

THE USE OF DISEASE-MODIFYING THERAPIES IN MULTIPLE SCLEROSIS:

Principles and Current Evidence

A Consensus Paper by the
Multiple Sclerosis Coalition



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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: A writing and development team comprised of professional staff representing the Coalition organizations (Rosalind Kalb, Kathleen Costello, June Halper, Lisa Skutnik, 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

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March 2017

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 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
- 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
 - Inadequate adherence to the treatment regimen
 - Availability of a more appropriate treatment option

*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, MS Views and News (since 2015), Multiple Sclerosis Association of America, Multiple Sclerosis Foundation, National Multiple Sclerosis Society and United Spinal Association.

- 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 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 collaboratively by the individual and his or her treating clinician.

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.
- 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.

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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 in light of 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 patients untreated with a disease-modifying therapy, have demonstrated a reduction in survival of 8-12 years.¹⁵

Epidemiology, Demographics, Disease Course

It is estimated that there are more than two million people with MS worldwide with approximately 450,000 in the United States.¹⁶⁻¹⁹ Women are affected at least three times more than men²⁰ and Caucasians are affected more than other racial groups.²¹ However, a recent study²² suggested that African-American women have a higher than previously reported risk of developing MS and several studies have suggested that African-Americans may have a more active, rapidly progressive disease course.²³⁻²⁷ MS is typically diagnosed in early adulthood, but the age range for disease onset is wide with both pediatric cases and new onset of disease in older adults. Historically, a geographic gradient has been observed with a higher incidence of MS with increased distance from the equator.^{28,29} However, some recent studies have not demonstrated the same latitudinal gradient,^{30,31} 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 the majority of 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% would do so by 25 years.³²⁻³⁴ Approximately half of patients would no longer be able to walk unaided by 15 years.³³

Inflammation and CNS Damage

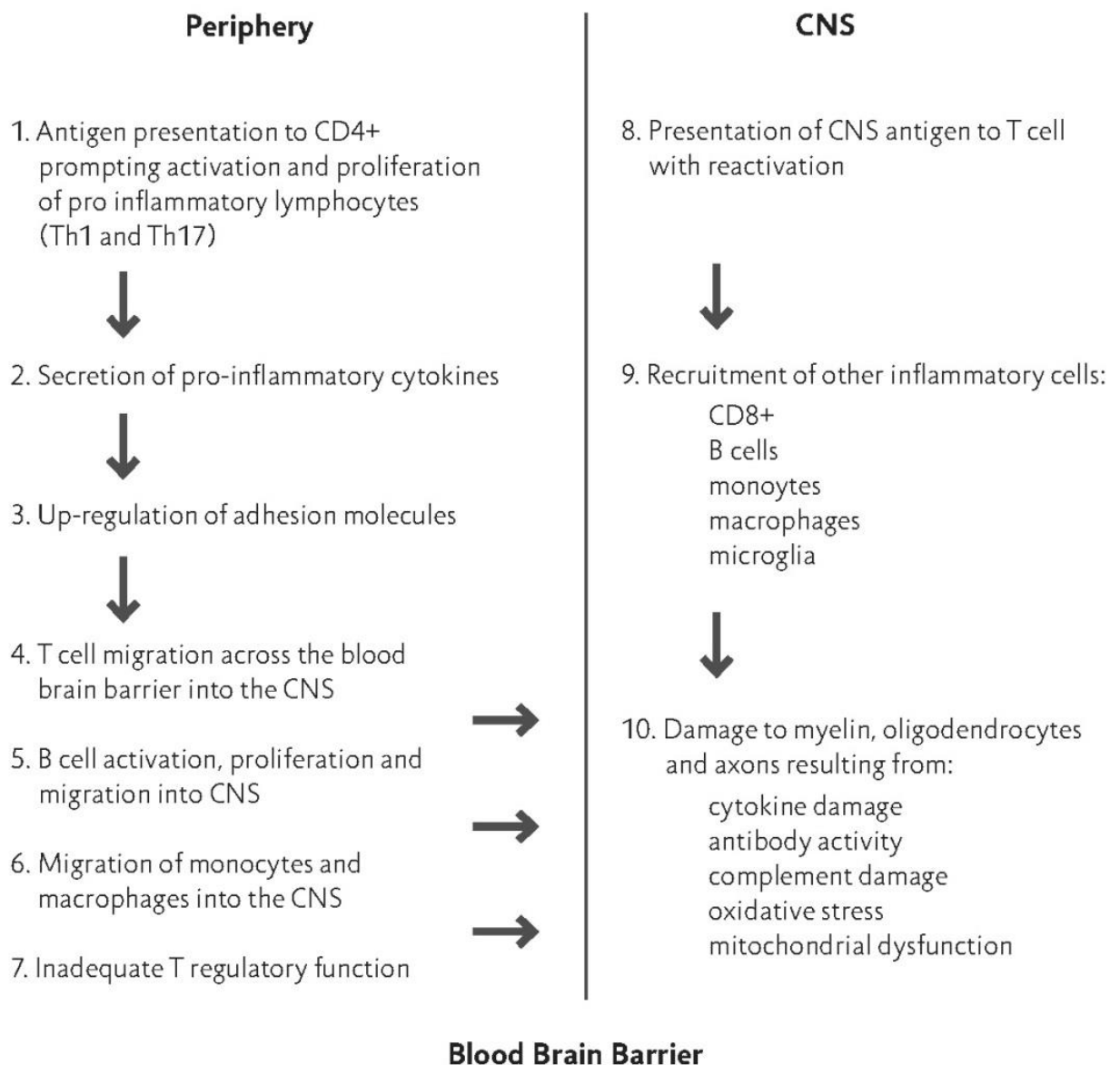
At present, much of the CNS damage in MS is believed to result from an immune-mediated process. This process includes components of the innate immune system (including macrophages, natural killer cells and others) as well as adaptive immune system activation of certain lymphocyte populations in peripheral lymphoid organs.³⁵ 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).³⁵⁻³⁷ In people with MS, there is a bias towards a Th1 and Th17 environment with T regulatory dysfunction that allows inflammation to predominate.³⁸ Secreted cytokines and matrix metalloproteinases disrupt the blood-brain barrier.³⁹ 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.⁴⁰ 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.⁴¹

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.⁴² 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.⁴³

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.⁴⁴⁻⁴⁶

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.^{46,47} Axons that survive acute attacks may require increased energy to compensate for damage leading to later death from metabolic stress.⁴⁶ Axonal loss, which correlates best with disability, begins early in the disease process as evidenced by identified pathological changes as well as imaging studies.^{47,48}

Figure 1: Inflammatory cascade in multiple sclerosis



OVERVIEW OF FDA-APPROVED DISEASE-MODIFYING AGENTS IN MS

To date, 15 disease-modifying agents have been approved by the U.S. Food and Drug Administration (FDA).

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

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. 30)

Agent - Self-Injected	Proposed MoA	Side Effects	Warnings/Precautions
<p>daclizumab⁴⁹ (Zinbryta®)</p> <p>150mg SC once monthly</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: No category assigned due to changes to FDA labeling procedures for pregnancy and lactation. No human data: animal data in monkeys suggest that administration during organogenesis may pose risks⁴⁹</p>	<p>Mechanism of action is not fully understood but is presumed to involve modulation of IL-2 mediated activation of lymphocytes through binding to CD-25, a sub-unit of the high-affinity IL-2 receptor, reducing inflammatory lymphocyte proliferation and expanding CD56bright NK regulatory cells.⁵⁰</p>	<p>Study 1: compared with interferon beta-1a:⁵¹</p> <ul style="list-style-type: none"> -nasopharyngitis -upper respiratory tract infection -rash -influenza -dermatitis -oropharyngeal pain -bronchitis -eczema -lymphadenopathy -tonsillitis -acne <p>Study 2: compared with placebo:⁵²</p> <ul style="list-style-type: none"> -upper respiratory tract infection -depression -rash -pharyngitis -↑ALT, AST -rhinitis -anemia -pyrexia -dermatitis 	<ul style="list-style-type: none"> -hepatic injury including autoimmune hepatitis -other immune-mediated disorders, including skin reactions, lymphadenopathy and non-infectious colitis -hypersensitivity reactions -↑risk of infections, including serious infections -depression and suicide <p>Boxed Warning</p> <p>Hepatic injury including autoimmune hepatitis and other immune-mediated disorders</p>
<p>glatiramer acetate^{53,54} (Copaxone®)</p> <p>20mg SC daily or 40mg SC three times weekly</p> <p>Indication: relapsing forms of MS</p> <p>(Glatopa® - therapeutic equivalent)</p> <p>20mg SC daily</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 into Th2 and T-reg cells, leading to bystander suppression in CNS⁵⁵ -increased release of neurotrophic factors from immune cells⁵⁵ -deletion of myelin-reactive T cells⁵⁵ 	<ul style="list-style-type: none"> -injection-site reactions -lipoatrophy -vasodilation, rash, dyspnea -chest pain -lymphadenopathy⁵³ 	<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

