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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aReviewed original and March 2015 and July 2016 updates
bReviewed original only
cReviewed March 2015 and July 2016 updates
THE USE OF DISEASE-MODIFYING THERAPIES IN MULTIPLE SCLEROSIS

Principles and Current Evidence

A Consensus Paper by the Multiple Sclerosis Coalition

ABSTRACT

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

Development Process: 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 eight Coalition members, and subsequently by Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS), and published in November 2014.

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

March 2015

July 2016

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 disease, 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 indefinetely 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, 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 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.\(^3\) 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.\(^4\) 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.\(^5-8\)

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,\(^9\) potentially limiting the achievement of life goals. The free-spirit spontaneity so highly valued by young adults needs to shift to deliberative 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.\(^10\) Productivity and participation are affected for many, including early departure from the workforce and inability to fulfill household responsibilities.\(^11\) The lifetime financial cost of MS, including both direct and indirect cost of the disease, has been estimated at $1.2 million.\(^12\) In addition, 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.\(^13\)

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.\(^14-17\) Women are affected at least three times more than men\(^18\) and Caucasians are affected more than other racial groups.\(^19\) However, a recent study\(^20\) suggested that African-American women have a higher than previously reported risk of developing MS. 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.\(^21,22\) However, some recent studies have not demonstrated the same latitudinal gradient,\(^23,24\) 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 with 85-90 percent of individuals demonstrating a relapsing-remitting 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 steady progression of symptoms over time (primary progressive MS), of which some will subsequently experience inflammatory activity by clinical or MRI criteria.\(^1\) This primary progressive disease pattern of the disease is generally diagnosed at an older age and is distributed more equally in men and women.

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.\(^25\) 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 repertoire 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).\(^25-27\) In people with MS, there is a bias towards a Th1 and Th17 environment with T regulatory dysfunction that allows inflammation to
predominate. Secreted cytokines and matrix metalloproteinases disrupt the blood brain barrier. 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. 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-B secreting) and CD56bright NK cells. Proliferation of progenitor oligodendroglia and remyelination contribute to recovery at least in the early stages of the disease.

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. 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 progressive disease; and the presence of B-cell enriched meningeal follicles in progressive patients.

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.

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. Axonal loss, which correlates best with disability, begins early in the disease process as evidenced by identified pathological changes as well as imaging studies.

Figure 1: Inflammatory cascade in multiple sclerosis

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**Periphery**

1. Antigen presentation to CD4+ prompting activation and proliferation of pro inflammatory lymphocytes (Th1 and Th17)

2. Secretion of pro-inflammatory cytokines

3. Up-regulation of adhesion molecules

4. T cell migration across the blood brain barrier into the CNS

5. B cell activation, proliferation and migration into CNS

6. Migration of monocytes and macrophages into the CNS

7. Inadequate T regulatory function

---

**CNS**

8. Presentation of CNS antigen to T cell with reactivation

9. Recruitment of other inflammatory cells: CD8+ B cells monocytes macrophages microglia

10. Damage to myelin, oligodendrocytes and axons resulting from:

   - cytokine damage
   - antibody activity
   - complement damage
   - oxidative stress
   - mitochondrial dysfunction

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**Blood Brain Barrier**
OVERVIEW OF FDA-APPROVED DISEASE-MODIFYING AGENTS IN MS

