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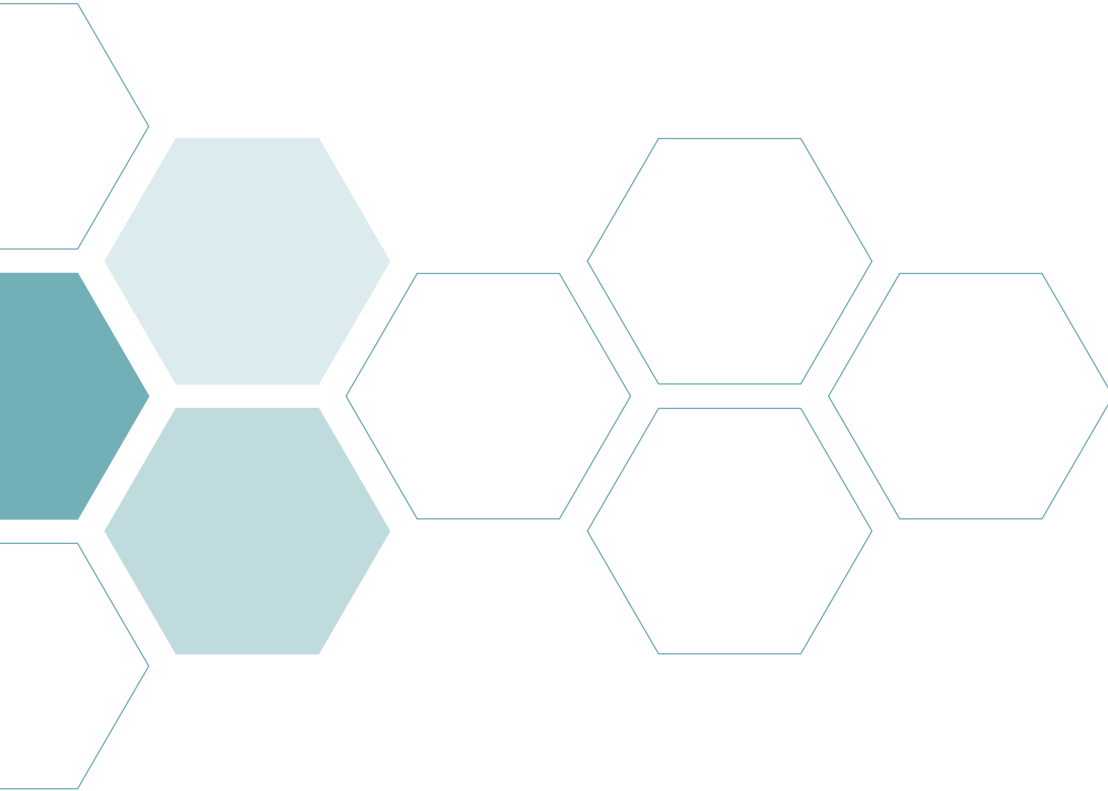
New Horizons in the Treatment of Multiple Sclerosis: Best Practices for Improved Patient Outcomes

New Horizons in the Treatment of Multiple Sclerosis:
Best Practices for Improved Patient Outcomes

Instructions for CME/CNE: Activity is valid from April 25, 2017 to April 30, 2019.
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Learning Objectives:
1. Apply recent data on the efficacy, safety, and tolerability of approved disease-modifying therapies into the development of management strategies for patients with relapsing forms of multiple sclerosis
2. Analyze treatment options and strategies for MS patients who have had an inadequate response to previous treatment regimens
3. Review patient, disease, and treatment characteristics that factor into relapsing MS treatment selection and considerations for predicting treatment response and identifying when to switch therapies
4. Examine recent guideline updates on the role of MRI in evaluating prognosis, disease progression and therapeutic decision-making for improved relapsing MS patient outcomes
5. Describe the pathophysiology of MS as it relates to T- and B-cell behavior and mechanisms of action of MS therapies
6. Apply methods to enable optimal cost management of disease-modifying therapy to be realized by multiple MS stakeholders including managed care organizations
7. Analyze the role of auto-injectors in the management of relapsing MS and discuss which patients could benefit from their use
8. Summarize findings from observational and interventional studies of vitamin D in MS susceptibility and clinical outcomes

Faculty Disclosure:
Dr. Bermel serves as a consultant to Biogen, Genentech, Genzyme and Novartis. He receives research support from Biogen and Genentech.
Dr. Bernard and Dr. Henson have no real or perceived financial relationships to disclose.
Dr. Coyle serves as a consultant to Accordant, Acorda, Bayer, Biogen, Celgene, Genentech/Roche, Genzyme/Sanofi, Novartis, Serono and receives grant/research support from Actelion, Genentech/Roche, NINDS, Novartis, Opexa.
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Dr. Owens serves as a consultant AbbVie, Biogen, Novartis and Roche.
All material has been peer reviewed for bias.

Planning Committee Disclosure
Bill Williams, MD; Jacquelyn Smith, RN, BSN, MA, CMCN; Katie Eads and Will Williams have no real or perceived financial relationships to disclose.

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Post-Test Questions

1. Which of the following best describes the pathophysiology of multiple sclerosis.?
   a. Over activation of the nuclear factor-like 2 (Nrf2) antioxidant pathway causing axonal/neuronal injury.
   b. Residual Varicella virus in CNS triggers immune system to attack myelin leading to neuronal destruction.
   c. Unregulated release of cytokines, especially TNF-α, IL-6 and IL-1, causes inflammation in the myelin sheath.
   d. Auto reactive T-cells and B-cells attack myelin causing demyelination and axonal/neuronal injury.

2. Which of the following is NOT a risk factor for developing MS??
   a. Vitamin D deficiency   b. Smoking
   c. Low birth weight   d. Obesity in adolescense

3. Which subtype of MS is defined as episodes of acute worsening of neurologic functioning with total or partial recovery and no apparent progression of disease?
   a. CIS   b. RRMS   c. SPMS   d. PPMS

4. Which of the following MRI measures identifies inflammatory lesions in CNS?
   a. Size of lateral ventricles   b. DTI weighted images
   c. Width of corpus callosum   d. gadolinium-enhancing T1 images

5. Which of the following do patients need to be screened for before receiving natalizumab?
   a. Hypertension   b. Seizure disorder
   c. JC virus   d. Liver disfunction

6. Achievement of No Evidence of Disease Activity (NEDA) with the current DMT is not optimal and is less than 50 percent even with most effective agents.
   a. True   b. False

7. Which of the following is NOT an accurate statement about disease modifying therapy (DMT) in MS?
   a. Daclizumab and natalizumab's efficacy is superior to the oral agents.
   b. All the DMTs reduce annualized relapse rate (ARR).
   c. Patients who start DMT within 2 years of diagnosis have a significant advantage in terms of disability accumulation compared with those who start later.
   d. There are differences in efficacy, safety, ease of use and tolerability between agents.

