

# International Journal of **MS**CARE

The Official Publication of the Consortium of Multiple Sclerosis Centers



## Risk-Benefit Analysis and Personalized Treatment in Multiple Sclerosis

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This supplement is supported by educational grants from Biogen,  
Novartis Pharmaceuticals Corporation, and Sanofi Genzyme.

Release Date: October 10, 2018 • Expiration Date: October 10, 2019

Estimated time to complete this activity is 1.0 hours.



# Risk-Benefit Analysis and Personalized Treatment in Multiple Sclerosis

## Basing Treatment Goals on the Latest Evidence

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### PROGRAM OVERVIEW/STATEMENT OF NEED

In the last decade, there have been significant advances in the treatment of multiple sclerosis (MS) and newer disease-modifying therapies (DMTs) can provide control of disease activity in many patients, especially when more aggressive treatment is started early in appropriate patients. There is good evidence to support the new treatment outcome of “no evidence of disease activity” (NEDA) based on an absence of relapses, no sustained progression on EDSS disability score, and no new or enlarging lesions on MRI.

With more than a dozen approved first-line therapies, initial treatment selection can be complicated by risk/benefit, efficacy, and long- and short-term safety profiles. There are evidence-based benefits with aggressive, early treatment regimens, so clinicians must make the optimal initial treatment choice. *Risk-Benefit Analysis and Personalized Treatment in Multiple Sclerosis: Basing Treatment Goals on the Latest Evidence* will provide participants with the most up-to-date evidence on current and emerging MS therapies and treatment goals, as well as treatment strategies to achieve those goals.

### TARGET AUDIENCE

This activity is intended for MS specialists, neurologists, nurses, and other healthcare professionals who manage patients with MS.

### EDUCATIONAL OBJECTIVES

This program is designed to address the following IOM competencies: provide patient-centered care and employ evidence-based practice.

At the conclusion of this activity, participants should be able to demonstrate the ability to:

- Describe the benefits of starting an optimal DMT early to achieve the new treatment goal of “no evidence of disease activity” (NEDA)

- Evaluate the short-and long-term safety, tolerability, immunologic profiles, and efficacy of available DMTs for MS
- Apply knowledge of the benefits and risks of available DMTs to select an optimal personalized MS treatment.

### JOINT PROVIDER STATEMENT



JOINT ACCREDITATION  
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# Risk-Benefit Analysis and Personalized Treatment in Multiple Sclerosis

## Basing Treatment Goals on the Latest Evidence

*Multiple sclerosis (MS) is a complex immune-mediated disorder. MS phenotypes are now better defined with recognition of pre and early disease clinical courses. They are better characterized through the use of improved clinical descriptive terminology, objective MRI and other imaging findings, and analyses of biological and surrogate biomarkers. Emerging treatment principles include initiation of treatment early to minimize the risk of patients developing progressive disease and establishing treat-to-target goals such as the composite measures of no evidence of disease activity (NEDA) and minimal evidence of disease activity (MEDA). There are numerous disease modifying therapies (DMTs) available to optimize treatment of MS. They have differing mechanisms of action and safety/tolerability profiles. Therapy selection is a shared decision-making process with patients based on discussions of the benefits of a treatment and its risk and monitoring requirements. Selected DMTs are discussed with respect to the latest evidence regarding risk-benefit considerations, early initiation of treatment, and strategies for initial selection of and switching between DMTs.*

**M**ultiple sclerosis (MS) is the major acquired central nervous system (CNS) disease of young adults, aside from trauma.<sup>1</sup> It predominantly affects women (3:1), a trend that may be increasing particularly in women over 50 years of age.<sup>2</sup> While it is more common in Caucasians, MS affects all ethnic groups.<sup>1</sup> The onset of MS occurs at a young age: 90% present between the ages of 15 and 50 years. Individuals with MS can experience significant morbidity (motor, cognitive, vocational) if their disease is untreated. The lifespan of persons with MS is shortened by 6 to 8 years, due to secondary complications of disability, brainstem involvement, and suicide. A large retrospective analysis that compared median survival from birth in patients with MS with a control population matched for sex, year of birth, and region found that comorbidity was associated with an increased mortality risk in patients with MS.<sup>3</sup> The analysis showed a 2-fold increased risk of death, and the median survival from birth was 75.9 years vs 83.4 years for MS patients vs controls.

### CLINICAL COURSE OF MULTIPLE SCLEROSIS

The clinical courses (phenotypes) of MS were first defined and characterized in 1996 and modified in 2013 by the US National Multiple Sclerosis Society Advisory Committee on Clinical Trials in Multiple Sclerosis.<sup>4</sup> One of the goals for the revision was to better characterize core MS phenotypes by including improved clinical descriptive terminology, objective MRI and other imaging findings, and analyses of biological and surrogate biomarkers. Figures 1 and 2 illustrate the progress that has been made in linking objective clinical findings with the course of MS and the resulting changes in the characterization of MS phenotypes.<sup>4</sup> As the figures illustrate, assessments of the clinical phenotype rely on the patient's current status and historical data, and since MS is a dynamic disease, the subtype may change over time. The revision also included recognition of two new disease courses, clinically isolated syndrome (CIS) and radiologically isolated syndrome (RIS).<sup>4</sup> CIS is a first attack that exhibits characteristics that could be MS but does not yet fulfill criteria of dissemination. It is classified as