To date, 14 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

<table>
<thead>
<tr>
<th>Agent - Self-injected</th>
<th>Proposed MoA</th>
<th>Side Effects</th>
<th>Warnings/Precautions</th>
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<tbody>
<tr>
<td>daclizumab&lt;sup&gt;39&lt;/sup&gt; (Zinbryta™)</td>
<td>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.&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Compared with interferon beta-1a:&lt;sup&gt;41&lt;/sup&gt; -nasopharyngitis -upper respiratory tract infection -rash -influenza -dermatitis -oropharyngeal pain -bronchitis -eczema -lymphadenopathy -tonsillitis -acne</td>
<td>-hepatic injury including autoimmune hepatitis -other immune-mediated disorders, including skin reactions, lymphadenopathy and non-infectious hepatitis -hypersensitivity reactions -↑ risk of infections, including serious infections -depression and suicide Boxed Warning: Hepatic injury including autoimmune hepatitis and other immune-mediated disorders</td>
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<tr>
<td>150mg once monthly</td>
<td>Indication: relapsing forms of MS – generally for patients who have had an inadequate response to two or more MS therapies</td>
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<tr>
<td>Pregnancy Cat: No category assigned due to changes to FDA labeling procedures for pregnancy and lactation. No human data: animal data in monkey suggests that administration during organogenesis may pose risks&lt;sup&gt;39&lt;/sup&gt;</td>
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<p>| glatiramer acetate&lt;sup&gt;43,44&lt;/sup&gt; (Copaxone&lt;sup&gt;®&lt;/sup&gt;) | Mechanism of action in MS is not fully understood. Subsequent research suggests: -promotes differentiation into Th2 and T-reg cells, leading to bystander suppression in CNS&lt;sup&gt;45&lt;/sup&gt; -increased release of neurotrophic factors from immune cells&lt;sup&gt;45&lt;/sup&gt; -deletion of myelin-reactive T cells&lt;sup&gt;45&lt;/sup&gt; | Injection-site reactions -lipoatrophy -vasodilation, rash, dyspnea -chest pain&lt;sup&gt;43&lt;/sup&gt; | -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 |
| 20mg SC daily or 40mg SC three times weekly | | | |
| Indication: relapsing forms of MS (Glatopa™ - therapeutic equivalent) | | | |
| 20mg SC daily | | | |
| Indication: relapsing forms of MS | | | |
| Pregnancy Cat: B | | | |</p>
<table>
<thead>
<tr>
<th>Agent - Self-Injected</th>
<th>Proposed MoA</th>
<th>Side Effects</th>
<th>Warnings/Precautions</th>
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</thead>
<tbody>
<tr>
<td>interferon beta-1a&lt;sup&gt;46&lt;/sup&gt; (Avonex®)</td>
<td>Mechanism of action in MS is not known. Subsequent research suggests: -promotes shift from Th1-Th2 -reduces trafficking across BBB&lt;sup&gt;47,48&lt;/sup&gt; -restores T-reg cells&lt;sup&gt;49&lt;/sup&gt; -inhibits antigen presentation&lt;sup&gt;45&lt;/sup&gt; -enhances apoptosis of autoreactive T-cells&lt;sup&gt;45&lt;/sup&gt;</td>
<td>-flu-like symptoms -depression -↑hepatic transaminases</td>
<td>-depression, suicide, psychosis -hepatic injury -anaphylaxis and other allergic reactions -CHF -↓peripheral blood counts -seizures -other autoimmune disorders -thrombotic microangiopathy</td>
</tr>
<tr>
<td>IM 30mcg weekly</td>
<td>Indication: relapsing forms of MS</td>
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<tr>
<td>Pregnancy Cat: C</td>
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| interferon beta-1a<sup>49</sup> (Rebif®) | 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 |
| SC 22mcg or 44mcg three times weekly | Indication: relapsing forms of MS | | |
| Pregnancy Cat: C | | | |

| interferon beta-1b<sup>50,51</sup> (Betaseron®) (Extavia®) | Same as above | -flu-like symptoms -injection-site reactions -↑hepatic transaminases -↓WBC -see warnings<sup>50,51</sup> | -hepatic injury -anaphylaxis and other allergic reactions -depression and suicide -CHF -injection-site necrosis -↓WBC -flu-like symptoms -seizures -thrombotic microangiopathy |
| 0.25mg SC every other day | Indication: relapsing forms of MS | | |
| Pregnancy Cat: C | | | |

<p>| peginterferon beta-1a&lt;sup&gt;52-54&lt;/sup&gt; (Plegridy®) | Same as above | -flu-like symptoms -injection-site reactions -↑hepatic transaminases -↓WBC -see warnings&lt;sup&gt;46,49&lt;/sup&gt; | -depression, suicide -hepatic injury -anaphylaxis and other allergic reactions -CHF -↓peripheral blood counts -seizures -other autoimmune disorders -thrombotic microangiopathy |
| SC 125mcg every two weeks | Indication: relapsing forms of MS | | |
| Pregnancy Cat: C | | | |</p>
<table>
<thead>
<tr>
<th>Agent - Oral</th>
<th>Proposed MoA</th>
<th>Side Effects</th>
<th>Warning/Precautions</th>
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<tbody>
<tr>
<td>dimethyl fumarate(^{55}) *(Tece(f)idera(^{\text{®}})) 240mg PO twice daily</td>
<td>Mechanism of action in MS is unknown. It has been shown to: - promote anti-inflammatory and cytoprotective activities mediated by Nrf2 pathway</td>
<td>-flushing -GI symptoms (abdominal pain, diarrhea, and nausea)(^{55}) -pruritis -rash -erythema</td>
<td>-anaphylaxis and angioedema -progressive multifocal leukoencephalopathy (PML) -lymphopenia -flushing</td>
</tr>
<tr>
<td>fingolimod(^{56}) *(Sile(n)ya(^{\text{®}})) 0.5mg PO daily</td>
<td>Mechanism of action in MS most likely involves blocking of S1P receptor on lymphocytes thus preventing their egress from secondary lymph organs(^{56})</td>
<td>-headache -influenza -diarrhea -back pain -↑hepatic enzymes -cough -bradycardia during first dose -macular edema -lymphopenia -bronchitis/pneumonia</td>
<td>-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 -progressive multifocal leukoencephalopathy (PML) -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 -contraindications: recent MI, unstable angina, stroke, TIA, decompensated heart failure or class III or IV heart failure; history of Mobitz Type II 2(^{\text{nd}}) or 3(^{\text{rd}}) degree AV block or sick sinus syndrome unless patient has pacemaker; baseline QTc interval &gt; 500 msec; treatment with class Ia or III antiarrhythmic drugs -↓lymphocyte counts for 2 months after drug d/c</td>
</tr>
<tr>
<td>teriflunomide(^{57}) *(Aubagio(^{\text{®}})) 7mg or 14mg PO daily</td>
<td>Mechanism of action in MS is unknown.(^{57,58}) It has been shown to: -have a cytostatic effect on rapidly dividing T- and B-lymphocytes in the periphery -inhibit de novo pyrimidine synthesis It is a metabolite of leflunomide (used in rheumatoid arthritis (RA))</td>
<td>-ALT elevation -alopecia -diarrhea -influenza -nausea -paresthesia(^{57})</td>
<td>-hepatotoxicity -risk of teratogenicity -elimination of teriflunomide can be accelerated by administration of cholestyramine or activated charcoal for 11 days -↓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 immunsuppressants has not been evaluated Note: some of these were carried over from leflunomide use in RA</td>
</tr>
</tbody>
</table>