8. If a patient has a suboptimal response to interferon beta 1b, which of the following would be an inappropriate DMT switch?
   a. Glatiramer   b. Interferon beta 1a
   c. Fingolimod   d. Dimethyl fumarate

9. According to the Canadian Agency for Drugs and Technologies in Health systematic review of vitamin D, there is evidence supporting the potential benefit of vitamin D supplementation for prevention of MS.
   a. True   b. False

10. Which of the following is an accurate combination barrier with the self-injectable DMTs for MS and solution?
    a. Frequent skin reactions - Change to every other day injection
    b. First dose bradycardia - Give under 2 hour observation protocol
    c. Infusion reaction - Give prednisone and diphenhydramine before injection
    d. difficulty with injection - Autoinjectors

Activity Evaluation and Improvement Process
(Please rate this activity on the following scale:
4 - Excellent   3 - Good   2 - Fair   1 - Poor)

1. Based on the content presented I am better able to:

   Apply recent data on the efficacy, safety, and tolerability of approved disease-modifying therapies into the development of management strategies for patients with relapsing forms of multiple sclerosis.

   4   3   2   1

   Analyze treatment options and strategies for MS patients who have had an inadequate response to previous treatment regimens.

   4   3   2   1

   Review patient, disease, and treatment characteristics that factor into relapsing MS treatment selection and considerations for predicting treatment response and identifying when to switch therapies.

   4   3   2   1

   Examine recent guideline updates on the role of MRI in evaluating prognosis, disease progression and therapeutic decision-making for improved relapsing MS patient outcomes.

   4   3   2   1

   Describe the pathophysiology of MS as it relates to T- and B-cell behavior and mechanisms of action of MS therapies.

   4   3   2   1

   Apply methods to enable optimal cost management of disease-modifying therapy to be realized by multiple MS stakeholders including managed care organizations.

   4   3   2   1

   Analyze the role of auto-injectors in the management of relapsing MS and discuss which patients could benefit from their use.

   4   3   2   1

   Summarize findings from observational and interventional studies of vitamin D in MS susceptibility and clinical outcomes

   4   3   2   1

2. The activity met my expectations.   4   3   2   1
3. The activity and presenters were free of bias.   4   3   2   1
4. The activity was applicable to my position.   4   3   2   1
5. Do you expect that the information you learned during this activity will help you improve your skills or judgement within the next six months?
   (4 definitely will change - 1 definitely will not change)

   4   3   2   1

6. How confident are you in managing patients based on this activity?
   (4 very confident - 1 not confident)

   4   3   2   1

7. What other topics interest you? _____

8. My goal of participating in this activity was: _____
   _____

9. Did the content of the activity help in meeting your above goal?

   ☐ Yes   ☐ No

10. Due to the content of this activity, I will change my practice patterns by:

    ☐ Identifying opportunities to improve treatment options for patients.
    ☐ Providing guidelines and resources on new therapies to providers.
    ☐ My practice patterns will not change.
    ☐ Other (specify): _____

11. Will the content presented increase your abilities in any of the following areas? Please check all that apply.

    ☐ Management and leadership skills
    ☐ Business and/or financial expertise to manage the medical loss ratio.
    ☐ Exchange ideas and network with colleagues to improve patient outcomes.
    ☐ Be aware of updates of Congress, pharmaceutical, Health and Human Services and other regulatory services.
    ☐ Clear knowledge of practice of medicine, especially common disease.
    ☐ Stay updated on clinical conditions.

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New Horizons in the Treatment and Management of Multiple Sclerosis: Best Practices for Improved Patient Outcomes

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MULTIPLE SCLEROSIS (MS) IS AN IMMUNE-mediated inflammatory disease of myelin, the insulating sheath around axons, first described by Charcot in 1868. Characterized by inflammatory plaques or scars predominantly in the deep white matter of the brain and spinal cord, it is the most common cause of non-traumatic neurologic disability in young adults. Fifty percent of patients require a cane to walk after 15 years of disease.

MS affects 0.1 percent of the population, with an estimated 300,000 to 400,000 patients in the United States (U.S.) and more than 2.3 million people worldwide.[1] This is a disease of young people with the median age of onset of 28 years. It is also a predominately female disease with a 3:1 female to male ratio.

Pathogenesis
In MS, auto reactive T lymphocytes (CD4+/helper or CD8+/cytotoxic) and B-cells attack myelin, causing demyelination and axonal/neuronal injury. Irreversible axonal damage occurs from the onset of disease but is clinically silent until a threshold of axonal loss is exceeded. Inflammation predominates in the early phases of the disease and is thought to be responsible for axonal damage.[2] Although inflammation diminishes over time, the number and extent of inflammatory events in the early phase of the disease have been associated with earlier disease progression. Thus, therapy aimed at reducing inflammation by targeting the underlying inflammatory cascade should be started early in the course of disease.

The blood–brain barrier is normally not permeable to T-cells and B-cells, unless triggered by infection or a virus, which decreases the integrity of the tight junctions. In MS, circulating T-cells and B-cells move, by an unknown mechanism, from the circulation across the blood–brain barrier. Macrophages and activated T-cells attack myelin and activate other immune cell types, including B-cells, which become plasma cells. Exhibit 1 illustrates how activated T-cells and B-cells begin to destroy myelin.

B-cells release cytokines, act as antigen presenting cells (APCs), and ultimately produce autoantibodies (via plasma cells). Oligoclonal B-cell bands are present in the cerebrospinal fluid of a majority of MS patients and those with clinically isolated syndrome (CIS, the first episode of MS symptoms). Presence of B-cell bands is a strong predictor of conversion from CIS to clinically definite MS.[3] All the FDA approved disease-modifying therapies (DMTs) for MS, except natalizumab, induce a relative decrease in circulating memory B-cells with concomitant expansion of circulating B-cell precursors and/or naïve B-cells.[4] B-cell function is also altered; most DMTs induce B-cell production of the anti-inflammatory cytokine interleukin-10 while inhibiting B-cell expression of pro-inflammatory cytokines. CD20, CD52, and integrins are all markers expressed on T- and B-cells targeted by medications discussed later.

Risk Factors
MS has complex genetic and environmental risk factors, including vitamin D deficiency (which is addressed in a separate section below), smoking, Epstein Barr virus infection, place and season of birth, ultraviolet radiation, early life infections, microbiome, and obesity in adolescence.[1,5] While MS is not hereditary, having a first-degree relative such as a parent or sibling with MS does significantly increase