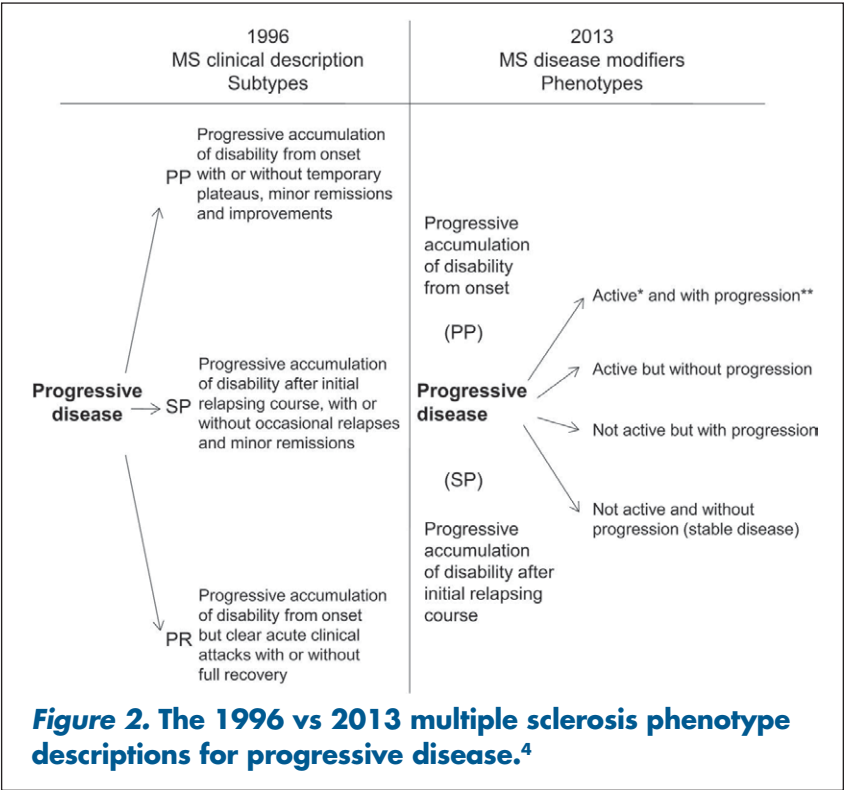
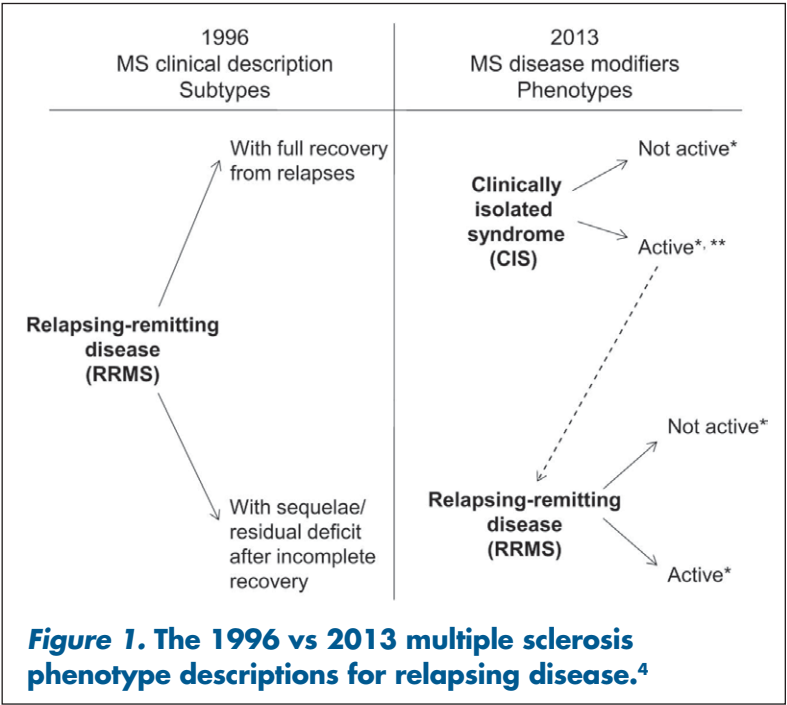
either high risk if the MRI shows otherwise unexplained brain lesions or low risk if the brain MRI is normal. Although not yet considered an MS phenotype as there is no clinical evidence of demyelinating disease, RIS may represent silent or pre-symptomatic MS. It is characterized by incidental abnormal brain imaging findings without any clinical signs or symptoms of MS.

As Figure 1 illustrates, if CIS becomes active and fulfills MS diagnostic criteria, it then becomes relapsing-remitting disease (RRMS), which is the principal initial presentation for MS.<sup>4</sup> Figure 2 illustrates the progressive subphenotypes of MS. Primary progressive MS (PPMS) affects a small percentage of MS patients (10% to 15%), has an older age of onset, affects men and women equally, and is characterized by gradual worsening of disease from onset—progressive accumulation of disability. Secondary progressive MS (SPMS) is characterized by progressive accumulation of disability after an initial relapsing course and is often diagnosed retrospectively based on history. All patients with RRMS are at risk of developing progressive disease, particularly in midlife.

In addition to identifying the core phenotypes of MS, the group defined two terms that better serve as descriptors of the clinical course of MS over a given time period by using objective findings rather than subjective views of MS.<sup>4</sup> The first is active/not active over the last year and covers all phenotypes. Activity is determined by clinical relapse and/or new MRI activity, which may be contrast-enhancing lesions and/or new or unequivocally enlarging T2 lesions. The second is progressing/not progressing, which refers only to the progressive phenotypes, is measured by clinical evaluation (no MRI measure) and can be assessed at least yearly. If the neurological examina-

tion shows that MS is stable, the patient is classified as not progressing (stable disease). Thus, the clinical descriptors for patients with MS are active/not active or progressing/not progressing.

As a complex immune-mediated disease, genetic variants of MS have been studied in an effort to deter-



mine susceptibility to the disease and clinical outcomes. Endophenotypes of MS include the at-risk population, which may be a genetically defined subset of the population. The at-risk population may develop RIS. There appears to be a poorly understood prodromal period that lasts 5 to 10 years.<sup>5</sup> The person may be declared as having MS when they experience a CIS as the first relapse of their relapsing disease, or gradually progressive disease. Recent studies examined the existence of prodromal MS. Findings from a matched cohort study (14,428 MS cases, 72,059 matched controls) using data from health administrative and clinical databases from four Canadian provinces suggested the existence of a measurable MS prodromal period based on healthcare usage patterns: hospital admissions, physician visits/claims, and prescriptions, increased steadily between 5 years and 1 year before the first demyelinating disease claim in patients with MS compared with controls.<sup>6</sup>

A Norwegian nested case-control study of conscription examinations at age 18/19 years of men born between 1950 and 1995 linked their cognitive performance to the MS registry to identify those who later developed MS (n= 924). Selected controls were frequency-matched on year of birth from the Norwegian Conscript Service database (n=19,530).<sup>7</sup> The study found that men who developed relapsing MS symptoms up to 2 years following their cognitive assessment had significantly lower cognition scores compared with controls as did men who developed PPMS up to 20 years after their assessment, suggesting that cognitive problems may be present before apparent symptoms of MS. A second nested case-control study using the same Norwegian population-based database and MS registry found that a body mass index  $\geq 25$  was significantly associated with an increased risk of MS in men and that exercise may be a modifiable protective factor for MS.<sup>8</sup> The prodromal period for MS requires additional study to better characterize it and to recognize the progression to clinical MS.

## EMERGING TREATMENT PRINCIPLES

The natural history of MS is that it begins as CIS-relapsing disease in the majority of patients, and if left untreated, relapsing MS can transition to SPMS.<sup>1</sup> Patients who enter into the progressive neurodegenerative stages of MS have gradual worsening leading to inevitable disability. The goal is to minimize the risk of patients developing progressive disease by initiating

treatment early. Organ-specific immune mediated diseases show a window of opportunity to minimize damage by limiting epitope spread and ongoing accumulating permanent central nervous system (CNS) damage. Since virtually all studies report better results with early versus delayed initiation of therapy, current guidelines recommend treating CIS/high-risk patients, MS patients who have had their first attack, and patients with active-relapsing MS.<sup>1</sup> They also recommend that physicians consider treating patients with active SPMS and PPMS.