**Boxed Warning**

hepatotoxicity and risk of teratogenicity
<table>
<thead>
<tr>
<th>Agent - Intravenous</th>
<th>Proposed MoA</th>
<th>Side Effects</th>
<th>Warnings/Precautions</th>
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<tr>
<td>alemtuzumab&lt;sup&gt;59-61&lt;/sup&gt; (Lemtrada®)</td>
<td>Mechanism of action in MS is presumed to involve binding to CD52, a cell surface antigen present on T and B lymphocytes, and on natural killer cells, monocytes and macrophages. This results in antibody-dependent cellular cytolysis and complement-mediated lysis.</td>
<td>-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.</td>
<td>-infusion reactions -autoimmunity (thyroid disorders, immune thrombocytopenia (ITC), glomerular nephropathies, other cytopenias) -infections -No live virus vaccinations following infusion -malignancies (thyroid, melanoma, lymphoproliferative) -pneumonitis 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.</td>
</tr>
<tr>
<td>mitoxantrone&lt;sup&gt;63&lt;/sup&gt; (Novantrone®)</td>
<td>-disrupts DNA synthesis and repair; inhibits B cell, T cell, and macrophage proliferation; impairs antigen presentation, as well as the secretion of interferon gamma, TNFa and IL-2.</td>
<td>-temporary blue discoloration of sclera and urine -nausea -alopecia -menstrual disorders including amenorrhea and infertility -infections (URI, UTI, stomatitis) -cardiac toxicity (arrhythmia, abnormal EKG, congestive heart failure)</td>
<td>-severe local tissue damage if there is extravasation -cardiotoxicity -acute myelogenous leukemia -myelosuppression Boxed Warning cardiotoxicity and secondary leukemia (monitoring required long-term)</td>
</tr>
<tr>
<td>natalizumab&lt;sup&gt;64&lt;/sup&gt; (Tysabri®)</td>
<td>The mechanism of action in MS has not been fully defined. It has been shown to: -block α&lt;sub&gt;4&lt;/sub&gt;integrin on lymphocytes, thus reducing trafficking of lymphocytes into the CNS&lt;sup&gt;68&lt;/sup&gt;</td>
<td>-headache -fatigue -urinary tract infection -lower respiratory tract infection -arthralgia -urticaria -gastroenteritis -vaginitis -depression -diarrhea&lt;sup&gt;64&lt;/sup&gt;</td>
<td>-progressive multifocal leukoencephalopathy (PML) -hepatotoxicity -herpes encephalitis and meningitis caused by herpes simplex and varicella zoster viruses -hypersensitivities -immunosuppression/infections Boxed Warning Because of the risk of PML, natalizumab is available only through a restricted distribution program called the TOUCH® Prescribing Program.</td>
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**BBB- Blood Brain Barrier**

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.

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.

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. 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.\(^5\)\(^6\)
  - Inflammatory activity has been observed in patients with both relapsing and progressive forms of the disease.\(^2\)
  - Abnormalities are evident in normal appearing white matter as well as gray matter in the absence of focal inflammation and are seen early in the disease process.\(^5\)
  - Brain atrophy has been identified in early MS, even at the time of the first clinical attack.\(^6\)
  - Atrophy has been seen in radiographically isolated syndrome (the incidental finding of MS-like lesions in the absence of known clinical relapses).\(^6\)
  - Inflammatory changes continue to be seen in secondary progressive and primary progressive MS.\(^2\)
  - Once a threshold is reached, disability progression continues at a rate that is unrelated to the prior relapse history.\(^7\)

  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 central nervous system (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). 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. 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.

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

**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) is the result of residual impairments from partially-resolved relapses. Natural history studies suggest that relapses in the first two years of disease impact early progression, with the impact of early relapses diminishing later in the disease course.
- 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. 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 colleagues 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.

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.