Exhibit 1: Role of Immune Cells in MS Pathogenesis

Periphery

BBB

CNS

Neuron

Myelin sheath

DC

1. Activation

2. Adhesion

4. Reactivation

T

T

APC

3. Invasion

T

T

Macrophage

Macrophage

Plasma cell

B

B

B

5. Demyelination and neuronal/neural damage

DC = dendritic cell
T = T-cell
B = B-cell
APC = antigen presenting cell
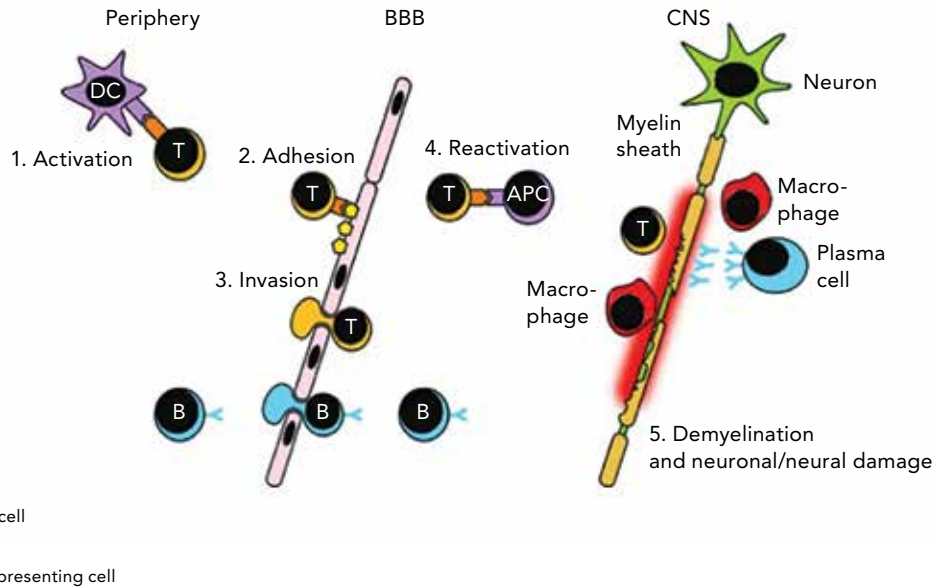
an individual's risk of developing the disease. Studies have shown that there is a higher prevalence of certain genes in populations with higher rates of MS. It is theorized that MS develops because a person is born with a genetic predisposition to react to some environmental agent that, upon exposure, triggers an immune-mediated response.

Vitamin D in MS Pathology

Growing evidence suggests that vitamin D plays an important role in the development of MS. Prevalence of MS increases with distance from the equator; it is most common in those of northern European descent. People who live closer to the equator are exposed to greater amounts of sunlight year-round and, as a result, they tend to have higher levels of naturally-produced vitamin D, which is thought to support immune function and may help protect against immune-mediated diseases like MS.

Interestingly, migrants moving from an area of lower risk to an area of higher risk retain lower MS risk of their country of origin.[6,7] Migrants moving from area of high risk to lower risk have lower than expected MS prevalence, particularly if the move is made before age 15.[8]

Individuals with MS tend to have low vitamin D levels. MS patients who live farthest from the equator or have proven low vitamin D levels tend to have increased odds of moderate to high disability from MS disability and increased relapses over the previous year.[9-11] Periods of low vitamin D have been shown

to precede occurrence of high magnetic resonance imaging (MRI) lesion activity, and periods of high vitamin D precede low lesion activity.[12] There is an association between low vitamin D status at start of MS and early conversion to progressive disease and low levels during CIS being a risk for converting to clinically definite MS.[13-15]

Vitamin D may be related to MS because it affects production of inflammatory cytokines including interleukin-2 (IL-2), tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and IL-17. Higher vitamin D levels result in lower inflammatory cytokine levels and supplementation in those with MS has been shown to improve inflammatory cytokine levels.[16-18]

Polymorphisms of vitamin D receptor genes may be another explanation for impact on MS risk. Certain genotypes appear to be protective against MS, whereas other genotypes increase risk.[19-21] Genes associated with vitamin D metabolism (CYP27B1 and CYP24A1) are also associated with MS risk.[22]

Vitamin D has a role in MS development that starts with pregnancy. Maternal vitamin D deficiency during early pregnancy is associated with a nearly twofold increase of MS in offspring compared with women with no deficiency.[23] The risk of MS is greater in those who were primarily in utero during the winter months. In the northern hemisphere, the risk of MS is greater in those born in May and lower in those born in November. Those born in May were in utero during the winter months. The

Exhibit 2: MS Subtypes[28,29]

RELAPSING-REMITTING MS

SECONDARY PROGRESSIVE MS

PRIMARY PROGRESSIVE MS

Relapsing course can be:
- Active or inactive
- Worsening or not worsening

Progressive course can be:
- Active without progression
- Not active with or without progression
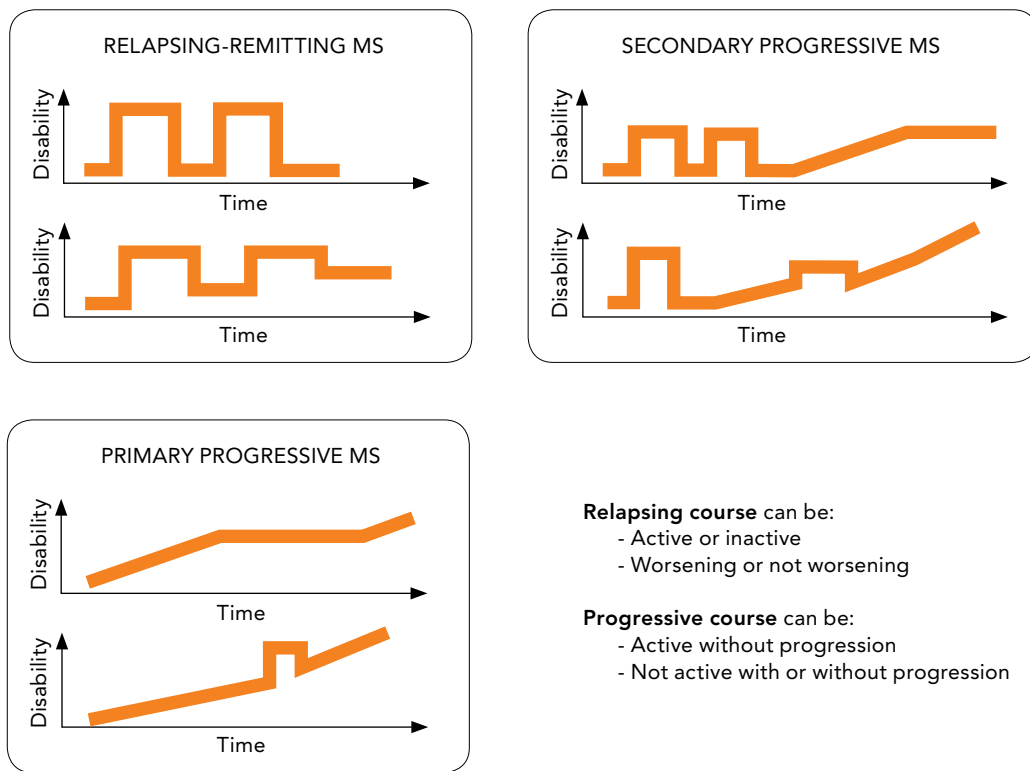
opposite is seen in those born in the southern hemisphere. Low levels of vitamin D in neonates is also associated with increased risk of MS.[24]

Vitamin D levels also influence the age of MS onset. Younger age at onset is significantly associated with low exposure to summer sun in adolescence, higher BMI at 20 years of age, and HLA-DRB1★1501 risk allele.[25] A study of MS risk and vitamin D supplementation with cod liver oil at different ages found that supplementation during adolescence (from 13 to 18 years) was associated with reduced risk of MS compared with childhood supplementation or nonsupplementation. The dose which prevented MS in adolescence was 600 to 800 IU/day.[26]

Vitamin D supplementation in adulthood has also been shown to reduce risk of MS. The Nurses' Health Study (92,253 women) and Nurses' Health Study II (95,310 women) examined the effects of dietary and supplement vitamin D intake in relation to risk of MS. Intake of vitamin D was inversely associated with risk of MS.[27]

Clinical Subtypes of MS
There are four clinical subtypes of MS and one possible MS precursor. Radiologically isolated syndrome (RIS) is evidence of CNS damage suggestive

of MS on MRI but no clinical symptoms and is not a subtype per se since clinical evidence of demyelinating disease (a current criterion for MS diagnosis) is lacking. This is found incidentally when a person has an MRI for an unrelated medical indication. The prognostic implications of RIS are controversial, but there are some data to suggest that patients with RIS are at increased risk of developing MS within five years. Clinically isolated syndrome (CIS) is the first acute or subacute episode of neurologic disturbance of the sort seen in MS and is due to a single white matter lesion.[28] Up to 85 percent of MS cases start with CIS. It most commonly presents as optic neuritis, partial myelitis, or brainstem/cerebellar syndrome.