Agent - Self-Injected	Proposed MoA	Side Effects	Warnings/Precautions
interferon beta-1a ⁵⁶ (Avonex®) 30mcg IM weekly Indication: relapsing forms of MS Pregnancy Cat: C	Mechanism of action in MS is unknown. Subsequent research suggests: - promotes shift from Th1-Th2 - reduces trafficking across BBB ^{57,58} - restores T-reg cells ⁵⁵ - inhibits antigen presentation ⁵⁵ - enhances apoptosis of autoreactive T-cells ⁵⁵	- flu-like symptoms - depression - ↑ hepatic transaminases	- depression, suicide, psychosis - hepatic injury - anaphylaxis and other allergic reactions - CHF - ↓ peripheral blood counts - seizures - other autoimmune disorders - thrombotic microangiopathy
interferon beta-1a ⁵⁹ (Rebif®) 22mcg or 44mcg SC three times weekly Indication: relapsing forms of MS Pregnancy Cat: C	Same as above	- injection-site reactions - flu-like symptoms - abdominal pain - depression - ↑ hepatic transaminases - hematologic abnormalities	- depression, suicide - hepatic injury - anaphylaxis and other allergic reactions - injection-site reactions including necrosis - ↓ peripheral blood counts - seizures - thrombotic microangiopathy
interferon beta-1b ^{60,61} (Betaseron®) (Extavia®) 0.25mg SC every other day Indication: relapsing forms of MS Pregnancy Cat: C	Same as above	- flu-like symptoms - injection-site reactions - ↑ hepatic transaminases - ↓ WBC - see warnings ^{60,61}	- hepatic injury - anaphylaxis and other allergic reactions - depression and suicide - CHF - injection-site necrosis - ↓ WBC - flu-like symptoms - seizures - thrombotic microangiopathy
peginterferon beta-1a ⁶²⁻⁶⁴ (Plegridy®) 125mcg SC every two weeks Indication: relapsing forms of MS Pregnancy Cat: C	Same as above	- flu-like symptoms - injection-site reactions - ↑ hepatic transaminases - ↓ WBC - see warnings ⁶²	- depression, suicide - hepatic injury - anaphylaxis and other allergic reactions - CHF - ↓ peripheral blood counts - seizures - other autoimmune disorders - thrombotic microangiopathy

Agent - Oral	Proposed MoA	Side Effects	Warnings/Precautions
<p>dimethyl fumarate⁶⁵ (Tecfidera®)</p> <p>240mg PO twice daily</p> <p>Indication: relapsing forms of MS</p> <p>Pregnancy Cat: C</p>	<p>Mechanism of action in MS is unknown. It has been shown to:</p> <ul style="list-style-type: none"> -promote anti-inflammatory and cytoprotective activities mediated by Nrf2 pathway⁵⁸ 	<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 (discontinue treatment in patients with persistent lymphopenia (<500) over 6 months) -flushing -liver injury
<p>fingolimod⁶⁶ (Gilenya®)</p> <p>0.5mg PO daily</p> <p>Indication: relapsing forms of MS</p> <p>Pregnancy Cat: C</p>	<p>Mechanism of action in MS most likely involves blocking of S1P receptor on lymphocytes thus preventing their egress from secondary lymph organs⁶⁶</p>	<ul style="list-style-type: none"> -headache -influenza -diarrhea -back pain -↑hepatic enzymes -cough -bradycardia during first dose -macular edema -lymphopenia -bronchitis/pneumonia 	<ul style="list-style-type: none"> -bradyarrhythmia 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) -↓pulmonary function tests (FEV1) -hepatic injury -↑BP -basal cell carcinoma -fetal risk: women should avoid conception for two months after treatment d/c -↓lymphocyte counts for 2 months after drug d/c

Agent - Oral	Proposed MoA	Side Effects	Warnings/Precautions
<p>teriflunomide⁶⁷ (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.^{67,68} 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 -paresthesia⁶⁷ 	<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) -↓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 -↑ renal uric acid clearance -interstitial lung disease -Stevens-Johnson syndrome and toxic epidermal necrolysis (stop treatment) -↑ 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>alemtuzumab^{69–71} (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.^{69,72}</p>	<p>->90% of patients in clinical trials experienced infusion reactions: skin rash, fever, headache, muscle aches, temporary reoccurrence of previous neurologic symptoms. More serious but uncommon infusion reactions: anaphylaxis and heart rhythm abnormalities.</p> <p>-serious adverse reactions: autoimmunity, infusion reactions, malignancies, immune thrombocytopenia (ITP), glomerular nephropathies, thyroid disorder, other autoimmune cytopenias, infections, pneumonitis</p> <p>-immediate and significant depletion of lymphocytes; herpes simplex and zoster 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>	<p>-infusion reactions</p> <p>-autoimmunity (thyroid disorders, immune thrombocytopenia (ITP), glomerular nephropathies, other cytopenias)</p> <p>-infections</p> <p>-no live virus vaccinations following infusion</p> <p>-malignancies (thyroid, melanoma, lymphoproliferative)</p> <p>-pneumonitis</p> <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>
<p>mitoxantrone⁷³ (Novantrone®)</p> <p>12mg/m² IV every three months; maximum cumulative dose: 140mg/m²</p> <p>Indication: worsening relapsing-remitting, progressive-relapsing, 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, 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>natalizumab⁷⁴ (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 CNS⁵⁸</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>-diarrhea⁷⁴</p>	<p>-PML</p> <p>-hepatotoxicity</p> <p>-herpes encephalitis and meningitis caused by herpes simplex and varicella zoster viruses</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>ocrelizumab⁷⁵ (Ocrevus™)</p> <p>600mg IV every 6 months</p> <p>Indication: relapsing or primary progressive forms of MS</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</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, which 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>

Agent - Intravenous	Proposed MoA	Side Effects	Warnings/Precautions
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.	complement-mediated cytolysis.		-infections, including respiratory tract infections, herpes and potentially PML -hepatitis B reactivation -possible increased immunosuppressive effect if immunosuppressant used prior to or after ocrelizumab -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 -malignancies

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 2013,⁵⁸ with supplemental data from the Full Prescribing Information for each agent: [Zinbryta](#) (2016), [Copaxone](#) (2016), [Glatopa](#) (2016), [Avonex](#) (2016), [Plegridy](#) (2015), [Rebif](#) (2015), [Betaseron](#) (2016), [Extavia](#) (2016), [Gilenya](#) (2016), [Aubagio](#) (2016), [Tecfidera](#) (2017), [Lemtrada](#) (2016), [Novantrone](#) (2008), [Tysabri](#) (2016), [Ocrevus](#) (2017); Graber et al, 2010.^{49,53–56,59–62,65–67,69,73–75}

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.⁷⁶
- 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.