**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; 30-54 percent will experience a major depressive disorder; and up to 92 percent will experience significant fatigue, 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.
- Some studies suggest that cognitive deficits may precede the onset of MS by as much as 1.2 years. 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.
- Early cognitive changes are also known to progress, even in people with little or no physical changes, and deterioration can be expected over a three-year period in approximately one-third of people with short disease duration.
- Cognitive deficits are detected in approximately 30 percent of pediatric MS patients.
- 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\textsuperscript{66,65} – 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.\textsuperscript{66,65} 

- 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) \( \leq 3 \) at 10 years\textsuperscript{102,103} – 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.\textsuperscript{105}
  - 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.\textsuperscript{106}
  - 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.\textsuperscript{107}

  Based on these findings, it is clear that \textit{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.\textsuperscript{108}

**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 five published placebo-controlled Phase III trials of injectable medications in patients with clinically-isolated syndrome (CIS)\textsuperscript{71–74,77} demonstrated that early treatment successfully delayed conversion to CDMS (as defined at the time of these trials) by 43–45 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,\textsuperscript{109} 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.\textsuperscript{110}

**Reducing brain atrophy and disability worsening**

In a meta-analysis of three CIS treatment trials, each of two years duration (ETOMS, PreCISE, TOPIC),\textsuperscript{71,77,111} brain atrophy was attenuated after one year of treatment.

In a large cohort of CIS patients, disease-modifying treatments reduced 3-month confirmed and 12-month sustained disability worsening.\textsuperscript{82}

**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. \textit{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 of specific agents across trials.}

**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)*

<table>
<thead>
<tr>
<th>Agent - Self-Injected</th>
<th>Effect on Relapse Rate Compared to Placebo or Active Comparator*</th>
<th>Effect on Disability Progression Compared to Placebo or Active Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>daclizumab39,41,42</td>
<td>45% relative reduction41  mean # relapses per person (96 weeks): 0.393 interferon beta-1a; 0.216 daclizumab (p&lt;0.001) 54% relative reduction mean # relapses per person (52 weeks): 0.458 placebo; 0.211 daclizumab (p&lt;0.0001)</td>
<td>Incidence of disability progression in a 144-week study period as measured by EDSS confirmed at 12 weeks: 20% interferon beta-1a; 16% daclizumab (N.S.)</td>
</tr>
<tr>
<td>glatiramer acetate113</td>
<td>29% reduction mean # relapses per person (24 months): 1.68 placebo; 1.19 treated (p=0.007) 34% reduction annualized relapse rate at 12 months: 0.505 placebo; 0.331 treated (p&lt;0.0001)</td>
<td>Disability progression between baseline and 52 weeks as measured by EDSS confirmed at 12 weeks: 13% placebo; 6% daclizumab (HR=0.43 daclizumab, p=0.021).</td>
</tr>
<tr>
<td>interferon beta-1a subcutaneous115</td>
<td>33.2% reduction (44mcg tiw vs. placebo) mean # relapses per person (24 months): 2.56 placebo; 1.73 treated (p&lt;0.005)</td>
<td>30% decrease in proportion of patients with sustained disability progression 11.9 months placebo; 21.3 months treated (p&lt;0.05)</td>
</tr>
<tr>
<td>interferon beta-1a intramuscular116</td>
<td>18% reduction48 mean # exacerbations per patient year: 0.82 placebo; 0.67 treated (p=0.04)</td>
<td>37% decrease in time to sustained disability progression 34.9% placebo; 21.9% treated (p=0.04)</td>
</tr>
<tr>
<td>interferon beta-1b117</td>
<td>34% reduction annualized relapse rate over two years: 1.27 placebo; 0.84 treated (p=0.0001)</td>
