Accessed March 28, 2017.
39. Kosmidis ML, Dalakas MC. Practical considerations on the use of rituximab in autoimmune neurological disorders. *Ther Adv Neurol Disord*. 2010;3(2):93-105.
40. Bourdette D. Rituximab for treating multiple sclerosis: Off-label but on target. *Neurology*. 2016;87(20):2070-2071.
41. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med*. 2008;358(7):676-688.
42. Hawker K, O'Connor P, Freedman MS, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. *Ann Neurol*. 2009;66(4):460-471.
43. Alping P, Frisell T, Novakova L, et al. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. *Ann Neurol*. 2016;79(6):950-958.
44. Salzer J, Svenningsson R, Alping P, et al. Rituximab in multiple sclerosis: A retrospective observational study on safety and efficacy. *Neurology*. 2016;87(20):2074-2081.
45. Atkins HL, Bowman M, Allan D, et al. Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial. *Lancet Lond Engl*. 2016;388(10044):576-585.

46. Nash RA, Hutton GJ, Racke MK, et al. High-dose immunosuppressive therapy and autologous HCT for relapsing-remitting MS. [*Neurology*. 2017;88\(9\):842-852.](#)
47. Curro' D, Vuolo L, Gualandi F, et al. Low intensity lympho-ablative regimen followed by autologous hematopoietic stem cell transplantation in severe forms of multiple sclerosis: A MRI-based clinical study. [*Mult Scler Houndmills Basingstoke Engl*. 2015;21\(11\):1423-1430.](#)
48. Burt RK, Balabanov R, Han X, et al. Association of nonmyeloablative hematopoietic stem cell transplantation with neurological disability in patients with relapsing-remitting multiple sclerosis. [*JAMA*. 2015;313\(3\):275-284.](#)
49. Burt RK, Balabanov R, Snowden JA, et al. Non-myeloablative haematopoietic stem cell transplantation versus continued disease modifying therapies (DMT) in patients with highly active relapsing remitting multiple sclerosis (RRMS) - SS2-8. European Society for Blood and Marrow Transplantation (EBMT) 44th Annual Meeting of the EBMT, Lisbon, Portugal. March 2018. <http://www.professionalabstracts.com/ebmt2018/iplanner/#/presentation/636>. Accessed September 21, 2018.

THE MULTIPLE SCLEROSIS COALITION

The Multiple Sclerosis Coalition (MSC) was founded in 2005 by three independent multiple sclerosis organizations in an effort to work together to benefit individuals with MS. Since that time, the MSC has grown to nine member organizations, all of whom provide critical MS programs and services.

Vision: To improve the quality of life for those affected by MS through a collaborative national network of independent MS organizations.

Mission: To increase opportunities for cooperation and provide greater opportunity to leverage the effective use of resources for the benefit of the MS community.

The primary objectives of the MSC are to educate, advocate, collaborate and improve the efficiency of services for individuals with MS and those who are close to them. With so much on the horizon in terms of MS research, treatments, advocacy and symptom management, the MSC provides critical momentum to work together to enhance these exciting MS initiatives and to ensure this collective support continues.

Members:

Accelerated Cure Project for Multiple Sclerosis (ACP)

Accelerated Cure Project is a national nonprofit dedicated to curing MS by determining its causes. Our repository contains samples and data from people with MS and other demyelinating diseases. Samples are available to researchers who submit all data they generate back to the repository to be shared with others.

acceleratedcure.org | 781-487-0008

Can Do Multiple Sclerosis (Can Do MS)

As a national nonprofit organization, Can Do Multiple Sclerosis is a leading provider of innovative lifestyle empowerment programs that empower people with MS and their support partners to transform and improve their quality of life.

mscando.org | 800-367-3101

Consortium of Multiple Sclerosis Centers (CMSC)

The Consortium of MS Centers is the preeminent North American organization of MS healthcare professionals and researchers with a network of more than 11,000 healthcare clinicians and scientists committed to MS care. CMSC promotes sustained improvements in MS healthcare practice through clinical research, education and training, networking and targeted advocacy efforts.

mscare.org | 201-487-1050

International Organization of Multiple Sclerosis Nurses (IOMSN)

The International Organization of Multiple sclerosis Nurses is the first and only international organization focused solely on the needs and goals of professional nurses, anywhere in the world, who care for people with multiple sclerosis. Mentoring, educating, networking, sharing – the IOMSN supports nurses in their continuing effort to offer HOPE.

iomsn.org | 201-487-1050

Multiple Sclerosis Association of America (MSAA)

The Multiple Sclerosis Association of America is a leading resource for the entire MS community, improving lives today through vital services and support. MSAA provides free programs and services, such as: a helpline; award-winning publications; website featuring educational videos and research updates; shared-management tools to assist the MS community in managing their MS; safety and

mobility equipment; cooling accessories for heat-sensitive individuals; educational events and activities; MRI funding and insurance advocacy; as well as other services.

mymsaa.org | 800-532-7667

Multiple Sclerosis Foundation (MSFocus)

The Multiple Sclerosis Foundation, known in the MS community as MS Focus, is a nonprofit organization focused on providing free services that address the critical needs of people with MS and their families and on helping them maintain the best quality of life. MS presents physical, emotional, and financial challenges families must face. MS Focus is here to provide the support, education, and assistance needed to adapt to these challenging circumstances. Our primary focus is on providing individuals with MS the help they need to maintain their health and well-being, to continue to be productive and independent, and to keep a roof over their heads and a safe environment in their home.

msfocus.org | 800-225-6495

National Multiple Sclerosis Society

The National MS Society mobilizes people and resources so that everyone affected by multiple sclerosis can live their best lives as we stop MS in its tracks, restore what has been lost and end MS forever.

nationalMSSociety.org | 800-344-4867

United Spinal Association

The United Spinal Association is a national VA-authorized non-profit organization committed to providing service programs and advocacy for those living with spinal cord injuries and disorders (SCI/D) such as multiple sclerosis, amyotrophic lateral sclerosis, and spina bifida. There are more than a million individuals throughout the country with SCI/D to whom the Association's work is dedicated. The United Spinal Association has close to 40,000 members, 30 chapters, close to 200 support groups nationwide and publishes the New Mobility and Life Action magazines. Throughout its history, United Spinal Association has devoted its energies, talents and programs to improving the quality of life for Americans with spinal cord injuries and disorders.

unitedspinal.org | 718-803-3782

Associate Member:

MS Views and News (MSVN)

MS Views and News is dedicated to the global collection and distribution of information concerning MS. Through partnering relationships, MSVN provides education, advocacy and service to empower and enhance the quality of life of the MS community.

msviews.org | 888-871-1664

© 2018: The Multiple Sclerosis Coalition