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.^{77,78}

The following points highlight the importance of early treatment:

- **Neuroinflammation and neurodegeneration occur early in the disease course**

It has long been thought that in early MS, inflammatory damage with associated demyelination and some axonal damage is the first of a two-stage disease process. In this initial stage, clinical relapses come and go, as do focal areas of CNS inflammation, with good recovery from neurologic symptoms. As the disease progresses, the second stage is characterized by degenerative changes, including more axonal and oligodendrocyte destruction with irreversible tissue damage and associated progressive clinical symptoms, which are thought to be a consequence of repeated, early inflammatory changes.³ More recent studies suggest that rather than two distinct stages that occur in sequence, both neuroinflammation and neurodegeneration may occur simultaneously and perhaps independently:

- Early in MS, new MRI activity, evidenced by gadolinium enhancement, occurs approximately 7-10 times more frequently than clinical activity.⁷⁹
- Inflammatory activity has been observed in patients with both relapsing and progressive forms of the disease.³
- 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.⁸⁰
- Atrophy has been seen in radiographically isolated syndrome (RIS – the incidental finding of MS-like lesions in the absence of known clinical relapses⁸¹).⁸²
- Inflammatory changes continue to be seen in secondary progressive and primary progressive MS.³
- Once a threshold is reached, disability progression continues at a rate that is unrelated to the prior relapse history.³²

Whether neuroinflammation and neurodegeneration are determined to be independent or interrelated, prompt initiation and optimization of treatment is designed 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).⁸³⁻⁸⁶ 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.^{87,88} 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.⁸⁸

The importance of delaying and limiting additional relapses early in the disease process was further supported by a CIS trial with teriflunomide⁸⁹ published in 2014.

The 2010 revision of the McDonald diagnostic criteria facilitated an earlier diagnosis of MS based on a first clinical event and MRI findings demonstrating dissemination in space and time.⁹⁰ 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.⁷⁸

- **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 data⁹¹ 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.^{92–95} 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.^{95,96} And, 20-30 percent of RIS patients demonstrate cognitive changes similar to those seen in patients with RRMS.^{97–99} In their review of these data, Labiano-Fontcuberta and Benito-Leon recommended that more study of RIS was needed before a general recommendation for treatment could be made. The ARISE (Assessment of Tecfidera in Radiologically Isolated Syndrome) study, which is currently recruiting, will compare time to first demyelinating event in patients receiving dimethyl fumarate and those receiving placebo.

- **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)¹⁰⁰ is the result of residual impairments from partially-resolved relapses.^{77,101–103} Natural history studies suggest that relapses in the first two years of disease impact early progression,¹⁰⁴ with the impact of early relapses diminishing later in the disease course.¹⁰⁵ 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.¹⁰⁶
- 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.¹⁰⁷ 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 colleagues¹⁰⁸

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 cohort study follow-up of the pivotal trial of interferon beta-1b suggest that long-term physical and cognitive outcomes may be determined early in the disease.¹⁰⁹

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.⁷⁷

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

It is currently recognized that approximately 60 percent of people with MS will experience cognitive impairment;¹¹⁰ 36-54 percent will experience a major depressive disorder;¹¹¹ and up to 92 percent will experience significant fatigue,¹¹² 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.¹¹³⁻¹¹⁹ In fact, cognitive deficits similar to those seen in RRMS have been found in 20-30 percent of individuals with RIS.⁹⁷⁻⁹⁹
- Some studies suggest that cognitive deficits may precede the onset of MS by as much as 1.2 years.¹¹³ 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.¹¹⁵
- Early cognitive changes are also known to progress, even in people with little or no physical changes,¹¹⁸ and deterioration can be expected over a three-year period in approximately one-third of people with short disease duration.¹²⁰
- Cognitive deficits are detected in approximately 30 percent of pediatric MS patients.¹²¹⁻¹²³
- 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^{124,125} – 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.^{78,118}

- **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 years¹²⁶ – 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.¹²⁷
- In another cohort of people with “benign MS” followed for 10.9 additional years, many developed higher EDSS scores, cognitive impairment, pain and depression, as well as a significant increase in new or enlarging T2 lesions and gadolinium (Gd)-enhancing lesions over time.¹²⁸
- 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.¹²⁹

Based on these findings, it is clear that *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.¹³⁰

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 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 medications^{83–86} in patients with clinically-isolated syndrome (CIS),^{83–86} as well as the CIS trial with teriflunomide,⁸⁹ 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,¹³¹ 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.¹³²

Reducing brain atrophy and disability worsening

In meta-analyses of CIS treatment trials, each of two years duration (ETOMS, PreCISe, TOPIC),^{83,89,133} the rate of brain atrophy was attenuated after one year of treatment.¹³⁴

In a large cohort of CIS patients, disease-modifying treatments reduced 3-month confirmed and 12-month sustained disability worsening.¹³⁵

Evidence Demonstrating the Impact of Treatment on Relapsing MS

Each of the approved disease-modifying therapies has been shown to provide significant benefit 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
daclizumab ^{49,51,52}	<p>Study 1: 54% relative reduction mean # relapses per person (52 weeks)⁺⁵²: 0.458 placebo; 0.211 daclizumab (p<0.0001)</p> <p>Study 2: 45% relative reduction mean # relapses per person (96 weeks)⁵¹: 0.393 interferon beta-1a; 0.216 daclizumab (p<0.001)</p>	<p>Study 1: Disability progression between baseline and 52 weeks as measured by EDSS confirmed at 12 weeks⁵²: 13% placebo; 6% daclizumab (HR=0.43 daclizumab, p=0.021)</p> <p>Study 2: Incidence of disability progression in a 144-week study period as measured by EDSS confirmed at 12 weeks⁺⁵¹: 20% interferon beta-1a; 16% daclizumab (N.S.)</p>
glatiramer acetate ¹³⁶ 20mg qd 40mg tiw ¹³⁷	<p>29% reduction in relapse rate over 24 months⁺: 1.68 placebo; 1.19 treated (p=0.007)</p> <p>34% reduction in annualized relapse rate at 12 months⁺: 0.505 placebo; 0.331 treated: (p<0.0001)</p>	<p>Progression free at 24 months: 75.4% placebo; 78.4% treated (N.S.)</p>
interferon beta-1a subcutaneous ¹³⁸	<p>33.2% reduction (44mcg tiw vs. placebo) mean # relapses per person (24 months)⁺: 2.56 placebo; 1.73 treated (p<0.005)</p>	<p>30% decrease in proportion of patients with sustained disability progression at 12 weeks⁺: 11.9 months placebo; 21.3 months treated (p<0.05)</p>
interferon beta-1a intramuscular ¹³⁹	<p>18% reduction⁵⁸ mean # relapses per patient year: 0.82 placebo; 0.67 treated (p=0.04)</p>	<p>37% decrease in time to disability progression sustained for at least 6 months⁺: 34.9% placebo; 21.9% treated (p=0.04)</p>
interferon beta-1b ¹⁴⁰	<p>34% reduction annualized relapse rate over two years⁺: 1.31 placebo; 0.9 treated (p=0.0001)</p>	<p>29% decrease (N.S.) insignificant change from baseline EDSS 28% placebo; 20% treated</p>
peginterferon beta-1a ^{63,64}	<p>36% reduction annualized relapse rate at 48 weeks⁺: 0.397 placebo; 0.256 treated (p=0.0007)⁶³</p> <p>Proportion of exacerbation-free patients⁺: 16% placebo; 25% treated (N.S.)⁶³</p> <p>Efficacy maintained beyond one year with every two week dosing providing greater efficacy than every four week dosing⁶⁴</p>	<p>38% relative risk reduction in disability progression at 48 weeks 10.5% placebo; 6.8% treated (p=0.0383)⁶³</p>