Relapsing-remitting MS (RRMS) is episodes of acute worsening of neurologic functioning (new symptoms or the worsening of existing symptoms) with total or partial recovery and no apparent progression of disease (Exhibit 2).[28,29] RRMS can be further characterized as active or not active and worsening or stable.[29]

Active disease classification requires either clinical or imaging evidence and patients can have both. Clinical evidence includes relapses which are acute or subacute episodes of new or increasing neurologic

Exhibit 3: Multiple Sclerosis Lesions

| T2/FLAIR | T1-Postcontrast | T1-Precontrast |
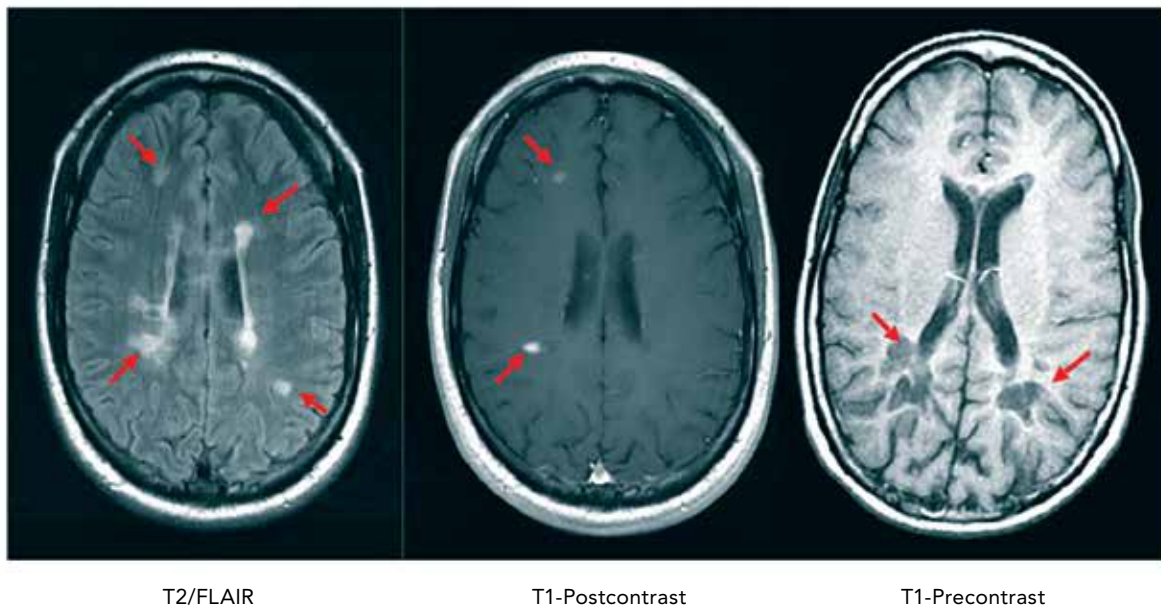
dysfunction followed by full or partial recovery, in the absence of fever or infection. Imaging evidence of active disease using MRI includes occurrence of contrast-enhancing T1 hyperintense lesions (indicating active inflammation) or new or unequivocally enlarging T2 hyperintense lesions (indicating scars and/or new inflammation) (Exhibit 3).

In RRMS, worsening disease is defined as increased disability confirmed over a specified time period following a relapse. Stable disease is defined as no evidence of increasing disability over a specified time period following a relapse.

Primary progressive MS (PPMS) is steadily worsening neurologic function from the onset of symptoms without initial relapses or remissions. Like RRMS, PPMS can be further characterized as active or not active and progressive or stable. Progressive disease is evidence of disease worsening on an objective measure of change such as the Expanded Disability Status Scale (EDSS), confirmed over a specified period of time, with or without relapses.

Secondary progressive MS (SPMS) is defined as an initial relapsing-remitting course that then becomes more steadily progressive, with or without relapses. These patients have an insidious onset of disability. Again, SPMS can be additionally characterized by activity and progression.

Overall, RRMS accounts for 50 to 55 percent of cases, SPMS 30 percent, and PPMS 5 to 10 percent.[30, 31] Without disease-modifying treatment, fifty percent of patients with RRMS develop SPMS within 10 years and 90 percent will eventually develop progressive MS.[31] Forty- three to 65 percent of patients will develop cognitive impairments.[31]

Early in the disease, patients tend to recover between episodes pretty well if they are young and do not have a lot of other medical comorbidities. As the disease progresses, CNS damage and disability accumulate. MS is unpredictable but Exhibit 4 illustrates the prototypic course of MS from preclinical stage through RRMS and SPMS.[32-34] There is much heterogeneity with MS; some patients have a much milder course and others much more severe. Causes and factors that contribute to its heterogeneity are unknown.

Evidence that DMTs are truly modifying the course of this disease is beginning to be published. In a study examining effects of interferon over 15 years, the group who had received the most interferon doses had a much lower proportion converting to SPMS compared with those who received the fewest doses (20.8% vs 52.1%).[35]

Measuring Disease Progression with Imaging

Conventional MRI (gadolinium-enhancing T1 images and T2-weighted images) represents the tip of the iceberg of identifying MS pathology in the CNS. Advanced MRI techniques including magnetization transfer ratio (MTR), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), and measurement of brain atrophy provide more information on neurodegeneration, the

Exhibit 4: Prototypic Course of Relapsing MS[32-34]

CIS

Preclinical   RRMS   SPMS

0   5 - 10   15 - 20+

Disease Duration (Years)

CIS = clinically isolated syndrome
RRMS = relapsing-remitting MS
SPMS = secondary progressive MS

— Relapses and Impairment
↑ MRI Activity
— MRI Burden of Disease
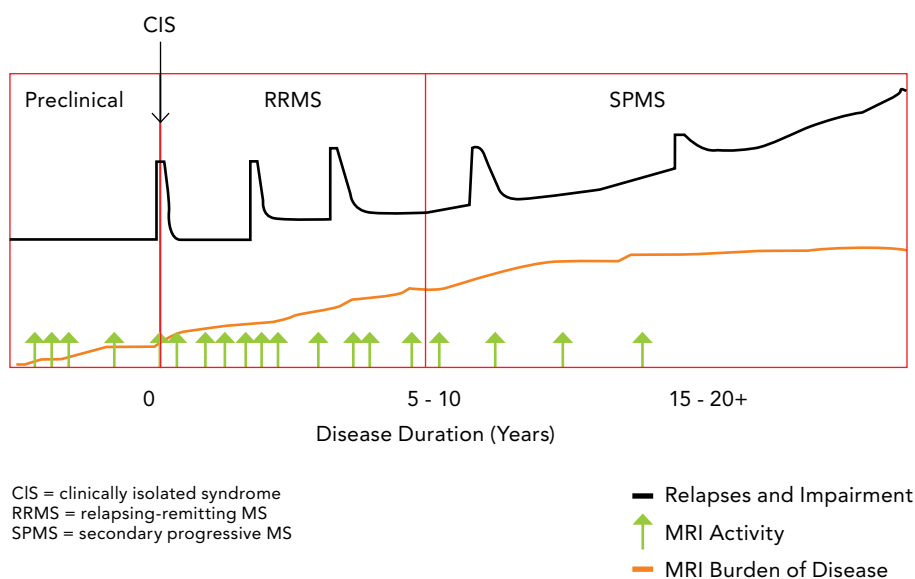
key component of MS disability.[36] MTR, DTI, and MRS are helpful in evaluating dynamic changes in pathology, but more data are needed on clinical utility for diagnosis and monitoring disease activity.