The benefit of early treatment has been shown in rheumatoid arthritis. A meta-analysis of 18 randomized controlled trials that reported outcome data in early rheumatoid arthritis in relation to symptom duration at treatment initiation found a strong independent association between disease-modifying anti-rheumatic drug-free remission and symptom duration and radiographic progression.<sup>9</sup> Treatment guidelines for rheumatoid arthritis endorse early therapy (disease duration  $\leq 6$  months), treat to target, and reassess every 3 months.<sup>10</sup> As in rheumatoid arthritis, evidence supports early treatment of MS. A Swedish retrospective observational study of MS Registry patients (n=2,477) treated between 2002 and 2012 showed that patients who started therapy within 6 months after onset had a 36% lower risk of requiring a full-time disability pension compared with patients who started treated 18 months after onset.<sup>11</sup>

Emerging treatment principles in MS based on lessons learned with rheumatoid arthritis are summarized in Table 1.<sup>12</sup> A wellness program may be considered a disease-modifying therapy for MS, as increasing evidence shows that maintaining health favorably changes and/or improves CNS reserve, function, and repair. Components of a wellness program are listed in Table 2.

## Treat-To-Target Goals

The treat-to-target goal is a newer treatment principle in MS. A treat-to-target goal in MS is no evidence of disease activity (NEDA), which is a composite measure defined as an absence of relapses, sustained Expanded Disability Status Scale (EDSS) score worsening, and new or enlarging T2 or T1 gadolinium-enhancing lesions on an annual MRI.<sup>13-15</sup> Cumulative NEDA scores are more important than an annual score for a treat-to-target goal. However, a limitation of NEDA is that it does not address microscopic injury



**Table 1. Emerging treatment principles in multiple sclerosis<sup>12</sup>**

- Treat early—within 3 to 6 months of evidence of a clinically isolated syndrome with high-risk for MS
- Treat young—treatment at a younger age may offer maximum response to disease-modifying therapies
- Use shared decision-making
- Use a treat-to-target approach—minimal to no evident disease activity
- Identify and manage comorbidities
- Emphasize wellness—help preserve CNS and brain health
- Analyze disease activity (clinical and MRI measures) and prognostic profile
- Follow closely (clinically and brain surveillance MRI) after initiating treatment
  - MRI: at 3 to 6 and 12 months, then every 12 to 24 months
  - More frequent monitoring of high-risk PML patients: every 3 to 6 months
- Switch therapy—consider if  $\geq 1$  attack,  $\geq 2$  new MRI lesions, or disability over 1 year on treatment

Abbreviations: ARR = annualized relapse rate; CNS = central nervous system; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy.

**Table 2. Wellness/health maintenance program**

- High normal vitamin D levels and vitamin B12  $>400$
- Regular aerobic exercise, optimum body mass index (BMI)/body weight
- No smoking, limited alcohol and salt intake, healthy diet
- Regular mental and social stimulation
- Good sleep hygiene
- Manage stress
- Monitor blood pressure, lipid levels, hemoglobin A1C, bone density, prostate health

or activity biomarkers,<sup>14,15</sup> such as with diffusion tensor imaging atrophy or neurofilament light protein.<sup>16</sup> The persistence of NEDA over time was evaluated in 219 patients from the CLIMB cohort study who had an initial diagnosis of CIS or RRMS and a minimum of 7 years of prospective follow-up.<sup>14</sup> The investigators found that 46% of patients met NEDA at year 1, but only 7.9% maintained NEDA status after 7 years. Meeting NEDA at 2 years had a positive predictive value of 78.3% for no progression as measured by the EDSS at year 7. However, another prospective study of 517 MS patients found that NEDA by clinical and MRI criteria at year 2 did not predict long-term (10-year) outcomes.<sup>15</sup>

Blood brain barrier permeability in normal-appearing white matter, as measured by dynamic contrast-enhanced MRI imaging, was studied as a predictor of NEDA in 35 relapsing MS patients treated with either fingolimod or natalizumab.<sup>17</sup> A single determination of blood brain barrier permeability measured by calculating the influx constant  $K_i$  performed 6 months after initiating treatment predicted NEDA failure at 2 years. Those patients who lost NEDA at 2 years had a 51% increase in mean  $K_i$  compared with those who maintained NEDA ( $P < 0.002$ ). The threshold value of  $K_i$  in normal-appearing white matter for detecting NEDA loss was 0.136 mL/100 g/min, which yielded an odds ratio of 12.4 for loss of NEDA at 2 years. This study suggests that blood brain barrier permeability may be a reliable predictor of suboptimal response and that there may be a predictive threshold for disease activity.

NEDA-4 adds the criterion of annual brain volume loss of 0.4%, making it a more comprehensive assessment of disease activity, worsening disease, and structural damage.<sup>18</sup> Several other parameters not addressed in either NEDA or NEDA-4 proposed for future updates are cognition, vision, patient-reported outcomes, quality of life, and biomarkers such as neurofilament light protein. The corollary to NEDA for progressive disease is NEPAD or no evidence of progression or active disease, which includes no confirmed (12-week) worsening on the EDSS score, and 25-foot timed walk (by 20% or more), no worsening on the 9-hole peg test (by 20% or more), no relapses, and no new MRI lesions. These treat-to-target goals may set too high a bar for clinical practice.

A more realistic treat-to-target goal may be minimal evidence of disease activity (MEDA), which allows for some breakthrough activity. A recent longitudinal study based on two cohorts of RRMS patients treated with interferon- $\beta$  ( $n=516$ ), however, reported disappointing results as neither MEDA nor NEDA predicted long-term disability.<sup>19</sup> In the study, MEDA was defined as  $<3$  new T2 lesions, or  $<2$  contrast-enhancing lesions, or 1 relapse with 0 or 1 to 2 new T2 lesions. While MEDA may be more practical clinically, criteria to define MEDA will need to be identified.

## DISEASE-MODIFYING THERAPIES FOR MULTIPLE SCLEROSIS

Over the last 25 years, the number of treatments for MS has expanded greatly, and several more are in

development [Figure 3]. The consensus now is to initiate treatment early to minimize disease activity and disability, including in patients with CIS to reduce the percentage of patients who convert to MS over the 2 years following diagnosis.<sup>1</sup> Comparative information for selected disease-modifying therapies (DMT) approved for the treatment of MS are summarized in Table 3 and discussed below.

### Injectable Therapies

Interferon  $\beta$ , a naturally occurring polypeptide primarily produced by fibroblasts, is one of the first treatments for MS and has an established efficacy and safety profile,<sup>20-22</sup> including in patients with CIS.<sup>23</sup> The exact mechanism of action of interferon  $\beta$  is unknown, but appears to have several immunological effects.<sup>24,25</sup> Among its effects are increased production of anti-inflammatory cytokines, decreased production of pro-inflammatory cytokines, increased T suppressor cell activity, limited migration of T cells into the CNS, decreased monocyte activation and MHC-2 expression. Interferon  $\beta$  also has antiviral activity.