Agent – Oral	Effect on Relapse Rate Compared to Placebo or Active Comparator*	Effect on Disability Progression Compared to Placebo or Active Comparator
dimethyl fumarate ^{141,142}	<p>Study 1: 49% reduction in proportion relapsing within two years⁺: 46% placebo; 27% treated (p<0.001)¹⁴¹</p> <p>Study 2: 44% reduction in annualized relapse rate at two years⁺: 40% placebo; 22% DMF bid (p<0.001)¹⁴²</p>	<p>Study 1: 38% decrease in risk of disability progression at 12 weeks⁺¹⁴¹ 27% placebo; 16% treated (p=0.005)¹⁴¹</p> <p>Study 2: Estimated proportion of patients with progression at 2 years: 17% placebo; 13% DMF bid (N.S.)¹⁴²</p>
fingolimod ^{143,144} (compared to IFN beta-1a) ¹⁴⁵	<p>Study 1: 54% reduction in annualized relapse rate over two years⁺: 0.40 placebo; 0.18 0.5mg dose (p<0.001)¹⁴³</p> <p>Study 2: 48% reduction in annualized relapse rate over two years⁺: 0.40 placebo; 0.21 0.5mg dose (p<0.0001)¹⁴⁴</p> <p>Study 3: annualized relapse rate over 12 months⁺: 0.33 IFN; 0.16 0.5mg dose (p<0.001)¹⁴⁵</p>	<p>Study 1: 30% decrease in risk of disability progression (p=0.03 0.5mg dose)¹⁴³ % with absence of disability progression at three months: 75.9% placebo; 82.3% 0.5mg dose (p=0.03)¹⁴³</p> <p>Study 2: % with absence of disability progression at three months: 71.0% placebo; 74.7% 0.5mg dose (N.S.)¹⁴⁴</p> <p>Study 3: % with absence of disability progression at three months: 92.1% IFN; 94.1% 0.5mg dose (p=0.25)¹⁴⁵</p>
teriflunomide ^{146,147}	<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)¹⁴⁶</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)¹⁴⁷</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)¹⁴⁶</p> <p>Study 2: Risk of sustained accumulation of disability compared to placebo: 7mg dose (N.S.); 31.5% 14mg dose (p=0.04)¹⁴⁷</p>

Agent – Intravenous	Effect on Relapse Rate Compared to Placebo or Active Comparator*	Effect on Disability Progression Compared to Placebo or Active Comparator
alemtuzumab ^{70,71} (compared to IFN beta-1a 44mcg tiw)	<p>Study 1: 55% reduction in annualized relapse rate over two years⁺: 0.39 IFN; 0.18 alemtuzumab (p<0.0001)⁷⁰</p> <p>Study 2: 49% reduction in annualized relapse rate over two years⁺: 0.52 IFN; 0.26 alemtuzumab (p<0.0001)⁷¹</p>	<p>Study 1: 30% relative risk reduction at year two sustained disability accumulation confirmed over six months⁺: 11% IFN; 8% alemtuzumab (N.S.)⁷⁰</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)⁷¹</p>

Agent – Intravenous	Effect on Relapse Rate Compared to Placebo or Active Comparator*	Effect on Disability Progression Compared to Placebo or Active Comparator
mitoxantrone ¹⁴⁸	66% reduction in annualized relapse rate over two years: 1.02 placebo; 0.35 treated (p=0.001)	3 months confirmed EDSS change during study: 22% placebo; 8% treated (p=0.036) ↑0.23 EDSS over 24 months placebo; ↓0.13 EDSS over 24 months 12mg/m ² dose [absolute and relative risks not reported]
natalizumab ¹⁴⁹	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)	42% decrease in risk of confirmed disability progression cumulative probability of sustained progression at 2yrs*: 29% placebo; 17% treated (p<0.001)
ocrelizumab ^{150,151} (Relapsing MS: comparison with IFN beta-1a 44mcg tiw) (Primary progressive MS: comparison with placebo)	Relapsing MS: Annualized relapse rate*: Study 1: IFN 0.292; ocrelizumab 0.156: 46% relative reduction (p<0.0001) ¹⁵⁰ Study 2: IFN 0.290; ocrelizumab 0.155: 47% relative reduction (p<0.0001) ¹⁵⁰	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) ¹⁵⁰ 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) ¹⁵¹ 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 25ft 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 Kappos et al, 2015;⁵¹ Gold et al, 2013;⁵² Oh & Calabresi in Rae-Grant, et al, 2013;⁵⁸ Calabresi et al, 2014;⁶³ Kieseier et al, 2015;⁶⁴ Cohen et al, 2012;⁷⁰ Coles et al, 2012;⁷¹ Johnson et al, 1995;¹³⁶ Khan et al, 2013;¹³⁷ PRISMS Study Group 1998;¹³⁸ Jacobs et al, 1996;¹³⁹ IFNB MS Study Group, 1993;¹⁴⁰ Gold et al, 2012;¹⁴¹ Fox et al, 2012;¹⁴² Kappos et al, 2010;¹⁴³ Calabresi et al, 2014;¹⁴⁴ Cohen et al, 2010;¹⁴⁵ O'Connor et al, 2011;¹⁴⁶ Confavreux et al, 2014;¹⁴⁷ Hartung et al, 2002;¹⁴⁸ Polman et al, 2006;¹⁴⁹ Hauser et al, 2017;¹⁵⁰ Montalban et al, 2017.¹⁵¹

* 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 measureable and sustained impact on disability.^{103,106} While it remains unclear the exact extent to which reducing relapses impacts ultimate 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.^{103,152}

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.^{1,153}

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*
<p>daclizumab</p> <p>150mg once monthly^{51,52}</p> <p>(compared to placebo)</p> <p>(compared to IFN beta-1a 30mcg weekly)</p>	<p>Study 1: mean # at 52 weeks: 4.79 placebo; 1.46 treated relative reduction 69% (p<0.0001)⁵²</p> <p>Study 2: mean # at week 96: 1.0 (±2.8) IFN; 0.4 (±1.4) daclizumab odds ratio 0.25 (p<0.001)⁵¹</p>	<p>Study 1: mean # at 52 weeks: 8.1 placebo; 2.4 treated relative reduction 69% (p<0.0001)⁵²</p> <p>Study 2: mean # at 96 weeks: 9.44 IFN; 4.31 daclizumab relative reduction 54% (p<0.001)⁵¹</p>
<p>glatiramer acetate</p> <p>20mg qd¹⁵⁴</p> <p>(non-pivotal trial data)</p> <p>40mg tiw¹³⁷</p>	<p>29% reduction in mean total # of new contrast enhancing lesions: 36.8 placebo; 25.96 GA 20mg cumulative # Gd lesions at nine months: 17 placebo; 11 GA 20mg (p=0.003)</p> <p>cumulative # Gd lesions at months 6 and 12: 1.639 placebo; 0.905 GA 40mg (p<0.0001)^{53,137}</p>	<p>mean # total new T2: 13.7 placebo; 9.4 GA 20mg (p<0.003)¹⁵⁴</p> <p>not reported in PI</p> <p>cumulative new or enlarging T2 at months 6 and 12: 5.59 placebo; 3.65 GA 40mg (p<0.0001)^{53, 137}</p>
<p>interferon beta-1a subcutaneous^{59,138}</p>	<p>median # of active lesions per patient per scan: 2.25 placebo; 0.5 44mcg dose (p<0.0001)⁵⁹</p>	<p>median % change of MRI PD-T2 lesion area at two years: 11% placebo; -3.8% 44mcg dose (p<0.0001)¹³⁸</p>
<p>interferon beta-1a intramuscular¹³⁹</p>	<p>mean # contrast enhancing lesions at two years: 1.65 placebo; 0.80 treated (p=0.05)</p>	<p>median % change T2 lesion volume from study entry to year 2: -6.55% placebo; -13.2% treated (N.S.)</p>
<p>interferon beta-1b⁶⁰</p>	<p>no Gd outcomes from phase III pivotal trial</p>	<p>median % change in MRI area (n=52, scans q 6wks): 16.5% placebo; -1.1% 0.25mg dose (p<0.0001)</p>
<p>peginterferon beta-1a⁶³</p>	<p>mean # contrast enhancing lesions at 48 wks: 1.4 placebo; 0.2 treated (p<0.0001)</p>	<p>mean # new or newly enlarging T2 lesions at 48 wks: 10.9 placebo; 3.6 treated (p<0.0001)</p>