Brain atrophy has been proposed to be a measure of the net effect of tissue destruction by MS. It is demonstrated by increased size of lateral ventricles, prominent sulci, increased volume of cerebrospinal fluid spaces, decreased width of corpus callosum or decreased anteroposterior diameter of the cervical spinal cord which can be measured on conventional MRI. Brain parenchymal loss is a global process that occurs in patients with MS at a rate of 0.6 to 1.0 percent per year.[37] This MRI-related measure is also not without problems, and the pathological basis of MS–related atrophy is still unclear. Although it is intuitive that myelin and axonal loss contribute to atrophy (46% of brain white matter bulk consists of axons; about 24% of myelin), the role of other factors is largely unexplored. Brain atrophy begins as early as disease manifestation and has been correlated to concurrent and future disability. Many studies of DMT now include brain atrophy as an outcomes measure.

Diagnosis
Diagnosis of MS requires two or more attacks of symptoms with objective clinical evidence of two or more MRI lesions or objective clinical evidence of one lesion with reasonable historical evidence of a prior attack.[38] A MS attack or relapse is a neurological disturbance of the kind seen in MS based on subjective report or neurological examination and occurs for at least 24 hours duration in absence of fever or infection. The most common early symptoms of MS are fatigue, vision problems, tingling and numbness, vertigo and dizziness, muscle weakness and spasms, and problems with balance and coordination. These symptoms are caused by the damage to axons which disrupts the transmission of nerve signals that communicate a desired action from the brain, through the spinal cord, to various parts of the body.[1] Other symptoms include speech and swallowing problems, cognitive dysfunction, difficulty with walking, bladder and bowel dysfunction, sexual dysfunction, and depression which tends to occur later in the disease process.

Management with DMT
RRMS management strives to address existing symptoms/disease sequelae, shorten relapses and improve recovery with intravenous corticosteroids, reduce the number and severity of relapses with DMT, prevent or extend time to disability milestones, prevent or extend time to onset of SPMS, prevent or reduce the number and size of new and enhancing lesions on MRI, and limit overall MRI lesion burden in the CNS. It is also important to manage comorbidities which are known to worsen MS (diabetes, smoking, high cholesterol, depression) and achieve wellness. Ideally, therapy could reverse disability and repair neurological damage, but no therapies currently achieve this.

Clinicians are well-equipped to treat RRMS

with the 14 approved therapies. Effective therapy for PPMS is a major unmet need as there are not currently any FDA approved therapies. The available medications represent a range of mechanisms of action which overall are aimed at modulating the immune system to prevent attack on the CNS. The mechanisms of action include immunomodulation (interferon-beta, glatiramer acetate, dimethyl fumarate, daclizumab), inhibition of immune cell replication (teriflunomide), immune cell depletion (alemtuzumab), and altered immune cell trafficking (natalizumab, fingolimod). Mitoxantrone, an intravenous chemotherapy agent, is FDA approved for worsening RRMS but is rarely used because of the typical chemotherapy adverse effects and potential for secondary leukemia and cardiac toxicity.

Clinical trials of medications for MS include several outcome measures which one should be familiar with. Annualized relapse rate (ARR) is the total number of relapses divided by the total person-time at risk of relapse. MRI lesion changes over time are measured by active gadolinium-enhancing lesions (Gd +, T1) or T2 burden of disease. The Expanded Disability Scale Score (EDSS) is the standard for measuring disability. Other measures of disability such as the timed 25-foot walk (T25-FW) may also be done. Changes in brain atrophy as measured on MRI and previously discussed are also a typical outcome measure in MS clinical trials. Optical coherence tomography (OCT), a non-invasive, relatively inexpensive and well-tolerated imaging method measures retinal nerve fiber thinning of unmyelinated axons and is being used more often to measure axonal pathologic changes in MS, especially in clinical trials.[39]

Individual DMT Agents

Interferon-beta (IFNβ) was the first therapy approved for RRMS and has been used for more than 20 years. It leads to inhibition of lymphocyte proliferation; immunomodulatory effects, including a shift from pro-inflammatory Th1 cytokines to anti-inflammatory Th2 cytokines, decreased major histocompatibility complex (MHC) expression; and decreased inflammatory cell migration across the blood-brain barrier.[40] MRI lesion activity at six to 12 months after starting IFNβ predicts an inadequate treatment response long term. This MRI evidence of response at six to 12 months is extrapolated to other DMTs by many clinicians.

IFNβ is available as four different products which all have different dosing schedules but are considered equivalent to each other in terms of efficacy. Pegylated interferon is a longer acting formulation which is given every 14 days. Exhibit 5 outlines the available dosage forms, typical adverse effects, necessary monitoring, and pregnancy category for the FDA approved DMTs.

Glatiramer (GA), a random polymer of four amino acids found in myelin, is thought to work by competitive binding to MHC on antigen-presenting cells in preference to myelin protein antigens. The antigen-specific interaction of glatiramer-MHC with antigen receptors on T-cells induces tolerance and GA-specific Th2 cells with bystander suppression in both the periphery and CNS. Essentially, this agent induces a more tolerant immune system.

Glatiramer is one DMT that is available as a generic. Switching from brand name to generic glatiramer acetate is treated as a change in therapy in some practices, with a follow-up MRI in three to six months after the switch.

Interferon and glatiramer have good safety and extensive track records and modest efficacy. Some patients do very well on these agents, but many experience disease breakthrough. Selected patients benefit from switching between DMT classes, but data does not support switching among IFNβs. In most cases, clinicians should consider moving to a more potent agent. Many patients dislike the frequent injections and bothersome side effects of these agents.

Most clinicians do not routinely advise RRMS patients with effective disease control on IFNβ or GA and good tolerability to change therapy. Clinicians still sometimes use IFNβ or GA as initial therapy for RRMS patients. However, postmarketing studies and use in clinical experience generally supports using the newer agents because of better efficacy and good safety. The newer agents include orals and injectable monoclonal antibodies.