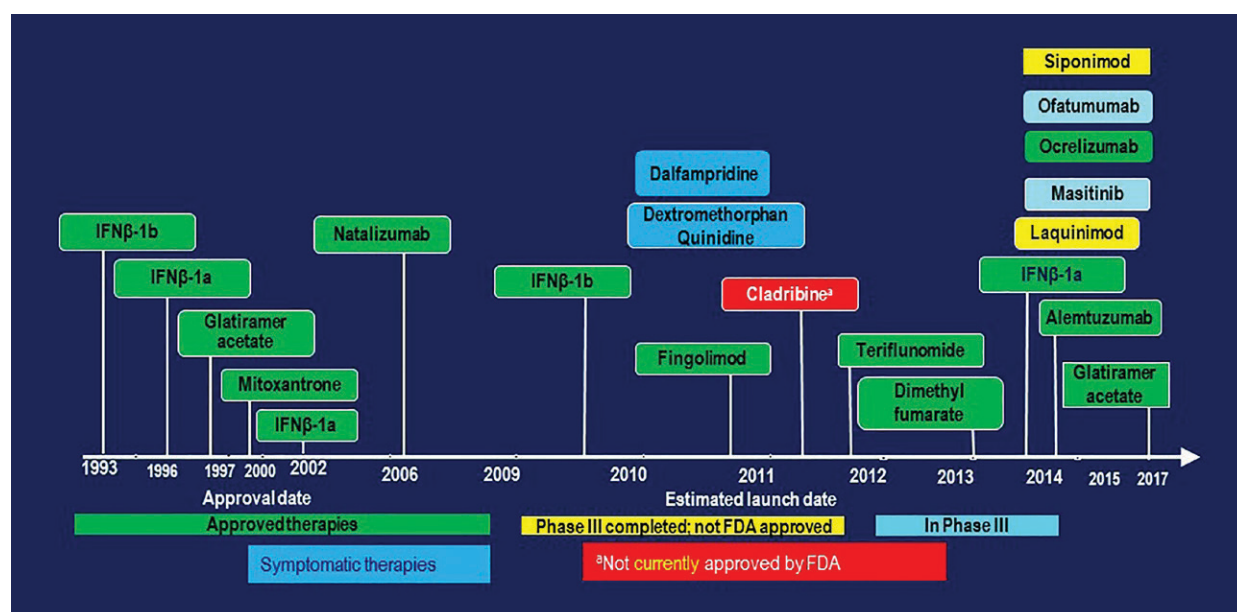
Glatiramer acetate, a copolymer comprised of a random mix of glutamic acid, lysine, arginine, and tyrosine, is another injectable drug with lengthy experience in the treatment of MS. It is well tolerated and has the most favorable pregnancy data.<sup>24-26</sup> Similar to interferon  $\beta$ , its exact mechanism of action is unknown but

is probably multifocal. It is thought to increase CD4+ and CD8+ T-regulatory cells, increase expression of anti-inflammatory cytokines, promote regulatory B cells, and alter antigen-presenting cells by binding HLA class II molecules and diminishing CD40 expression on dendritic cells. This correlates inversely with MS relapse activity. It also may alter the CNS milieu through bystander suppression and may increase brain-derived neurotrophic factor. In head-to-head clinical trials, glatiramer and interferon  $\beta$  demonstrated comparable clinical efficacy, including percent of patients free from relapse, and annualized relapse rates, [Figure 4] as well as the number of and change in volume of T2 active lesions.<sup>27,28</sup> In the CombiRx study, no efficacy advantage was noted for the combination of glatiramer and interferon  $\beta$ .<sup>28</sup>

### Oral Therapies

#### Fingolimod

Fingolimod, introduced in 2010, was the first oral treatment for MS with demonstrated efficacy.<sup>24,25</sup> Its mechanism of action is not completely understood. Fingolimod is an oral sphingosine 1-phosphate (S1P) receptor modulator that binds in particular to S1P 1, and to a lesser extent to S1P receptors 3, 4, or 5, after phosphorylation. Binding to S1P-1 on lymphocytes subsequently leads to internalization and degradation of the receptor. Loss of this surface receptor blocks



**Figure 3. Existing and emerging MS therapies 2018.**

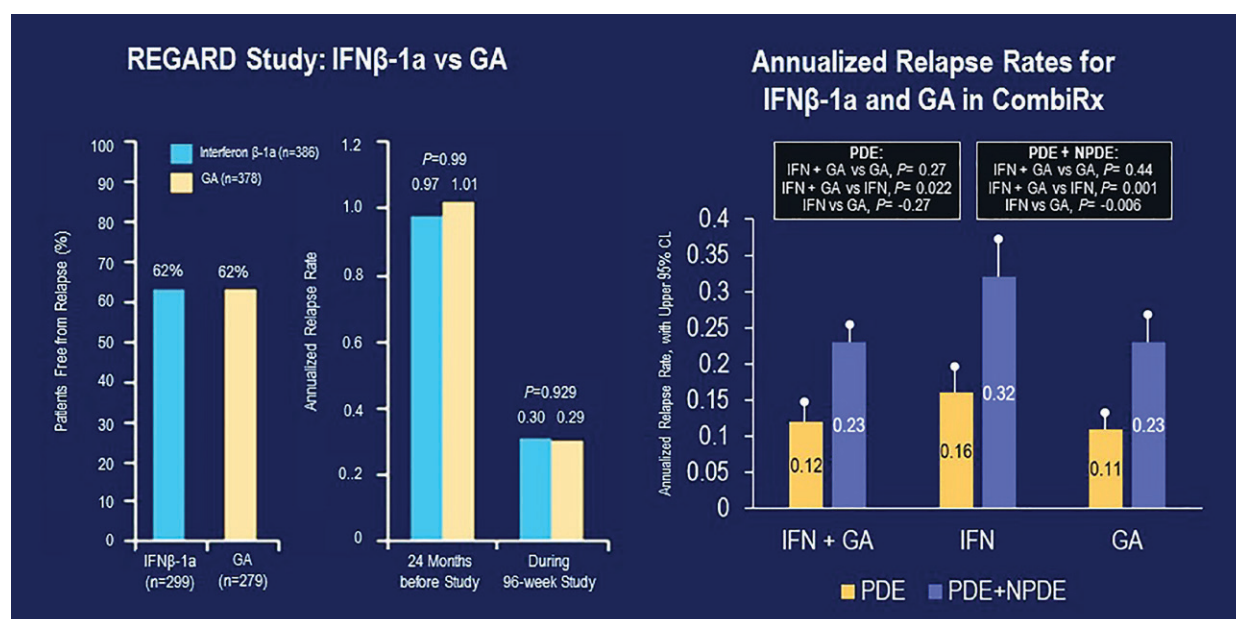
**Table 3. Comparison of established treatments for multiple sclerosis.**<sup>24,25,41,42,44,46,47</sup>