Agent – Oral	Effect on Gd Lesions*	Effect on New or Enlarging T2 Lesions*
<p>dimethyl fumarate^{141,142}</p>	<p>Study 1: mean # Gd+ lesions at two years: 1.8 placebo; 0.1 240mg bid dose (p<0.0001)¹⁴¹</p> <p>Study 2: mean # Gd+ lesions at two years: 2.0 placebo; 0.5 240mg bid dose (p<0.0001)¹⁴²</p>	<p>Study 1: mean # new or enlarging T2 lesions at two years: 17 placebo; 2.6 240mg bid dose (p<0.0001)¹⁴¹</p> <p>Study 2: mean # new or enlarging T2 lesions at two years: 17.4 placebo; 5.1 240mg bid dose (p<0.0001)¹⁴²</p>
<p>fingolimod^{143,144}</p>	<p>Study 1: mean # T1 Gd+ lesions at month 24: 1.1 placebo; 0.2 0.5mg dose (p<0.001)¹⁴³</p> <p>Study 2: mean # T1 Gd+ lesions at month 24: 1.2 placebo; 0.4 0.5mg dose (p<0.0001)¹⁴⁴</p>	<p>Study 1: mean # new or newly enlarging T2 lesions over 24 months: 9.8 placebo; 2.5 0.5mg dose (p<0.001)¹⁴³</p> <p>Study 2: mean # new or newly enlarging T2 lesions over 24 months: 8.9 placebo; 2.3 0.5mg dose (p<0.0001)¹⁴⁴</p>
<p>teriflunomide¹⁴⁶</p>	<p>mean # Gd+ lesions per scan: 1.331 placebo; 0.261 14mg dose (p<0.0001)¹⁴⁶</p>	<p>median change from baseline in total lesion volume (mL) (T1 +T2) at week 108: 1.127 placebo; 0.345 14mg dose (p=0.0003)</p>

Agent – Intravenous	Effect on Gd+ Lesions*	Effect on New or Enlarging T2 Lesions*
alemtuzumab ^{70,71} (compared to interferon beta-1a 44mcg tiw)	% patients with Gd+ lesions at 24 months (tertiary outcome): Study 1: 19% IFN; 7% alemtuzumab (p<0.0001) ⁷⁰ Study 2: 23% IFN; 9% alemtuzumab (p<0.0001) ⁷¹	patients with new or enlarging T2 lesions (tertiary outcome): Study 1: 58% IFN; 48% alemtuzumab (p=0.04) ⁷⁰ Study 2: 68% IFN; 46% alemtuzumab (p<0.0001) ⁷¹
mitoxantrone ¹⁴⁸	# 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 # 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)
natalizumab ¹⁴⁹	median # Gd+ lesions at two years: 0 placebo; 0 treated percent with two or more enhancing lesions: 16% placebo; 1% treated (p<0.001) mean # Gd+ lesions at two years: placebo 1.2; treated 0.1 (p<0.001) ¹⁴⁹	median # new or enlarging T2 lesions at two years: 5 placebo; 0 treated (p<0.001) mean # new or enlarging T2 lesions at two years: 11.0 placebo; 1.9 treated (p<0.001) ¹⁴⁹
ocrelizumab ^{150,151} (Relapsing MS: comparison with IFN beta-1a 44mcg tiw) (Primary progressive MS: comparison with placebo)	Relapsing MS: Mean # of T1 Gd+ lesions per scan: Study 1: IFN 0.286; ocrelizumab 0.016: 94% relative reduction (p<0.0001) ¹⁵⁰ Study 2: IFN 0.416; ocrelizumab 0.021: 95% relative reduction (p<0.0001) ¹⁵⁰	Relapsing MS: Mean # of new and/or enlarging T2 lesions per scan: Study 1: 1.413 IFN; 0.323 ocrelizumab: 77% relative reduction (p<0.0001) ¹⁵⁰ Study 2: 1.904 IFN; 0.325 ocrelizumab: 83% relative reduction (p<0.0001) ¹⁵⁰ Primary progressive MS: Study 3: Mean change in volume (cm ³) of T2 lesions from baseline to week 120: 0.79 placebo; -0.39 treated (p<0.0001) ⁷⁵ Mean % change in brain volume from week 24 to 120: -1.09 placebo; -0.90 treated (p=0.02) ¹⁵¹

Full Prescribing Information for each agent: [Zinbryta](#) (2016), [Copaxone](#) (2016), [Glatopa](#) (2016), [Avonex](#) (2016), [Plegridy](#) (2015), [Rebif](#) (2015), [Betaseron](#) (2016), [Extavia](#) (2016), [Gilenya](#) (2016), [Aubagio](#) (2016), [Tecfidera](#) (2017), [Lemtrada](#) (2016), [Novantrone](#) (2008), [Tysabri](#) (2016), [Ocrevus](#) (2017)^{49,53,54,56,59–62,65–67,69,73–75}

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

Subsequent to 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.¹⁵⁵
- 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.¹⁴²
- Data analysis from phase III clinical trials and subsequent studies demonstrate a variable effect on brain atrophy.^{70,71,143,144,156–162} 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,¹³⁶ 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 Arnold¹⁶³ 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 ¹⁶⁴	×	✓ 55% reduction vs. placebo	×
interferon beta-1a SC ¹⁶⁵	—	—	×
interferon beta-1b SC ^{166,167}	—	—	—
glatiramer acetate ^{156,168–170}	<p>×</p> <p>(Eur/Canadian GA trial)</p> <p>8% reduction vs. SC IFN-β-1a (REGARD)*</p> <p>No sig. difference with GA +/- SC IFN-β-1b (BEYOND)</p> <p>No sig. difference with GA +/- SC IFN-β-1a (CombiRx)</p>	<p>✓</p> <p>40% reduction vs. placebo (Eur/Canadian GA trial)</p> <p>22% reduction vs. SC IFN-β-1a (REGARD)*</p> <p>No sig. difference with GA +/- SC IFN-β-1b (BEYOND)</p> <p>No sig. difference with GA +/- SC IFN-β-1a (CombiRx)</p>	<p>×</p> <p>(Eur/Canadian GA trial)</p> <p>13% reduction vs. IFN-β-1a (REGARD)</p> <p>No sig. difference with GA +/- SC IFN-β-1b (BEYOND)</p> <p>No sig. difference with GA +/- SC IFN-β-1a (CombiRx)</p>
natalizumab ^{158,162}	<p>40% increase vs. placebo (AFFIRM)</p> <p>19% increase vs. placebo (SENTINEL)</p>	<p>✓</p> <p>44% reduction vs. placebo (AFFIRM)</p> <p>×</p> <p>23% reduction with natalizumab+ IM IFN-β-1a vs. IM IFN-β-1a + placebo (SENTINEL)</p>	<p>×</p> <p>(AFFIRM)</p> <p>×</p> <p>(SENTINEL)</p>
teriflunomide ¹⁴⁶			

Agent	Changes in Brain Volume Loss		
	Year 0-1	Year 1-2	Year 0-2
	37% reduction vs. placebo (TEMPO)	31% reduction vs. placebo (TEMPO)	×
dimethyl fumarate ^{171,172}	—	21% reduction vs. placebo (DEFINE) Significant effect (DEFINE) × [‡] (CONFIRM)	✓ 21% reduction vs. placebo (DEFINE) [‡] × [‡] (CONFIRM)
alemtuzumab ^{70,71}		—	✓ 24-42% reduction vs. IFN-β-1a
laquinimod ^{173,174}	—	—	✓ (ALLEGRO) 33% reduction vs. placebo (BRAVO) 28-34% reduction vs. placebo
daclizumab ⁵¹	✓ Significant effect (Week 0-24) 9% reduction vs. IM IFN-β-1a	✓ Significant effect (Week 24-96) 7% reduction vs. IM IFN-β-1a	—
fingolimod ^{143–145}	✓ 23-40% reduction vs. placebo ✓§ 45% reduction vs. IM IFN-β-1a (TRANSFORMS)	✓ 28-45% reduction vs. placebo —	✓ 33-35% reduction vs. placebo —

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; TEMPO: 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.¹⁷⁵ 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/>).