<td>29% decrease (N.S.) insignificant change from baseline EDSS 28% placebo; 20% treated</td>
</tr>
<tr>
<td>peginterferon beta-1a53,54</td>
<td>36% reduction annualized relapse rate at 48 weeks: 0.397 placebo; 0.256 treated (p=0.0007)</td>
<td>38% relative risk reduction in disability progression 10.5% placebo; 6.8% treated (p=0.0383)</td>
</tr>
<tr>
<td>Agent – Oral</td>
<td>Effect on Relapse Rate Compared to Placebo or Active Comparator*</td>
<td>Effect on Disability Progression Compared to Placebo or Active Comparator</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>dimethyl fumarate&lt;sup&gt;118,119&lt;/sup&gt;</td>
<td>49% reduction&lt;sup&gt;118&lt;/sup&gt; proportion relapsing within two years: 46% placebo; 27% treated (p&lt;0.001) 44% reduction&lt;sup&gt;119&lt;/sup&gt; annualized relapse rate at two years: 40% placebo; 22% treated (p&lt;0.001)</td>
<td>38% decrease in risk of disability progression&lt;sup&gt;118&lt;/sup&gt; 27% placebo; 16% treated (p=0.005)&lt;sup&gt;118&lt;/sup&gt; 24% placebo; 21% treated (N.S.)&lt;sup&gt;119&lt;/sup&gt;</td>
</tr>
<tr>
<td>fingolimod&lt;sup&gt;120,121&lt;/sup&gt;</td>
<td>54% reduction&lt;sup&gt;120&lt;/sup&gt; annualized relapse rate over two years: 0.40 placebo; 0.18 0.5mg (p&lt;0.001)&lt;sup&gt;120&lt;/sup&gt; 48% reduction&lt;sup&gt;121&lt;/sup&gt; annualized relapse rate over two years: 0.40 placebo; 0.21 0.5mg (p&lt;0.0001)&lt;sup&gt;121&lt;/sup&gt;</td>
<td>30% decrease in risk of disability progression (p=0.03 0.5mg)&lt;sup&gt;120&lt;/sup&gt; % with absence of disability progression at three months: 75.9% placebo; 82.3% 0.5mg (p=0.03)&lt;sup&gt;120&lt;/sup&gt; % with absence of disability progression at three months: 71.0% placebo; 74.7% 0.5mg (N.S.)&lt;sup&gt;121&lt;/sup&gt; % with absence of disability progression at 12 months: 92.1% IFN; 94.1% 0.5mg (p=0.25)&lt;sup&gt;122&lt;/sup&gt;</td>
</tr>
<tr>
<td>(compared to IFN beta-1a)&lt;sup&gt;122&lt;/sup&gt;</td>
<td>31% reduction annualized relapse rate over two years: 0.54 placebo: 0.37 for 7mg and 14mg (p&lt;0.001)</td>
<td>27.3% placebo; 21.7% 7mg (N.S.); 20.2% 14mg (p=0.03)</td>
</tr>
<tr>
<td>teriflunomide&lt;sup&gt;123&lt;/sup&gt;</td>
<td>48% reduction&lt;sup&gt;121&lt;/sup&gt; annualized relapse rate over two years: 0.54 placebo: 0.37 for 7mg and 14mg (p&lt;0.001)</td>
<td>38% decrease in risk of disability progression&lt;sup&gt;118&lt;/sup&gt; 27% placebo; 16% treated (p=0.005)&lt;sup&gt;118&lt;/sup&gt; 24% placebo; 21% treated (N.S.)&lt;sup&gt;119&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Agent - Intravenous</th>
<th>Effect on Relapse Rate Compared to Placebo or Active Comparator*</th>
<th>Effect on Disability Progression Compared to Placebo or Active Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>alemtuzumab&lt;sup&gt;60,61&lt;/sup&gt;  (compared to interferon beta-1a 44mcg tiw)</td>
<td>55% reduction&lt;sup&gt;60&lt;/sup&gt; annualized relapse rate over two years: 0.39 IFN beta-1a; 0.18 alemtuzumab (p=0.0001)&lt;sup&gt;65&lt;/sup&gt; 49% reduction&lt;sup&gt;61&lt;/sup&gt; annualized relapse rate over two years: 0.52 IFN beta-1a; 0.26 alemtuzumab (p=0.0001)&lt;sup&gt;65&lt;/sup&gt;</td>
<td>30% relative risk reduction at year two (N.S.) sustained disability accumulation confirmed over six months: 11% IFN beta-1a; 8% alemtuzumab&lt;sup&gt;60&lt;/sup&gt; 42% relative risk reduction at year 2 sustained disability accumulation confirmed over six months: 20% IFN beta-1a; 13% alemtuzumab (p=0.0084)&lt;sup&gt;61&lt;/sup&gt;</td>
</tr>
<tr>
<td>mitoxantrone&lt;sup&gt;124&lt;/sup&gt;</td>
<td>66% reduction annualized relapse rate over two years: 1.02 placebo; 0.35 treated (p=0.001)</td>
<td>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&lt;sup&gt;2&lt;/sup&gt; dose (absolute and relative risks not reported)</td>
</tr>
<tr>
<td>natalizumab&lt;sup&gt;125&lt;/sup&gt;</td>
<td>annualized relapse rate over two years: 68% reduction 1 year: 0.78 placebo; 0.27 treated (p&lt;0.001) 2 year: 0.73 placebo; 0.23 treated (p=0.001)</td>
<td>42% decrease in risk of confirmed disability progression cumulative probability of sustained progression at 2yr: 29% placebo; 17% treated (p&lt;0.001)</td>
</tr>
</tbody>
</table>