Drug	Dosage Regimens	Outcomes	Safety Profile	Monitoring Parameters
Interferon $\beta$ -1a	30 $\mu$ g IM weekly	30%-36% reduction	Flu-like symptoms,	hepatic enzymes,
	22 & 44 $\mu$ g SC 3X weekly	ARR in RMS; reduced risk of CIS progression;	injection site rxns,	CBC with differential,
	125 $\mu$ g SC Q2 weeks 250 $\mu$ g SC QOD (IFN $\beta$ -1b)	decreased new MRI lesions	depression, menstrual irregularities, micro-angiography (rare)	thyroid-stimulating hormone
Glatiramer Acetate	20 mg SC daily	29% -34% reduction	Well tolerated;	None
	40 mg SC 3X weekly	ARR in RMS; decreased new MRI lesions	injection site rxns; immediate, self-limiting systemic rxns	
<b>Oral Therapies</b>				
Fingolimod	0.5 mg PO daily	48%-55% reduction ARR in RMS; reduced rates of disability progression, new MRI lesions, rate of volume loss	Respiratory tract infections, headache, cough, diarrhea, back pain, transient bradycardia & AV block	ECG, avoid use in CVD, hepatic enzymes, eye exams, varicella zoster infection screening
Teriflunomide	7 mg PO daily	31% reduction ARR RMS; 31% reduction 3-month disability worsening; benefit maintained at 9 years	Infection, alopecia, diarrhea, paresthesia, increase in hepatic enzymes, decrease in lymphocytes & platelets, teratogenic	Hepatic enzymes, CBC and platelets, blood pressure, negative pregnancy test
	14 mg PO daily (preferred dose)			
Dimethyl Fumarate	240 mg BID	44%-53% reduction ARR at 2 years; 38% risk reduction 3-month disability worsening	Flushing, abdominal pain, diarrhea, increase in hepatic enzymes, decrease in lymphocytes, lymphopenia	Hepatic enzymes, CBC
<b>Recombinant Humanized Monoclonal Antibody Therapies</b>				
Natalizumab	300 mg IV Q4 weeks 68% reduction	Versus Placebo: Increased risk PML; ARR; 54% reduction in rate of disability progression; 90% reduction in MRI enhancing lesions	headache, fatigue test initially & Q6 increased risk of infections & rebound	anti-JCV antibody months during treatment
Alemtuzumab	12 mg/d x 5 days IV, followed in 12 months by 12 mg/d x 3 days IV	Versus IFN $\beta$ -1a: 49%-55% reduction ARR; 30%-42% reduction in rate of disability progression; 62% reduction in MRI enhancing lesions	headache, diarrhea, flu-like symptoms, Infusion-related rxns; increased risk of infections & autoimmune-mediated conditions	Monthly CBC & urine analyses for antibody formation for 4 years post last dose; thyroid function testing quarterly; annual skin exams

**Table 3. Comparison of established treatments for multiple sclerosis.**<sup>24,25,41,42,44,46,47</sup>

Drug	Dosage Regimens	Outcomes	Safety Profile	Monitoring Parameters
Ocrelizumab	300 mg IV days 1 & 15, followed every 6 months by 600 mg IV	Versus IFN $\beta$ -1a (RMS): 46% reduction ARR at 96 weeks; 40% reduction in 12- & 24-week confirmed disability progression; 95% reduction in T1 MRI enhancing lesions; 77%-83% reduction in new or enlarging T2 lesions Versus Placebo (PPMS): 24% & 25% reduction in time to sustained disability progression $\geq 12$ weeks & $\geq 24$ weeks; 34% relative reduction in volume of hyperintense T2 lesions; 17.5% relative reduction in whole brain volume loss; 29% reduction in change in timed 25-foot walk test	Well tolerated; infusion-related rxns, increased risk of infections & possibly neoplasms	

Abbreviations: ARR = annualized relapse rate; BID = two times daily; CBC = complete blood count; CIS = clinically isolated syndrome; CVD = cardiovascular disease; IM = intramuscular; ECG = electrocardiogram; IFN $\beta$  = interferon  $\beta$ ; JCV = Johnson Cunningham virus; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy; PPMS = primary progressive multiple sclerosis; PO = by mouth; Q = every; QOD = every other day; RMS = relapsing multiple sclerosis; rxns = reactions; SC = subcutaneous.

**Figure 4. Head-to-head trials show no differences in clinical efficacy between interferon  $\beta$  (IFN $\beta$ ) and glatiramer acetate (GA).**<sup>27,28</sup>

GA = glatiramer acetate; PDE = protocol-defined exacerbation; NPDE = non-protocol-defined exacerbation



lymphocyte egress from lymph nodes into the blood. There are S1P receptors on neurons and glial cells as well, which may contribute to a fingolimod effect within the CNS.

Compared with placebo, fingolimod reduced the risk of relapse by 52% in RMS and reduced the risk of sustained disability worsening at 24 weeks by 37%.<sup>29</sup> Reductions in mean number of new or increasing T2 lesions, T1 lesion volume, and brain volume loss were noted for fingolimod. Similar robust results favoring fingolimod were observed in a comparative trial with interferon  $\beta$ .<sup>30</sup> Although fingolimod is generally well tolerated, there are several safety and tolerability considerations because of its mechanism of action.<sup>24,25,29,30</sup>

It should be used with caution in patients with cardiovascular disease, respiratory disease, and diabetes. Fingolimod requires monitoring for 6 hours following the first dose, with hourly vital signs and an electrocardiogram at the beginning and end of the monitoring period to rule out bradycardia or heart block. Live virus vaccinations should be avoided. Fingolimod may cause macular edema, respiratory and herpetic infections, may reduce pulmonary function, and can be hepatotoxic. Other serious adverse effects reported with fingolimod are progressive multifocal leukoencephalopathy (PML), cryptococcal infections, and skin cancers. These effects may be more prevalent at doses higher than the recommended dose of 0.5 mg daily. There are reports of tumefactive MS and demyelination in patients treated with fingolimod,<sup>31,32</sup> and a minority may develop a rebound syndrome following discontinuation of the drug.<sup>33</sup>

### ***Teriflunomide***

Teriflunomide, a metabolite of leflunomide that is used to treat rheumatoid arthritis, is another oral drug with demonstrated efficacy in MS.<sup>24,25</sup> The mechanism of action of teriflunomide in MS is not known. It is an immunomodulatory agent that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase, which is the rate-limiting enzyme in the de novo pyrimidine synthesis pathway. This pathway is used by rapidly dividing cells. The salvage pyrimidine pathway is spared. By inhibiting pyrimidine synthesis and reducing DNA synthesis, teriflunomide has a cytostatic effect on proliferating lymphocytes. It also may interfere with the interaction between T cells and antigen-presenting cells resulting

in decreased T-cell activation, which is important in the immune response.