Evidence Demonstrating the Impact of Treatment on Progressive MS

Many agents have been investigated for use in secondary progressive or primary progressive MS.^{176,177} Sub-group analyses from some of these clinical trials indicated benefit in patients of younger age with more recent progression, recent relapse and/or MRI activity.¹⁷⁷ Only mitoxantrone, which is seldom used in the United States because of its high risk profile, has an FDA indication for secondary progressive MS⁷³. Only ocrelizumab has FDA approval for primary progressive MS.⁷⁵ 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 of time has limitations, including uncontrolled 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.¹⁷⁸
- 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 .¹⁷⁹
- 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.¹⁸⁰
- In a nine-year follow-up of the pivotal phase III teriflunomide trial (TEMSO), 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.¹⁸¹
- A long-term follow-up (greater than seven years) of a phase II fingolimod study demonstrated persistent positive effect on relapse and MRI activity.¹⁸²
- Approximately 90 percent of untreated RRMS patients will have SPMS after 15-26 years.^{183,184} 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.¹⁸⁵
- 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.¹⁸⁶
- 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.¹⁸⁷
- 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% reached an EDSS ≥ 6.0 , and 18.1% evolved to secondary progressive MS.¹⁸⁸
- 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,^{189,190} with evidence suggesting that long-term (physical *and* cognitive) outcomes may be largely determined early in the disease course.¹⁰⁹ 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,^{109,131,168,189} although much of the impact has been thought to take place early in the disease course.¹⁰⁹ In a more recent study, using data extracted from the global MSBase Registry, Jokubaitis and colleagues¹⁰⁶ 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% 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.^{191,192} In addition, some researchers have proposed adding no additional brain volume loss to this definition.^{193,194} Post-hoc analysis of several MS treatment trials has suggested that the goal of NEDA may be achievable for some individuals.^{191,192,195} 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.¹⁹²

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.¹⁸⁸

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 or for its use as an outcome measure in clinical trials.

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.¹⁹⁶

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.¹⁹⁷ 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.¹⁹⁸ 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 24.¹⁹⁹

Early treatment to reduce loss of mobility has been shown to help preserve people's ability to carry out instrumental activities of daily living,²⁰⁰ and the ability to work was found to improve after one year of treatment with natalizumab.²⁰¹

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.”²⁰²

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,^{83,85,106,180,203–206} 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.¹⁸⁰ 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.²⁰⁷

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.^{208,209}
- 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.²¹⁰
- In a review of the adherence literature, 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.²¹¹
- 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.²¹² In another study, active patients treated with interferon beta promptly returned to pre-treatment levels of disease activity following discontinuation of treatment,²¹³ 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.²¹⁴
- Relapse rates returned to baseline following interruption of natalizumab treatment in three large studies,²¹⁵ 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.²¹⁶ 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 beginning within one to six months.^{204, 218–220} 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.²²¹
- Cessation of fingolimod after a period of stability was followed by clinical relapse and multiple enhancing lesions on MRI in two patients,²²² and both patients had a significant worsening in EDSS score 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.²²³ A recent review reported five individuals experiencing increased disease activity within 4-16 weeks following discontinuation of fingolimod therapy (10.9% of 46 patients discontinuing the drug during the two year observation period) and identified 11 other reported cases of rebound disease activity.²²⁴

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.

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.^{225,226} Three to 10 percent of adult patients retrospectively report a possible first attack prior to age 18.²²⁷ More than 97 percent of children and adolescents experience a relapsing-remitting disease course,²²⁵ with annualized relapse rates 2-3 times that of adults with MS during the first three years of disease.²²⁸ 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.¹²¹⁻¹²³

The interferon beta medications and glatiramer acetate are generally considered the initial treatment options for children with MS.^{225,229} 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 change treatment. Some children and teens with particularly active disease that does not respond to the first treatment used, or even subsequent options, are generally offered other therapies, including oral and infused medications.²²⁹ 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.²²⁹ Several retrospective analyses regarding safety and tolerability of natalizumab support the use of natalizumab in pediatric MS patients with active or aggressive disease.²³⁰⁻²³³

The importance of evaluating therapies in the MS pediatric population has been emphasized²²⁵ and pediatric clinical trials of all new agents are now mandated by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), opening the door for clinical trials that inform the use of agents in children and teens with very active disease.^{234,235} Such trials are critical not only to provide patients and clinicians with efficacious treatments, but also to ensure safety, tolerability and appropriate dosing. Currently, phase III trials are underway with fingolimod, teriflunomide and dimethyl fumarate in children.²³⁶ However, enrollment in these trials has proved challenging, in large part due to the relative rarity of pediatric MS compared to adult-onset MS. Given that several trials are occurring concurrently, it is imperative to determine how best to ensure that all trials produce informative data on therapeutic safety and efficacy.

It is noteworthy that access to certain medications for pediatric MS patients in some world regions may be limited by regulation. When available, the use of many of the newer therapies in pediatric MS patients should be considered carefully given the absence of studies demonstrating safety in this population.

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.²³⁷⁻²³⁹

- No human data regarding prenatal development or breastfeeding are available for daclizumab. Animal studies show no effects on pre- or postnatal development for up to six

months after birth.⁴⁹ Women of childbearing potential are advised to use effective contraception while taking daclizumab and for four months after discontinuation.⁴⁹

- Glatiramer acetate does not cross the placenta and is likely safe for use during breastfeeding.²³⁷ Confirming earlier findings in small studies,²⁴⁰ 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).²⁴¹
- Beta-interferon crosses the placenta in minimal quantities; it is unknown whether it is excreted in breast milk.²⁴² 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.²⁴³
- 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.⁶⁷ 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.²⁴⁴ 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.
- 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.⁶⁶
- It is unknown whether dimethyl fumarate crosses the placenta or enters breastmilk.⁶⁵ Animal studies of teratogenicity have shown conflicting results.²³⁸ Because of its short half-life (approximately one hour), no washout may be necessary.^{65,239}
- Natalizumab crosses the placenta and is excreted in breast milk.^{74,237} 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.²⁴⁵
- Mitoxantrone crosses the placenta in limited amounts and is excreted in breast milk.⁷³ Patients should be instructed not to become pregnant while taking mitoxantrone and for at least six months after discontinuation.²³⁷
- 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.⁶⁹ There are no adequate and well-controlled studies in pregnant women.⁶⁹
- 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 the infant is unknown.⁷⁵

The current standard of care is to avoid the use of disease-modifying therapies during pregnancy and breastfeeding.^{238–240,246–249} Based on exponential decay, the commonly accepted timeframe for drug discontinuation before conception is five maximal half-lives – approximately two-six weeks,²⁴⁸ with two months recommended for fingolimod and at least three months for natalizumab.²⁴⁶ 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.^{246,247,250–252} 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.²³⁹ In a recent study, natalizumab started within 8 days of delivery successfully prevented post-partum relapses in five of six women with very active disease.²⁵³

Rationale for Access to Full Range of Treatment Options

At the present time, 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 effect 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. For all of the following reasons, access to the full range of options is essential in order to optimize the ability of people with MS and their clinicians to make optimal treatment decisions.

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 explored²⁵⁴ and alternative options need to be considered.⁷⁷ It is known, for example, that disease activity that occurs in spite of treatment with IFN beta or GA is associated with unfavorable long-term outcomes.^{106,255,256} Furthermore, MRI activity as well as relapses are key indicators of progression^{257,258} and the presence of Gd-enhancing lesions has been shown to correlate with worsening disability after 15 years.²⁵⁵

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” recommend swift action in the face of disease activity, including consideration of switching to another disease-modifying therapy with a different mechanism of action.²⁵⁹

Treatment with interferon beta and natalizumab is frequently 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,²⁶⁰ the phase III trials of the interferon beta medications,^{138–140} as well as subsequent direct comparison studies,^{261,262} 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.²⁶⁰ 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.²⁶¹ 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.^{263,264}

In two phase III clinical trials of natalizumab,^{149,265} 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.²⁶⁶ Persistent antibody positivity was also associated in both studies with a higher incidence of infusion-related adverse events, including hypersensitivity reactions.²⁶⁶

Of the 58 percent of patients in a prospective observational study of 73 consecutive patients²⁶⁷ 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.

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.⁷⁴
- The prescribing information for [Gilenya](#) (fingolimod) 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 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.⁶⁵ 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.⁷⁵

Individuals with contraindications need access to suitable options

For a variety of reasons (cited as contraindications in medication labeling),^{49,53,54,56,59–62,65–67,69,73–75} 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
- 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](#))^{56,59-61} 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.²⁶⁸⁻²⁷¹

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.