N.S. = Not Significant
Adapted from Kappos et al, 2015<sup>41</sup>; Gold et al, 2013<sup>42</sup>; Oh & Calabresi in Rae-Grant, et al, 2013;<sup>43</sup> Johnson et al, 1995<sup>44</sup>; Khan et al, 2013<sup>45</sup>; PRISMS Study Group 1998<sup>46</sup>; Jacobs et al, 1996<sup>47</sup>; IFNB MS Study Group, 1993<sup>48</sup>; Gold et al, 2012<sup>49</sup>; Fox et al, 2012<sup>50</sup>; Kappos et al, 2010<sup>51</sup>; Calabresi et al, 2014<sup>52</sup>; Cohen et al, 2010<sup>53</sup>; O’Connor et al, 2011<sup>54</sup>; Hartung et al, 2002<sup>55</sup>; Polman et al, 2006<sup>56</sup>.<sup>56</sup>

* 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. While it remains unclear the exact extent to which reducing relapses impacts long-term disability levels, it is evident that relapse reduction translates into increased comfort and quality of life, fewer days lost from work and other essential activities of daily life, and reduces the risk of residual deficits.

**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.

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

<table>
<thead>
<tr>
<th>Agent - Self-Injected</th>
<th>Effect on GD+ lesions*</th>
<th>Effect on new or enlarging T2 lesions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>daclizumab</td>
<td>mean # at week 96: 1.0 ± 2.8 interferon beta-1a; 0.4± 1.4 odds ratio 0.25 (p&lt;0.001)</td>
<td>mean # at 96 weeks: 9.44 interferon beta-1a; 4.31 daclizumab relative reduction 54% (p&lt;0.001)</td>
</tr>
<tr>
<td>150mg once monthly</td>
<td>mean # at 52 weeks: 4.79 placebo; 1.46 treated relative reduction 69% (p&lt;0.0001)</td>
<td>mean # at 52 weeks: 8.1 placebo; 2.4 treated relative reduction 69% (p&lt;0.0001)</td>
</tr>
<tr>
<td>glatiramer acetate</td>
<td>mean # total new T2: 13.7 placebo; 9.4 GA 20mg cumulative new or enlarging T2 at months 6 and 12: 5.59 placebo; 3.65 GA 40mg</td>
<td></td>
</tr>
<tr>
<td>20mg qd</td>
<td>mean # total new T2: 13.7 placebo; 9.4 GA 20mg cumulative new or enlarging T2 at months 6 and 12: 5.59 placebo; 3.65 GA 40mg</td>
<td></td>
</tr>
<tr>
<td>40mg tiw</td>
<td>mean # total new T2: 13.7 placebo; 9.4 GA 20mg cumulative new or enlarging T2 at months 6 and 12: 5.59 placebo; 3.65 GA 40mg</td>
<td></td>
</tr>
<tr>
<td>interferon beta-1a</td>
<td>median # of active lesions per patient per scan: 2.25 placebo; 0.5 44mcg</td>
<td>median % change of MRI PD-T2 lesion area at two years: 11% placebo; -3.8% 44mcg</td>
</tr>
<tr>
<td>subcutaneous</td>
<td>median % change T2 lesion volume from study entry to year 2: -6.55% placebo; -13.2% treated (N.S.)</td>
<td></td>
</tr>
<tr>
<td>interferon beta-1a</td>
<td>mean # contrast enhancing lesions at two years: 1.65 placebo; 0.80 treated</td>
<td>mean % change in MRI area (n=52, scans q6wks): 16.5% placebo; -1.1% 0.25mg</td>
</tr>
<tr>
<td>intramuscular</td>
<td>mean # contrast enhancing lesions at two years: 1.65 placebo; 0.80 treated</td>
<td>mean % change in MRI area (n=52, scans q6wks): 16.5% placebo; -1.1% 0.25mg</td>
</tr>
<tr>
<td>peginterferon beta-1a</td>
<td>mean # at 48 wks: 1.4 placebo; 0.2 treated</td>
<td>mean # at 48 wks: 10.9 placebo; 3.6 treated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Agent – Oral</th>
<th>Effect on GD+ lesions*</th>
<th>Effect on new or enlarging T2 lesions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>dimethyl fumarate</td>
<td>mean # Gd+ lesions at two years: 1.8 placebo; 0.1 240mg bid</td>
<td>mean # new or enlarging T2 hyperintense lesions at two years: 17 placebo; 2.6 240mg bid</td>
</tr>
<tr>
<td>118,119</td>
<td>mean # Gd+ lesions at two years: 2.0 placebo; 0.5 240mg bid</td>
<td>mean # new or enlarging T2 hyperintense lesions at two years: 17.4 placebo; 5.1 240mg bid</td>
</tr>
<tr>
<td>fingolimod</td>
<td>mean # T1 Gd-enhancing lesions at month 24: 1.1 placebo; 0.2 0.5mg</td>
<td>mean # new or newly enlarging T2 lesions over 24 months: 9.8 placebo; 2.5 0.5mg</td>
</tr>
<tr>
<td>120,121</td>
<td>mean # T1 Gd-enhancing lesions at month 24: 1.2 placebo; 0.4 0.5mg</td>
<td>mean # new or newly enlarging T2 lesions over 24 months: 8.9 placebo; 2.3 0.5mg</td>
</tr>
</tbody>
</table>
### Agent – Oral

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect on GD+ lesions*</th>
<th>Effect on new or enlarging T2 lesions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>teriflunomide</td>
<td>mean # Gd-enhancing lesions per scan: 1.331 placebo; 0.261 14mg</td>
<td>median change from baseline in total lesion volume (T1+T2) (ml) at week 108: 1.127 placebo; 0.345 14mg</td>
</tr>
</tbody>
</table>