The efficacy of teriflunomide is comparable to injectable therapies for MS and was sustained over 9 years of follow-up with no new safety concerns identified.<sup>34,35</sup> The relapse rate was reduced by 31%, and the risk of 3-month disability worsening was reduced by 30%. Among the adverse effects reported in clinical studies were hair thinning (which is usually transient over the first 6 months), gastrointestinal pain, diarrhea, elevated hepatic enzymes, peripheral neuropathy, and hypertension. Teriflunomide is teratogenic in animal models; patients should use effective birth control. Teriflunomide has a long half-life, but elimination from the body may be accelerated by an 11-day course of cholestyramine or activated charcoal.<sup>25</sup> Blood levels can be followed to document they are <0.02 mcg/mL.

### ***Dimethyl fumarate***

A third oral drug for the treatment of MS is dimethyl fumarate, an immunomodulatory agent with anti-inflammatory properties, that is metabolized to an active form, monomethyl fumarate.<sup>24,25</sup> Among its anti-inflammatory effects are down regulation of proinflammatory cytokines and infiltration of inflammatory cells into the CNS, neuroprotective effects via induction of Nrf-2-mediated anti-oxidative pathways, and inhibition of endothelial expression of ICAM-1, VCM-1, and E-selectin.<sup>24,25,36,37</sup> Dosed twice daily, dimethyl fumarate has demonstrated efficacy in reducing MS relapses, risk of disability worsening, and new MRI lesions compared with placebo and glatiramer acetate.<sup>38,39</sup> It is generally well tolerated with initial adverse effects being transient. Lymphopenia, which may be significant, occurs in a minority of those taking dimethyl fumarate. Although the occurrence of PML is uncommon, lymphocyte counts should be monitored closely when they reach 800 or below.

## **Recombinant Humanized Monoclonal Antibody Therapies**

### ***Natalizumab***

Natalizumab is a recombinant humanized monoclonal antibody administered intravenously every 4 weeks.<sup>24,25</sup> It selectively binds to  $\alpha 4\beta 1$  integrins expressed on the surface of all white blood cells except neutrophils, inhibiting adhesion of activated lymphocytes to vascular cell adhesion molecule-1 (VCAM-1)



on endothelial cells and their subsequent migration into the CNS. Natalizumab also increases the number of circulating CD34+ progenitor cells by interfering with homing to bone marrow. The CD4+/DC8+ ratio may be reduced with long-term treatment.

Compared with placebo, the relative risk reduction in the annualized relapse rate with natalizumab was 68% and the reduction of risk on EDSS disability worsening at 12 weeks was 42% in patients with RMS.<sup>40</sup> Natalizumab is generally well tolerated, but it is associated with an increased risk of infections, such as CNS herpes virus infections. The most serious risk associated with natalizumab is PML, a potentially life-threatening opportunistic CNS infection caused by the papovavirus JC virus.<sup>24,25</sup> Risk factors for PML include a positive anti-JCV virus antibody test with elevated antibody index, prior use of immunosuppressants, and >24 months of natalizumab therapy. The risk of PML increases by 20-fold if all 3 risk factors are present compared with having only a positive anti-JCV antibody titer, and by >100-fold compared with a negative anti-JCV antibody titer. Patients should be tested for anti-JCV antibodies before starting natalizumab therapy and retested every 3 to 6 months during therapy as seroconversion may occur at any time in patients who initially tested negative. Natalizumab also may cause hypersensitivity reactions with the formation of neutralizing antibodies, which are associated with a higher rate of infusion-related reactions, as well as breakthrough activity. Natalizumab must be stopped if there are persistent neutralizing antibodies; there is a risk of rebound in a minority of patients following natalizumab discontinuation.

### ***Alemtuzumab***

Alemtuzumab, administered by intravenous infusion, is a recombinant, humanized monoclonal antibody that targets the CD52 cell surface antigen expressed on B and T lymphocytes.<sup>24,25</sup> The mechanism of action of alemtuzumab in MS is thought to be due to depletion and repopulation of lymphocytes, which reduces the potential for relapses and disease-related disability. The depletion of T cells is long lasting with recovery approaching the lower limit of normal 12 months after alemtuzumab treatment, while B cells recover within 6 months. The slower recovery

of T cells may contribute to autoimmune phenomena associated with alemtuzumab.<sup>41,42</sup>

A comparative study in patients with RRMS who were naive to DMT showed a 55% decrease in the annualized relapse rate with alemtuzumab versus interferon  $\beta$ -1a; 77.6% versus 58.7% of patients, respectively, were relapse free at 2 years.<sup>41</sup> The rate of confirmed EDSS disability was low and similar with both drugs, as was the reduction in new or increasing T2 and contrast-enhancing T1 lesions on MRI and the reduction in brain volume loss. A second comparative study in patients with breakthrough RRMS on previous DMT also showed more favorable results for alemtuzumab versus interferon  $\beta$ -1a: 49% decrease in the annualized relapse rate; 65.4% versus 46.7% of patients relapse free at 2 years; 22% versus 9% reduction in confirmed EDSS disability over 6 months.<sup>42</sup> Both drugs were associated with reductions in new or increasing T2 and contrast-enhancing T1 lesions on MRI and in brain volume loss. In an observational cohort study of 87 patients at one clinical site, most of whom (52%) received the two planned alemtuzumab treatment cycles, and were followed for a median of 7 years, there was a 59.8% overall improvement in or stabilization of disability over the follow-up period.<sup>43</sup>

Tolerability concerns with alemtuzumab include infusion reactions requiring premedication, headache, dizziness, paraesthesias, arthralgia, fatigue, and gastrointestinal symptoms.<sup>24,25,41,42,44</sup> The primary safety concern with alemtuzumab is secondary autoimmunity which may occur in up to 47.7% of treated patients. It most commonly affects the thyroid gland (39%) and less commonly manifests as idiopathic thrombocytopenia purpura (2%) or glomerular nephropathy (0.2%). Other safety issues include increased risk of infections, (including herpes virus infections that are treated prophylactically with antiviral medications), increased risk of malignancies (eg, thyroid, melanoma, lymphoproliferative), and infrequently acute acalculous cholecystitis and hemophagocytic lymphohistiocytosis. Long-term safety data (up to 12 years) are consistent with that in clinical trials, with secondary autoimmunity the most frequently reported adverse effect.<sup>43,44</sup> Because of the risk of autoimmune disorders, there is a 4-year risk evaluation and mitigation strategies (REMS) program for alemtuzumab with defined monitoring parameters [Table 3].