Fingolimod (Gilenya®) is the first oral agent to discuss. This agent initially stimulates and then down-modulates sphingosine-1-phosphate receptor 1 (S1P1).[41] S1P1 is found on about 70 percent of lymphocytes. Downregulation interrupts lymphocyte recirculation by preventing lymphocytes from leaving the lymph nodes and entering the bloodstream and CNS compartment. Fingolimod treatment reduced ARR in RRMS by 54 percent over placebo in two trials. Significant benefit was seen in reducing MRI lesion activity and brain atrophy.[42,43] Significant benefit on ARR, MRI lesion activity, and atrophy was seen when fingolimod was compared to IFNb-1.[44]

Fingolimod targets four of the five S1P receptor subtypes (1, 3, 4, and 5). In adults, S1P affects many different T-cell types, not just lymphocytes, to regulate immune cell trafficking, vascular homeostasis, and cell communication in the CNS. In addition

Exhibit 5: DMT Use in Practice

Dose	Main Adverse Effects	Laboratory Monitoring	Pregnancy Category
Interferon			
IFNβ-1b (Betaseron®) 8 MIU SC QOD [vial, electronic autoinjector] IFNβ-1a (Avonex®) 30 µg IM qwk [vial, prefilled syringe, autoinjector] IFNβ-1a: (Rebif®) 22-44 µg SC 3/wk [prefilled syringe, autoinjector] pegIFNβ-1a (Plegridy®) 125 µg SC q14d [vial, prefilled syringe, autoinjector]	Injection site reactions, flu-like symptoms, lymphopenia , increased LFTs, accentuation of spasticity, headache, depression	CBC & LFT prior to therapy, at months 1, 3, 6, then every 6-12 months Pregnancy test prior to therapy and for suspected pregnancy NAbs after 1-2 years of therapy, particularly with ongoing activity	C
Glatiramer (Copaxone®, generic)			
20 mg SC daily 40 mg SC 3/wk [prefilled syringe]	Injection site reactions, immediate post-injection reaction, lipoatrophy	Pregnancy test prior to therapy and for suspected pregnancy No laboratory monitoring required on therapy	B
Fingolimod (Gilenya®)			
0.5 mg PO daily	Headache, back pain, 1st dose bradycardia, macular edema Infection (VZV, PML), hypertension, abnormal LFTs, SOB, cough	CBC & LFT prior to initiation, month 3 and 6, every 6 months Pregnancy test prior to initiation and for suspected pregnancy VZV titer prior to initiation in the absence of a history of chicken pox or shingles, VZV vaccine EKG prior to treatment Eye exam or OCT prior to treatment, at month 3 Pulmonary referral and/or PFTs for pulmonary symptoms	C
Dimethyl Fumarate (Tecfidera®)			
120 mg PO BID for 7 days 240 mg PO BID	Skin flushing,GI: dyspepsia, nausea, vomiting, abdominal pain, cramps, diarrhea Leukopenia, PML	CBC prior to initiation then every 6 months Pregnancy test prior to therapy and for suspected pregnancy Monitor for serious infection	C

Exhibit 5: DMT Use in Practice (continued)

Dose	Main Adverse Effects	Laboratory Monitoring	Pregnancy Category
Teriflunomide (Aubagio®)			
7 and 14 PO daily	Nausea, diarrhea alopecia, hepatotoxicity bone marrow suppression immune suppression peripheral neuropathy	LFTs prior to initiation and monthly for 6 months CBC prior to initiation and monitor for infection Pregnancy test prior to therapy and for suspected pregnancy Screen for TB Check BP prior to initiation and monitor on therapy Monitor for signs/symptoms of peripheral neuropathy	X
Natalizumab (Tysabri®)			
300 mg IV monthly	Headache, allergic reaction, hepatotoxicity, PML, hematologic effects	LFTs prior to initiation, at months 3 and 6, then every 6 months Pregnancy test prior to therapy and for suspected pregnancy NAbs at month 6 JCV serology prior to initiation then every 3 months MRI prior to therapy then every 6 months	C
Alemtuzumab (Lemtrada®)			
12 mg IV daily for 5 days 3 days at M12	Infusion reactions, Antibody-mediated autoimmunity, Infection, Malignancy, Pneumonitis	Pretreatment: CBC, Cr, LFTs, TSH, hepatitis panel, VZV IgG, HIV, pregnancy test, UA, skin exam, gynecologic exam, TB test, brain MRI Posttreatment: CBC, UA monthly for 4y, TSH q3M for 4y, annual skin and gynecological exams Monitor for serious infection	C Auto-Ab can transfer trans-placentally
Daclizumab (Zinbryta®)			
150 milligrams once monthly [prefilled syringe]	Cutaneous events [pruritis, rash, dermatitis (eczema, atopic, allergic, seborrheic, exfoliative), acne, erythema nodosum, angioedema], Infections, autoimmune hepatitis	Pretreatment: hepatitis panel, skin exam,TB test LFTs monthly, for 6 months after treatment stopped Monitor for serious infection	?

peg = pegylated
LFT = liver function test
CBC = complete blood count
NABs = neutralizing antibodies
VZV = varicella zoster virus
PML = progressive multifocal leukoencephalopathy
SOB = shortness of breath
EKG = electrocardiogram
OCT = optical coherence tomography
PFT = pulmonary function tests

TB = tuberculosis
BP = blood pressure
JCV = John Cunningham Virus
MRI = magnetic resonance imaging
UA = urinalysis
Cr = creatinine
TSH = thyroid stimulating hormone
IgG = immunoglobulin G
HIV = human immunodeficiency virus

to having an impact on the ability of lymphocytes to exit lymph nodes, S1P has an effect on bronchial smooth muscle (which can lead to cough and dyspnea), vascular endothelium (leading to angiogenesis and vasodilation), atrial myocytes (leading to bradycardia and atrioventricular block), vascular smooth muscle (leading to vasoconstriction and hypertension), and the retina (which can lead to swelling and macular edema). Bradycardia is most common with the first dose. It results in about a 10 bpm reduction in the first six hours after the initial dose. Despite these potential adverse effects, fingolimod is a well-tolerated agent.

Dimethyl fumarate (Tecfidera®), the second oral agent, was developed from Fumaderm, a mixture of mono- and dimethyl fumarate used to treat psoriasis in Europe. It appears to activate the nuclear-factor E2-related factor-2 (Nrf2) transcription pathway and inhibits nuclear-factor kappa B (NFkB) transcription pathway and has immunomodulatory effects and cytoprotective effects. In the Phase III approval trials, dimethyl fumarate treatment resulted in a 50 percent reduction in ARR and a 34 to 38 percent reduction in confirmed EDSS worsening. There were also benefits on MRI lesions.[45,46] One trial but not the other found benefits on brain atrophy.

Dimethyl fumarate is a twice a day medication which can make adherence more difficult than with once a day fingolimod. It is not effective if only taken once daily. Gastrointestinal (GI) adverse effects also limit the use of this agent. Specialty pharmacists can be used to help patients tolerate dimethyl fumarate and remain adherent with the dosing schedule. Strategies for improving tolerance include titrating the medication dose upward appropriately, taking with food, taking with Pepto-Bismol for GI upset, and taking with a baby aspirin daily or every other day if flushing occurs.

A few cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients receiving dimethyl fumarate. PML is a potentially fatal demyelinating disease of the CNS characterized by widespread lesions due to infection of oligodendrocytes by John Cunningham virus (JCV), which is a human polyomavirus.