### Agent - Intravenous

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect on GD+ lesions*</th>
<th>Effect on new or enlarging T2 lesions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>alemtuzumab</td>
<td>% patients with Gd-enhancing lesions at 24 months (tertiary outcome): 19% IFN; 7% alemtuzumab 23% IFN; 9% alemtuzumab</td>
<td>patients with new or enlarging T2 lesions (tertiary outcome): 58% IFN; 48% alemtuzumab 68% IFN; 46% alemtuzumab</td>
</tr>
<tr>
<td>mitoxantrone</td>
<td>#of patients with new Gd-enhancing lesions: 5/32 (16%) placebo; 4/37 (11%) 5mg/m²; 0/31 12mg/m²</td>
<td>change in # of T2-weighted lesions, mean (month 24 minus baseline): 1.94 placebo; 0.68 5mg/m²; 0.29 12mg/m²</td>
</tr>
<tr>
<td>natalizumab</td>
<td>median # Gd lesions at two years: 0 placebo; 0 treated; percent with two or more enhancing lesions: 16% placebo; 1% treated mean # Gd lesions at two years: placebo 1.2; treated 0.125</td>
<td>mean # new or enlarging T2 lesions at two years: 5 placebo; 0 treated mean # new or enlarging T2 lesions at two years: 11.0 placebo; 1.9 treated</td>
</tr>
</tbody>
</table>


*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 thought 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.129
- In a Phase III trial comparing BG-12 with placebo, which also included glatiramer acetate as an active comparator, BG-12 and glatiramer acetate significantly reduced the numbers of new T1 hypointense lesions as compared with placebo.89
- Treatment-naïve patients randomized to two doses of interferon beta or glatiramer acetate experienced no additional brain atrophy in years two and three – with overall median increases in brain volume from baseline to year three being similar across all groups – suggesting a neuroprotective effect of treatment.90
- Several studies utilizing differing designs have demonstrated the ability of intramuscular interferon beta-1a, alone or in combination with other medications, to reduce the progression of whole-brain or cortical-brain atrophy versus placebo or no treatment.109-133
- A study evaluating the effects of glatiramer acetate, intramuscular and subcutaneous interferon beta-1a, and interferon beta-1b on brain volume loss in relapsing-remitting MS over a five-year period found that all of the medications significantly reduced brain volume loss compared to no treatment.104
- In Phase III fingolimod studies, fingolimod reduced brain volume loss relative to the comparator groups (placebo or intramuscular interferon beta-1a) in all patient subgroups.
- In a two-year, placebo-controlled trial, brain atrophy was greater in year one and less in year two in natalizumab-treated patients.95
- In its Phase III trial program, alemtuzumab reduced brain volume loss compared with subcutaneous interferon beta-1a.60,61
Impact on long-term clinical outcomes

Following a cohort of people over an extended period of time has many limitations, including uncontrolled design, poor accounting for drop-outs and retrospective assessments in most cases. However, some important data have emerged:

- In a cohort observational study of 3060 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.\textsuperscript{137}
- 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 $\geq 4$.\textsuperscript{138}
- Most of the extension studies from the pivotal trials indicated a positive impact on conversion to clinically definite MS, relapse rates and disease progression,\textsuperscript{87,99,139,140} although much of the impact may take place early in the disease course.\textsuperscript{87}
- 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.\textsuperscript{141}
- 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.\textsuperscript{142}
- A long-term follow-up (greater than seven years) of a Phase II fingolimod study demonstrated persistent positive effect on relapse and MRI activity.\textsuperscript{143}
- Approximately 90 percent of untreated RRMS patients will have SPMS after 15-25 years.\textsuperscript{144,145} 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.\textsuperscript{146}
  - 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.\textsuperscript{147}
  - 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.\textsuperscript{148}
- 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,\textsuperscript{149,150} with evidence suggesting that long-term (physical and cognitive) outcomes may be largely determined early in the disease course.\textsuperscript{87} Another study demonstrated decreased mortality in patients treated early in the course of their disease compared with those treated somewhat later,\textsuperscript{13} a finding that needs to be confirmed with the newer agents in long-term studies.

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.\textsuperscript{99,90} In addition, some researchers have proposed adding no additional brain volume loss to this definition.\textsuperscript{151-153} Post-hoc analysis of several MS treatment trials has suggested that the goal of NEDA may be achievable for some individuals.\textsuperscript{90,99,105} 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.\textsuperscript{91}
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.\textsuperscript{155}

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 pretty stable for most people over the five years of the study.\textsuperscript{154} 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.\textsuperscript{157} 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.\textsuperscript{158}

Early treatment to reduce loss of mobility has been shown to help preserve people’s ability to carry out instrumental activities of daily living,\textsuperscript{159} and the ability to work was found to improve after one year of treatment with natalizumab.\textsuperscript{160}

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.”\textsuperscript{161}

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

Data suggest that benefits gained through early treatment, including conversion to clinically definite MS, relapse rates and disability, may not be equaled in those who start treatment later in the disease course,\textsuperscript{162,163,164} 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. 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.