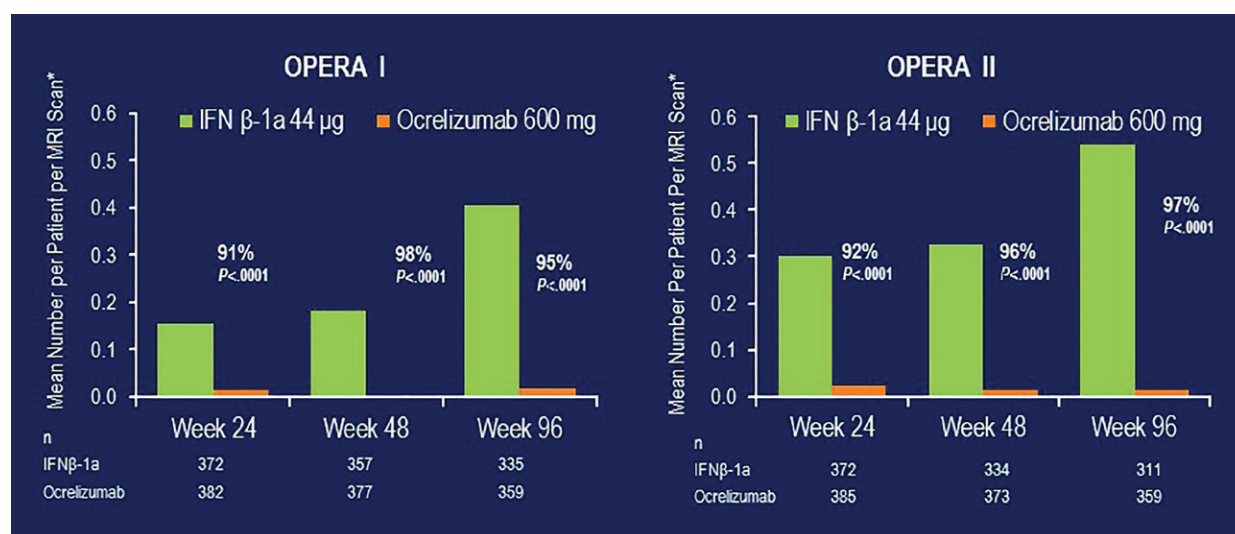
## Ocrelizumab

Ocrelizumab is the newest humanized, recombinant monoclonal antibody that targets CD20, which is widely expressed on mature B cells. Ocrelizumab results in circulating B cell depletion.<sup>24,45</sup> It does not bind to stem cells or plasma cells, thereby preserving these aspects of immune function. Ocrelizumab is administered intravenously every 6 months and has been studied in RMS compared with interferon  $\beta$ -1a (OPERA I and II) and PPMS compared with placebo (ORATORIO).<sup>46,47</sup>

Outcomes in RMS patients treated with ocrelizumab were robust compared with interferon  $\beta$ -1a: at 96 weeks the annualized relapse rate was 46% lower with ocrelizumab, and the confirmed disability worsening at 12- and 24-weeks was reduced by 40%, while a pooled analysis showed a 33% higher rate of improvement in disability at 12 weeks.<sup>46</sup> For the MRI-related endpoints, the number of T1 gadolinium-enhancing lesions per T<sub>1</sub>-weighted MRI scan was 95% lower with ocrelizumab [Figure 5].<sup>46</sup> The trial of ocrelizumab in patients with PPMS was the first to show a benefit in slowing disability progression in this patient population compared with placebo: relative risk reductions in time to confirmed disability progression was 24% at 12 weeks and 25% at 24 weeks, and the relative

reduction in the mean change in performance on the timed 25-foot walk at week 120 was 29.3%.<sup>47</sup> Brain MRI endpoints also showed favorable changes with ocrelizumab, particularly in patients who had active gadolinium-enhancing MRI lesions at baseline—35% reduction in risk.

Overall, ocrelizumab is well tolerated: the percentage of patients reporting adverse events with ocrelizumab was similar to those reported for interferon  $\beta$ -1a and placebo in comparative trials.<sup>46,47</sup> Infusion-related reactions and infections (upper respiratory tract, nasopharyngitis, and urinary tract) are the most commonly reported adverse events. The number of cases of neoplasms was higher with ocrelizumab than with interferon  $\beta$ -1a or placebo in the clinical trials. An analysis of the overall rate of first neoplasm among ocrelizumab-treated MS patients was 0.40 per 100 patient-years of exposure compared with 0.20 per 100 patient-years of exposure in the pooled comparator groups. This imbalance in the occurrence of neoplasms warrants continued evaluation. Other remaining questions with this newest monoclonal antibody DMT are which patients are the most appropriate candidates, is there greater benefit in men than in women, its use in older patients with possible immunosenescence, and the long-term safety of B cell depletion.



**Figure 5. Reduction in mean gadolinium-enhancing lesions in patients with relapsing MS treated with ocrelizumab compared with IFN $\beta$ -1a.<sup>46</sup>**

\*Adjusted by means calculated by negative binomial regression and adjusted for baseline T1 Gd lesion (present or not), baseline EDSS (<4.0 vs  $\geq$ 4.0) and geographical region (US vs ROW [Rest of World]). INF = interferon; Gd+ = gadolinium enhancing

## BALANCING RISK AND BENEFITS OF TREATMENT

### Case Presentation

CC is a 28-year-old single female accountant who presents with an internuclear ophthalmoplegia. Brain MRI shows a 3 mm enhancing pontine lesion. In addition, there are two non-enhancing lesions, periventricular and juxtacortical. Spinal-cord imaging shows no lesions. The CSF is oligoclonal band positive. Blood work is unremarkable except for a low vitamin D 25-hydroxy level.

**Question:** Does CC meet the criteria for a definite diagnosis of MS?

**Response:** CC does meet the criteria for a definite diagnosis of MS by the 2017 revised diagnostic criteria. She meets dissemination in space and time. She also is CSF oligoclonal band positive, which can substitute for DIT. Of course, other possible diagnoses must be ruled out to the best of one's ability.

**Case Presentation:** CC is told that she has relapsing MS with one attack. She is treated with high-dose steroids for 3 days and started on oral vitamin D3 replacement therapy.

In discussion with CC about selection of DMT, CC indicates that she is interested in a safe therapy that has no pregnancy issues since she is looking forward to starting a family at some point in the future. Therapy is initiated with a needle injectable, and the plan is for CC to have a surveillance brain MRI at 6 months.

**Question:** Is a surveillance MRI with contrast indicated?

**Response:** Because of the concern about deposition of gadolinium-based contrast agents into brain tissue, contrast should only be done when there is a clear benefit. One could elect not to do contrast imaging in this case since any new lesion should be detectable on T2/FLAIR.