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

- **Some adults have very active disease from onset**

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

- Scafari 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.¹⁰⁴
- Fisniku and colleagues⁸⁸ 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.²⁷² Although the majority were males and those with PPMS, there were also a significant number of female patients and patients with RRMS.
- 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.²⁷³
 - o EDSS of 4 within five years of onset;
 - o Multiple (>2) relapses with incomplete resolution within the past year;
 - o More than two MRI studies showing new or enlarging T2 lesions or Gd-enhancing lesions despite treatment;
 - o No response to therapy with one or more DMTs for up to one year.
- 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.²⁷⁴

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.²⁷⁵

In addition, there is evidence to support the use of natalizumab²⁷⁶ or mitoxantrone²⁷⁷⁻²⁸⁰ as an initial therapy for people with early aggressive disease characterized by frequent relapses with incomplete recovery and the accumulation of focal lesions in MRI.²⁸¹ However, as noted previously, mitoxantrone is seldom prescribed because of its high risk profile and studies looking at treatment interruption with natalizumab found an increase in clinical and/or MRI activity.^{215,216,221}

- **African-Americans appear to have more active disease**

Several studies have now pointed to a more active disease course in African-Americans 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.²³ 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.²⁴ 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.²⁵ More than one study has shown increased lesion volumes in African-Americans,^{26,27} with one also showing more tissue damage.²⁶ Given that there are also preliminary indications that African-Americans may not respond as well to some of the available disease-modifying therapies,^{282,283} 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.

- **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.

- **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 30-40 percent were adherent to treatment after two years.²⁸⁴ People who do not adhere to their treatment regimen are unlikely to receive the full benefit of the treatment.^{285,286} Factors associated with non-adherence include:

- Perceived lack of efficacy in relation to expectations^{286,287}
- Route of administration^{288,289}
- Perceived risks^{287,290,291}
- Tolerability issues with self-injectable medications, including flu-like symptoms and injection-site reactions²⁹²⁻²⁹⁵
- Length of time on treatment²⁹¹
- Costs²⁹⁶
- Psychosocial factors, including coping style,²⁹⁷ mood,^{217,298} and “forgetting.”^{291,294,295}

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 agents used off-label 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 B for further information about those 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 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
- Treatment with any given 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
 - Inadequate adherence to the treatment regimen
 - Availability of a more appropriate treatment option
- 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 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 collaboratively by the individual and his or her treating clinician.

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.
- 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.

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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 additional inflammatory activity occurs.

According to the 2010 revisions to the diagnostic criteria for MS (Lublin et al., 2014), the diagnosis of MS can be made when CIS is accompanied by MRI findings (old lesions or scars) that confirm that an earlier episode of damage occurred in a different location in the CNS. As MRI technology becomes more advanced, it is likely that the diagnosis of MS will be made more quickly and there will be fewer people diagnosed with CIS.

Continue on 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.

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 period **OR**

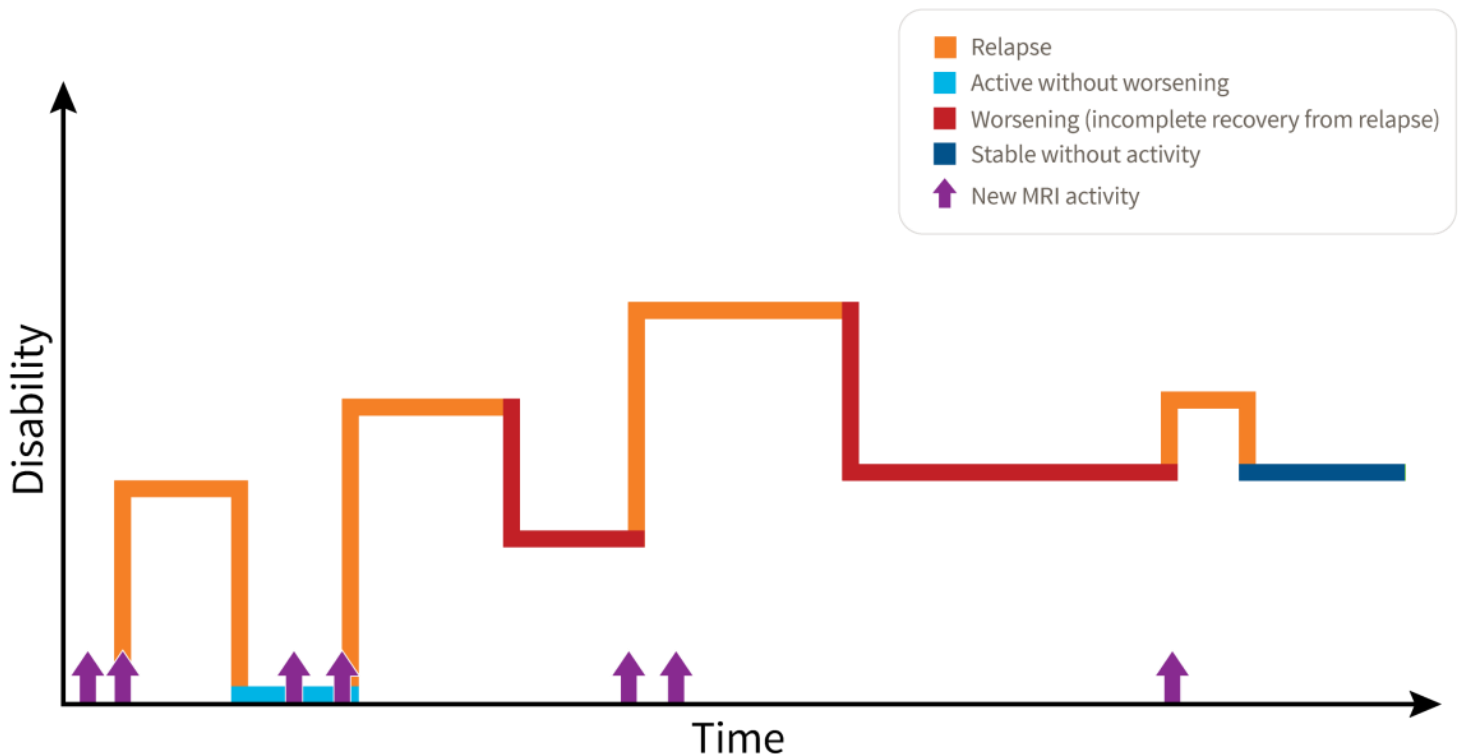
Not active – showing no evidence of disease activity

AND

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

Stable – no evidence of increasing disability over a specified time period 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 period **OR**

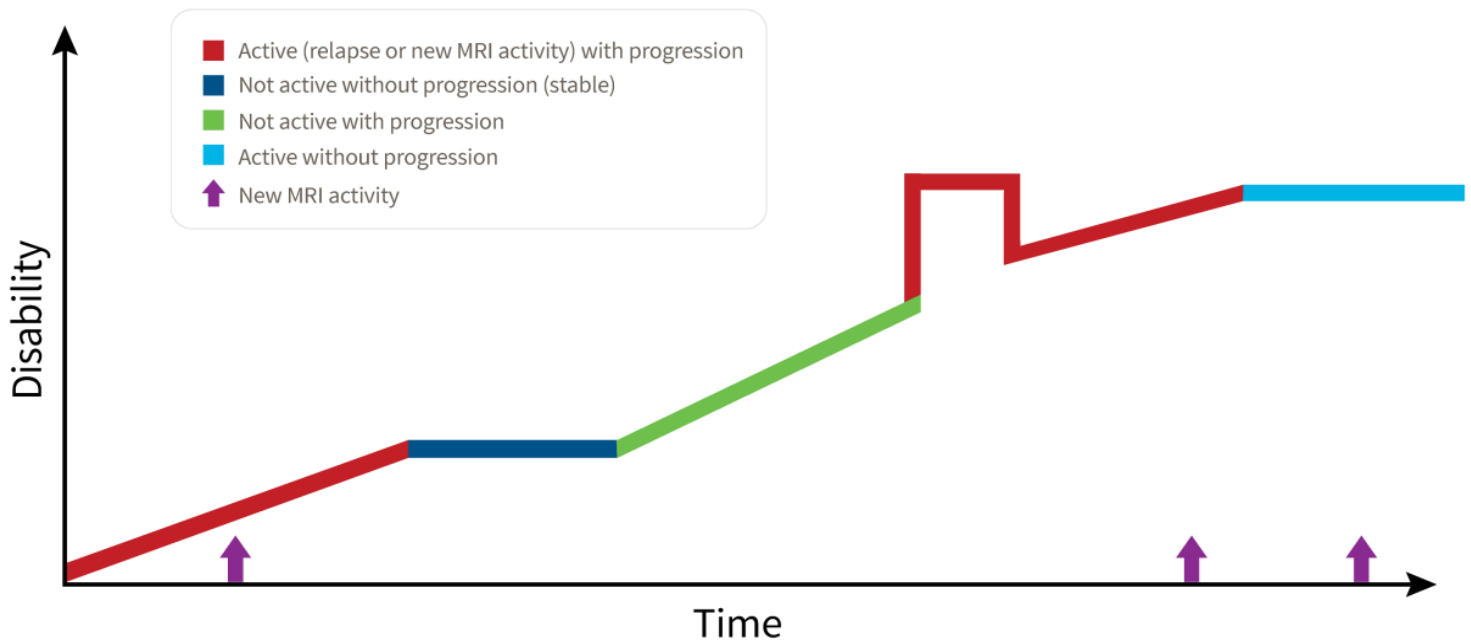
Not active – showing no evidence of disease activity