Teriflunomide (Aubagio®) is the active metabolite of leflunomide, which is used to treat rheumatoid arthritis. It blocks dihydroorotate dehydrogenase, which inhibits de novo pyrimidine synthesis in rapidly dividing cells. T- and B-cells are rapidly dividing cells; thus, this agent inhibits T-cell and B-cell proliferation. This oral agent results in about a 30 percent reduction in ARR and a 30 percent reduction in confirmed disability progression with 14 mg

daily when compared to placebo. Benefit on MRI lesions is more, with 14 mg daily compared with 7 mg.[47,48] When teriflunomide was compared with IFNβ-1a , no difference in rate of treatment failure or ARR was shown.[49] In patients with CIS, teriflunomide reduced risk of conversion to clinically definite MS by 37 percent (7 mg) and 43 percent (14 mg).[50]

Teriflunomide is a generally well-tolerated agent. It is a pregnancy category X agent, but this categorization comes from data with leflunomide which was primarily in animals. Slow elimination of teriflunomide is an issue in a patient with an unplanned pregnancy. Because of the very long elimination half- life, it takes an average of eight months to reach a plasma concentration less than 0.02 mg/L. Total washout can take up to two years in some individuals. Elimination can be accelerated by administration of cholestyramine (8 g q8h) or activated charcoal (50 g q12h) for 11 days. Because of the potential teratogenic risks and long elimination, many clinicians do not use this agent in child bearing potential women and men.

Natalizumab (Tysabri®) prevents activated T-cells and monocytes from crossing the blood-brain barrier into the CNS by binding to the α4-subunit of α4β1 and α4β7 integrins expressed on the surface of all leukocytes except neutrophils and inhibiting the α4-mediated adhesion of leukocytes to their counter-receptors. This agent is given as an infusion every four weeks. It is more effective in reducing ARR than interferon and glatiramer and is well tolerated.

Unfortunately, PML can occur with this agent. The overall risk of PML with natalizumab is about 4.11 in 1,000.[51] Factors that increase risk of PML include presence of JCV antibodies, treatment duration over 24 months, prior immune suppression, and possibly decreased body weight.[52] A general approach used by clinicians is to test for JCV antibodies prior to and during use. If someone is JCV negative, clinicians utilize natalizumab liberally. JCV titers have to be checked periodically during therapy because three to eight percent of patients will seroconvert annually. If someone is already JCV positive, clinicians may choose to treat if she or he has no history of immune suppression. The treatment duration would be one to two years. Most clinicians will check an MRI every six months and JCV status every three months while the patient is receiving. Rebound symptoms can occur after discontinuation of natalizumab; if a patient is going to stop therapy, there needs to be a transition plan.

Alemtuzumab (Lemtrada®) is a humanized monoclonal antibody that targets CD52, a surface protein

expressed by T-cells, B-cells, monocytes, and eosinophils. It produces rapid, profound, and prolonged lymphocyte depletion with a gradual reconstitution with altered cell profile and function. B-cells and monocytes come back long before T-cells (3-8 months vs. 30-60 months). After treatment, there is a sustained decrease in CD4+T-cells greater than CD8+ T-cells. Regulatory T-cells are relatively enriched during repopulation. This agent is given as a daily infusion for five days; then, one year later, it is given daily for three days. It then is not given again until the patient shows disease, which may be years later.

In a trial in patients with RRMS who were naïve to DMT, alemtuzumab was compared to IFN β-1a over two years.[53] Alemtuzumab significantly reduced the ARR by 55 percent compared with IFN β-1a (ARR 0.18 vs. 0.39). Seventy-eight percent of those treated with alemtuzumab were relapse free compared with 59 percent in the interferon group. There was a low occurrence of confirmed disability in both arms (8% vs. 11%, not significant). There were decreased patients with new or enlarging T2 lesions (48% vs. 58%, p=0.04); decreased patients with contrast lesions (7% vs. 14%, p<0.001), and decreased brain volume loss (-.867 vs. -1.488, p<0.0001). Thirty-nine percent of the alemtuzumab group had no evidence of disease activity compared with 27 percent treated with interferon (p=0.006). Other trials have found similar benefits over interferon.[54,55]

In an extension of two Phase III trials out to six years, 64 and 55 percent of patients received no additional alemtuzumab, 77 and 72 percent did not worsen on EDSS, and 34 and 43 percent actually had improved EDSS scores.[56,57] Brain volume loss over the six years was down to the level in people without MS (< 0.2% loss annually). This is a profound brain sparing effect. In another cohort of 87 patients, 68 percent were improved or stable over a median of seven years.[58]

Alemtuzumab is considered an induction therapy (i.e., long-lasting benefit without having to continue medication). It was previously FDA approved for chronic lymphocytic leukemia and approved for MS in 2014. Its advantages include potent efficacy, long-lasting effects, and convenience of annual administration. Disadvantages include safety concerns, a complicated start-up process, and complicated required monitoring. Safety concerns include immune-mediated thyroid disease, immune thrombocytopenia, anti–glomerular basement membrane disease, and malignancy (thyroid, melanoma, and lymphoproliferative disorders). Patients have to be monitored for four years after administration with monthly blood counts, urinalysis, and thyroid tests and ongoing annual skin and gynecologic exams including screening for human papilloma virus and cervical dysplasia. The principal indication for alemtuzumab is for patients with active RRMS who have failed several other therapies.

Alemtuzumab can cause causes serious and life-threatening infusion reactions. To minimize these reactions, a complex regimen is given before, during, and after the infusion. Cetirizine and ranitidine are given for 14 days prior to the infusion to block histamine. Methylprednisolone, acetaminophen, and diphenhydramine are given immediately before the infusion. The acetaminophen and diphenhydramine can be given as needed after the infusion. Patients must be monitored for two hours after each infusion. Acyclovir 200 mg twice a day is given for two years to prevent herpes infection.

Daclizumab (Zinbryta®) is a humanized monoclonal antibody against IL-2 receptor alpha chain (CD25). Binding to CD25 inhibits T-cell and B-cell activation by IL-2 and expansion of CD56 bright regulatory natural killer (NK) cells. Given subcutaneously monthly, this agent does not have immune depleting or broadly immunosuppressive effects. It was approved for prevention of renal allograft rejection by the FDA in 1997 and approved to treat RRMS in 2016.

Daclizumab results in a significant decrease in ARR with 150 mg (54%) compared to placebo.[59] There is also a significant increase in relapse-free patients, with 150 mg (81%) versus placebo (64%). It reduced three-month disability worsening and MRI lesion activity more than placebo. In a comparison to IFNb-1a, daclizumab decreased ARR by 45 percent and MRI lesion activity over IFNb-1a.[60] Similar 12-week confirmed disability progression was seen with these two agents (16% vs 20%, p=0.16). Overall, daclizumab's efficacy is similar to the oral agents.

There are significant safety issues which limit the clinical use of daclizumab. These include cutaneous events [pruritus, rash, eczema; acne, erythema nodosum, angioedema, and atopic, allergic, seborrheic, or exfoliative dermatitis], increased infections, and increased liver function tests. In one trial, several adverse events occurred more often with daclizumab than with interferon including cutaneous reactions (37% vs 19%; serious 2% vs <1%), hepatic (ALT/AST >5x ULN: 6% vs 3%), and infectious (65% vs 57%; serious 2% vs <1%).[60] Because of these adverse effects, daclizumab is not being used extensively.