**Case Presentation:** After several weeks of therapy, CC returns complaining bitterly about injection reactions. She is re-instructed on injection techniques by a training nurse, with instructions to avoid certain body sites that are particularly painful. At her next visit 3 months later, CC's major complaint involves injection issues—there are problems with every injection.

**Question:** What should be done to address her injection issues?

(1) Implement a skin cream to treat local pain

- (2) Tell CC she needs to give it another few months
- (3) Switch CC to a non-injectable agent
- (4) Confine injections to the body sites that are better tolerated
- (5) Assess CC's adherence/compliance with injections

**Response:** While an assessment of adherence/compliance with injections may be done, it is probably best to switch CC to an oral agent since she has had a several-months trial of injection therapy and is still experiencing significant uncontrolled side effects.

**Question:** In switching CC to an oral DMT, should you discuss planned blood work that would be done after starting therapy, and should the risk of PML be mentioned at the outset of therapy?

**Response:** The American Academy of Neurology guidelines recommend discussing the potential risks of therapy when therapy is initiated and when changes are made. This includes counseling about the risk of PML with natalizumab, fingolimod, dimethyl fumarate, and the anti-CD20s.

Strategies for the selection of a DMT and switching from one to another involve several considerations, including those related to the patient, the drug, and treatment regimen, that are summarized in Table 4. Developing a treatment plan involves engagement with the patient and involvement of the patient in the decision.

**Table 4. Strategies for the selection of initial therapy for multiple sclerosis and for switching from one disease modifying therapy to another**

- Identify therapeutic options based on clinical criteria and patient factors
  - Disease stage
  - Comorbidities
  - Allergies
  - Pregnancy, other short-term conditions
  - Cost and access
- Educate patients on risks and benefits of each therapeutic option, assess preferences
  - Route of administration
  - Dosage regimen
  - Safety and tolerability
  - Risk tolerance
- Develop treatment plan using shared decision-making with patient
  - Evaluate short-term versus long-term objectives
  - Evaluate induction versus escalation regimens
  - Consider monitoring parameters and sequencing of disease-modifying therapies
  - Utilize decision aids and decision-making tools/algorithms

## SUMMARY

Phenotypes of MS, a major acquired CNS disease, were redefined and recharacterized in 2013. CIS and RIS were added as pre MS phenotypes. Early initiation of treatment—that is, in patients with CIS, high-risk for MS, a first MS attack, and those with active relapsing MS—has become an accepted treatment principle to minimize the risk of patients developing progressive disease. An emerging treatment principle is treat-to-target goals, which are used in treating rheumatoid arthritis patients. However, the optimum clinically practical target goal for MS and its criteria needs to be defined.

There are now many DMT agents with multiple differing mechanisms of action to treat MS, which allows for individual optimization of therapy. Therapy selection is a shared decision-making process with patients based on discussions of the benefits of a treatment and its risk and monitoring requirements. Initiation of treatment early following the initial diagnosis of MS is an accepted principle, as newer agents may permit rapid early suppression of inflammatory disease activity in RRMS with potential long-term benefits on the course of MS. Important elements of early MS therapy include strategies for DMT selection, sequencing of agents, and monitoring of efficacy and safety. Data are only now beginning to emerge to develop these strategies for the individual patient. □

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# Post-test

## Risk-Benefit Analysis and Personalized Treatment in Multiple Sclerosis: Basing Treatment Goals on the Latest Evidence

In order to receive credit, please complete the online CME post-test and evaluation form at [www.rockpointe.com/MSsupplement](http://www.rockpointe.com/MSsupplement). The post-test questions listed below are identical to the post-test you will find online and are listed for your reference and convenience. If you are experiencing problems or have any questions, please email [contact@potomacme.org](mailto:contact@potomacme.org).

**1. What extra component does NEDA-4 include?**

- a. Annual brain volume loss  $\leq 0.3\%$
- b. Symbol digit modality test
- c. Diffusion tensor imaging
- d. Spinal cord imaging
- e. Annual brain volume loss  $\leq 0.4\%$

**2. A 40-year-old black male lawyer presents with an acute cerebellar syndrome that partially improved after 5 days of high-dose IV steroids. Exam shows persistent mild paraparesis, heel-to-shin dysmetria, and poor tandem. Brain MRI showed 15 lesions (3 enhanced, 2 of them were infratentorial). Spinal MRIs showed 5 lesions (2 enhanced). CSF was positive for oligoclonal bands. The patient states he is very interested in long-lasting therapy. Which of the following BEST represents your treatment approach for this patient?**

- a. This patient should be treated with injectable interferon beta-1a
- b. This patient should be treated with fingolimod
- c. This patient should be treated with alemtuzumab
- d. Any class of DMT is appropriate, depending on patient preference

**3. Which of the statements best describes the results of the ocrelizumab clinical trials?**

- a. Ocrelizumab demonstrated efficacy in patients with PPMS, but not in patients with RRMS
- b. The safety profile of ocrelizumab is similar to that of INF $\beta$ -1a
- c. The most common adverse event was leukopenia
- d. In patients with RRMS, relapse rates were reduced in the ocrelizumab arm compared to the INF $\beta$ -1 arm, while reduction in clinical disability was similar in the two arms

**4. CC is a 28-year-old single female accountant who presents with an internuclear ophthalmoplegia. Brain MRI shows a 3 mm enhancing pontine lesion. In addition, there are two non-enhancing lesions, periventricular and juxtacortical. Spinal-**

**cord imaging shows no lesions. CSF is oligoclonal band positive. Blood work is unremarkable except for low vitamin D 25 hydroxy level. Does this patient meet criteria for definite diagnosis of MS?**

- a. Yes
- b. No

**5. CC is told she has relapsing MS with one attack. She is treated with 3 days of high-dose steroids, and started on oral vitamin D3 replacement. In discussion about selection of a DMT, she is interested in a safe therapy that has no pregnancy issues, since she is looking forward to starting a family at some point in the future. She starts on a needle injectable. The plan is to do a surveillance brain MRI at 6 months. Would you do the surveillance MRI with contrast?**

- a. Yes
- b. No

**6. After several weeks, she is bitterly complaining about injection reactions. She is instructed on injection techniques by a training nurse. She is told to avoid certain body sites that are particularly painful. When you see her at 3 months, her major complaint involves injection issues with problems with every injection. What should you do to address her injection issues?**

- a. Implement a skin cream to treat local pain
- b. Tell her she needs to give it another few months
- c. Switch her to a non-injectable agent
- d. Confine injections to the body sites that are more tolerated
- e. Assess her adherence/compliance

**7. You decide to change her to one of the oral DMTs. Do you typically discuss the blood work you plan to do after starting therapy and do you mention any PML risk?**

- a. Yes
- b. No



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