AND

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

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

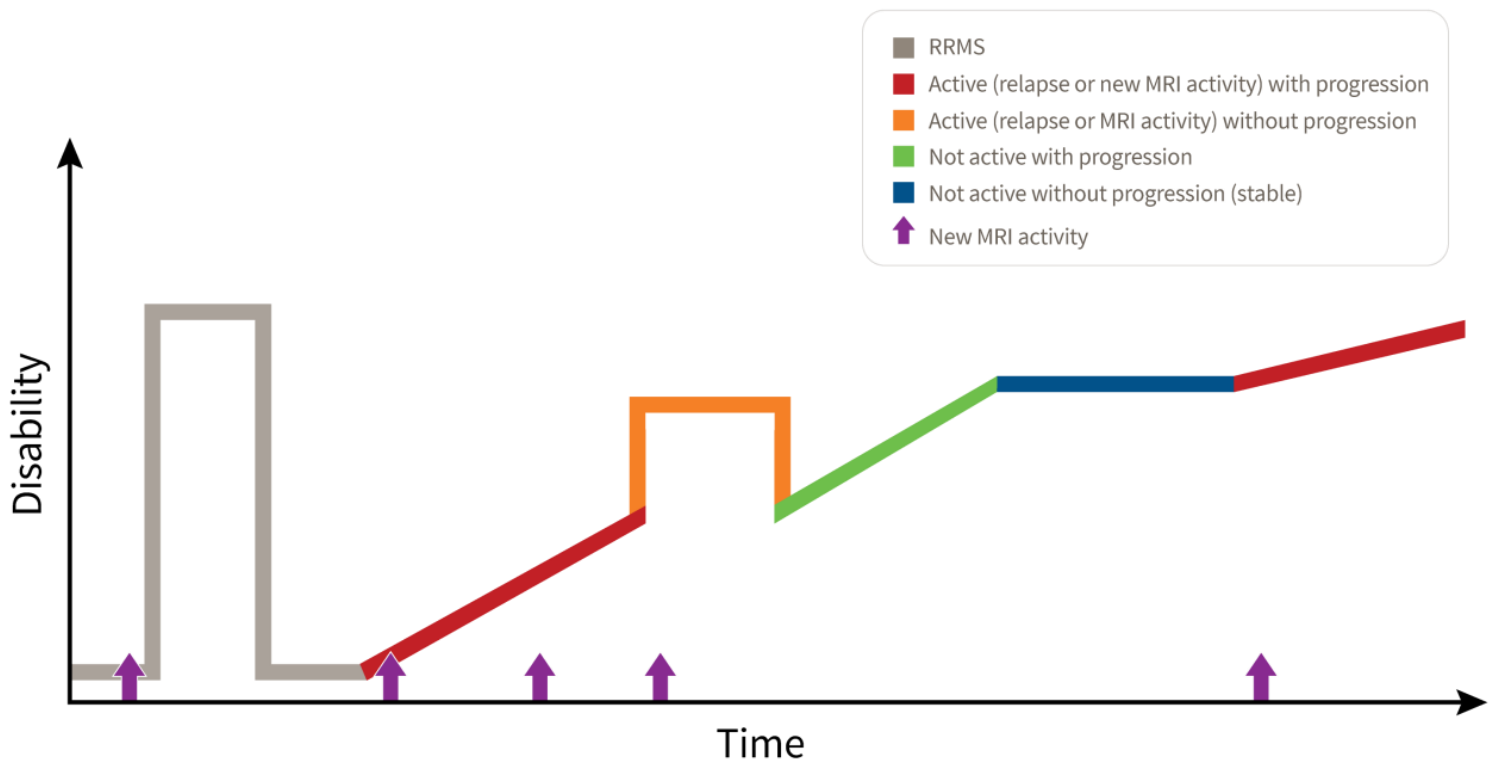
Not active – showing no evidence of disease activity

AND

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

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

SPMS



APPENDIX B

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 3 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% 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, but 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% 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, 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 benefit 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 1326 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, 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 but was denied approval in Europe. In 2011, the FDA also denied approval, stating that despite robust efficacy data in relapsing-remitting MS, more safety data were needed.

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, Merck has submitted a letter of intent to the European Medicines Agency to apply for marketing authorization.

Cyclophosphamide (Cytosan®)

Cyclophosphamide¹⁸ 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.¹⁹ 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.^{20,21} 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 6 months, sustained for at least 18 months after treatment onset, in patients with rapidly deteriorating relapsing-remitting MS.²²
- In a combination trial of cyclophosphamide and interferon beta, with follow-up at 12 and 24 months, Reggio and colleagues²³ found that the combination treatment halted disease progression in active, deteriorating MS patients who had received insufficient benefit 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 colleagues²⁴ 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.²⁵
- 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.²⁶

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

Minocycline²⁷ 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.²⁸
- 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.²⁹

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, central nervous system disorders. Minocycline is a pregnancy category D medication, indicating potential for fetal abnormalities.

Mycophenolate mofetil (Cellcept®)

Mycophenolate mofetil³⁰ 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 acetate³¹⁻³³ and in two blinded, placebo-controlled pilot studies in combination with interferon beta-1a.^{34,35}
- 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.³⁶

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, jaundice. Mycophenolate mofetil can cause fetal death or malformations.

Rituximab (Rituxan®)

Rituximab³⁷ 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.³⁸

Several clinical trials in MS have demonstrated that rituximab is effective in reducing clinical relapses and limiting new inflammation in the central nervous system.³⁹

- 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.⁴⁰
- 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.⁴¹
- 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.⁴²
- 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.⁴³

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, 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 3 to 6 months.

- In a multicenter, single-group phase 2 trial⁴⁴ involving 24 patients with aggressive relapsing MS that had not responded to other therapies, investigators reported a 69.6% MS activity-free survival rate at 3 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% 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 (presented by Nash and colleagues at the 2016 Annual Meeting of the Consortium of MS Centers), 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% of participants remained free of disease activity and required no disease-modifying therapy. Reported side effects included blood cell reductions and infections.
- Other studies using a low-intensity lympho-ablative regimen⁴⁵ or a non-myeloblastic regimen designed to reduce toxicity,⁴⁶ 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.

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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 9 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.

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)

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 IOMSN 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

MS Views and News (MSVN)

MSVN 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

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, 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 is a collective of passionate individuals who want to do something about MS NOW – to move together toward a world free of multiple sclerosis. The Society mobilizes people and resources to drive

research for a cure and to address the challenges of everyone affected by MS.

nationalMSSociety.org | 800-344-4867

United Spinal Association

United Spinal Association is a national non-profit organization founded by paralyzed veterans in 1946 and has since provided service programs and advocacy to improve the quality of life of those across the life span 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 and to whom the Association's work is dedicated. United Spinal has close to 40,000 members, 30 chapters and close to 200 support groups nationwide. Throughout its history, United Spinal Association has devoted its energies, talents and programs to improving the quality of life for these Americans and for advancing their independence. United Spinal Association is also a VA-authorized veteran's service organization serving veterans with disabilities of all kinds. United Spinal Association publishes the New Mobility and Life in Action magazines.

unitedspinal.org | 718-803-3782

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