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.\textsuperscript{165,166}

- In a review of studies looking at treatment discontinuation, the authors 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.\textsuperscript{167}

- 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.\textsuperscript{168}

- 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.\textsuperscript{169} In another study, active patients treated with interferon beta promptly returned to pre-treatment levels of disease activity following discontinuation of treatment,\textsuperscript{170} 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.\textsuperscript{171}
• Relapse rates returned to baseline following interruption of natalizumab treatment in three large studies,\textsuperscript{92} 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.\textsuperscript{73} 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 an exit strategy may risk return of disease activity or rebound, typically beginning within one to six months.\textsuperscript{74–77} 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.\textsuperscript{98}

• Cessation of fingolimod after a period of stability was followed by clinical relapse and multiple enhancing lesions on MRI in two patients,\textsuperscript{79} 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.\textsuperscript{80}

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.\textsuperscript{80,82} Three to 10 percent of adult patients retrospectively report a possible first attack prior to age 18 in childhood.\textsuperscript{83} More than 97 percent of children and adolescents experience a relapsing-remitting disease course,\textsuperscript{84} with annualized relapse rates 2–3 times that of adults with MS during the first three years of disease.\textsuperscript{84} 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.\textsuperscript{99–103}

The interferon beta medications and glatiramer acetate are generally considered the initial treatment options for children with MS.\textsuperscript{80,85} 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.\textsuperscript{86} 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.\textsuperscript{85} Several retrospective analyses regarding safety and tolerability of natalizumab support the use of natalizumab in pediatric MS patients with active disease.\textsuperscript{86–88}

The importance of evaluating therapies in the MS pediatric population has been emphasized\textsuperscript{89} 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 will inform the use of agents in children and teens with very active disease.\textsuperscript{89,90} Such trials are critical not only to provide patients and clinicians with efficacious treatments, but also to ensure safety, tolerability and appropriate dosing. It is important to note 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.

**Rationale for Access to Full Range of Treatment Options**

At the present time, 14 medications are FDA-approved to treat MS (See Table 1), with eight 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 explored and alternative options need to be considered. It is known, for example, that disease activity that occurs in spite of treatment with IFN beta is associated with unfavorable long-term outcomes. Furthermore, MRI activity as well as relapses are key indicators of progression and the presence of Gd-enhancing lesions has been shown to correlate strongly with severe disability after 15 years.

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.

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, the Phase III trials of the interferon beta medications, as well as subsequent direct comparison studies, 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. 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. 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.

In two Phase III clinical trials of natalizumab, 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. Persistent antibody positivity was also associated in both studies with a higher incidence of infusion-related adverse events, including hypersensitivity reactions.

Of the 58 percent of patients in a prospective observational study of 73 consecutive patients, 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 with contraindications need access to suitable options

For a variety of reasons (cited as contraindications in medication labeling), 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

In addition to these contraindications, post-marketing data (Avonex; Rebif; Betaseron; Extavia)\textsuperscript{16,49–51} 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.\textsuperscript{205–208}

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:

- Scalfari and colleagues found that time to Expanded Disability Status Scale (EDSS) \(3\) highly and independently predicted time to EDSS \(6, 8\) and \(10\). The same group found that higher early relapse frequencies and shorter first inter-attack intervals increased the probability of \(-\) and hastened conversion to \(-\) secondary progression, and that although long-term outcomes were highly variable, some individuals who experienced frequent relapses and/or accumulated a large number of focal lesions on T2 MRI within the first five years were at greater risk of disability.\textsuperscript{45}
- Fisniku and colleagues\textsuperscript{76} 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) \(\geq 6\) within five years of MS onset; confirmed EDSS \(\geq 6\) 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.\textsuperscript{209} 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.\textsuperscript{210}
  o EDSS of 4 within five years of onset; multiple (\(\geq 2\)) 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.
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 a therapy with a higher risk profile.

In addition, there is evidence to support the early use of natalizumab\textsuperscript{212} or mitoxantrone\textsuperscript{213–216} as induction therapy for people with early aggressive disease characterized by frequent relapses with incomplete recovery and the accumulation of focal lesions in MRI.\textsuperscript{217} However, as noted above, several investigations looking at treatment interruption with natalizumab found an increase in clinical and/or MRI activity.\textsuperscript{172,173,178}

- **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.\textsuperscript{218} 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.\textsuperscript{219} 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.\textsuperscript{220} More than one study has shown increased lesion volumes in African Americans,\textsuperscript{211,222} with one also showing more tissue damage.\textsuperscript{221} Given that there are also preliminary indications that African-Americans may not respond as well to the available disease-modifying therapies,\textsuperscript{223,224} 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 mentioned above, 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.\textsuperscript{225} People who do not adhere to their treatment regimen are unlikely to receive the full benefit of the treatment.\textsuperscript{226,227} Factors associated with non-adherence include:
  - Perceived lack of efficacy in relation to expectations\textsuperscript{227,228}
  - Route of administration\textsuperscript{229,230}
  - Perceived risks\textsuperscript{228,229,232}
  - Tolerability issues with self-injectable medications, including flu-like symptoms and injection-site reactions\textsuperscript{231–236}
  - Length of time on treatment\textsuperscript{232}
  - Costs\textsuperscript{237}
  - Psychosocial factors, including coping style, mood\textsuperscript{238,239} and “forgetting.”\textsuperscript{232,235,236}

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

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

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

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

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 1,000 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

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 (MSF)
The MSF’s mission is to provide nationally accessible programs and services, to those affected by MS, which in turn, helps them maintain their health, safety, self-sufficiency, and personal well-being. We strive to heighten public awareness of MS in order to elicit financial support while promoting understanding for those diagnosed.

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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