Individualizing Therapy
Early treatment with DMTs is the norm in MS

Exhibit 6: Comparison of RRMS Treatments[40-60]

Drug	Potency	Safety	Tolerability	Ease of Use	NEDA
IFNβ's	+	+++	++	++	19% over placebo (OP)
Glatiramer	+	+++	+++	+++	2% over IFNβ
Teriflunomide	+	++	+++	++	13% OP
Fingolimod	++	++	+++	+	20% OP
Dimethyl fumarate	++	++	++	++	13% OP
Natalizumab	+++	+ or +++	+++	++	30 - 32% OP
Alemtuzumab	+++	+	+++	+	12 - 19% over IFNβ
Daclizumab	++	++	++	++	22% over IFNβ
Ocrelizumab*	+++	++	+++	+++	17.8% over IFNβ

* Investigational
IFN = interferon
Subjective ratings: + = low (worst), ++ = moderate, +++ = high (best)

management for several reasons. Most patients ultimately evolve into a secondary progressive course with some degree of permanent disability without intervention. The available treatments are effective in RRMS but not progressive disease and do not restore damaged tissue. Patients who start therapy early have a significant advantage in terms of disability accumulation over time compared with late starters (after 2 years of diagnosis). Although "benign" MS exists, it is rare and the ability to predict prognosis in individual patients is limited. Another reason to treat early is that clinical features correlate poorly with the ongoing inflammation and resultant irreversible tissue destruction in early RRMS. Additionally, standard MRI is difficult to quantify in clinical practice and captures MS pathology incompletely, so only using imaging for determining if therapy is needed is limiting.

Treat to Target in MS is a concept borrowed from rheumatoid arthritis management. There is a shared, explicit goal of therapy to maximize long-term outcomes (neurologic function and health-related quality of life) through effective prevention of MS-related CNS tissue damage. All of the FDA approved DMTs prevent the development of new brain lesions and reduce relapses, but there are differences in efficacy, safety, ease of use, and tolerability between agents and among individuals (Exhibit 6).[40-60] Interferon-b and glatiramer acetate are safe but cause common non-life-threatening adverse effects, have to be administered by frequent injection, and have modest potency. The monoclonal antibodies and oral agents are relatively more convenient, generally well tolerated, have more potent efficacy, and cause rare but potentially severe adverse effects. There is no biomarker to prospectively predict efficacy of specific treatments in individual patients.

Currently, clinicians are picking therapy and adjusting therapy based on prognostic factors, comorbid conditions and ongoing measurement of disease

Exhibit 7: The Cleveland Clinic General Approach to MS Treatment[68]
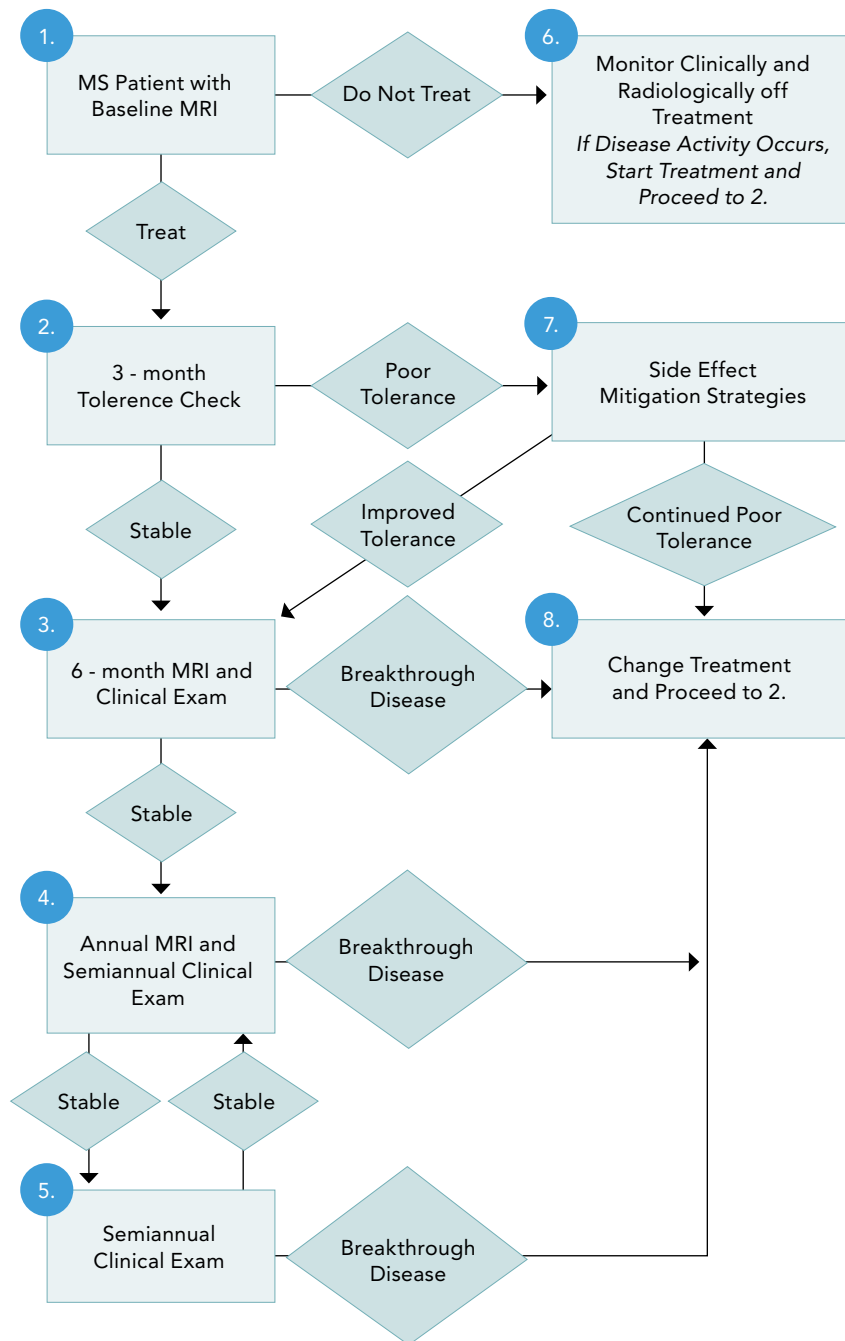
activity and severity. Thus, personalization of MS treatment selection is in its infancy. Disease features suggestive of poor prognosis suggest a need for early definitive therapy. Frequent relapses (particularly if severe), relapse with incomplete recovery, relapse with resultant increasing impairment or substantial MRI lesion burden, repeatedly active MRI scans with increasing lesion burden, two or more relapses in first year, high MRI lesion burden at first episode, progressive clinical course from onset, moderate-to-severe disability at five years, and continued activity despite treatment with a standard agent are all disease features suggestive of poor prognosis.[61-63] Unfavorable patient- related prognostic factors in-

clude male gender, late onset (age >40 years), African American race, cigarette smoking, and vitamin D deficiency.[64-67] It is important to note that prognosis and responsiveness to treatment are not synonymous. Patients with disease suggestive of poor long-term prognosis should receive aggressive therapy initially.

No evidence of disease activity (NEDA) has become the goal with treat to target in MS. It is increasingly being reported in clinical trials and in practice. NEDA is complete absence of detectable disease activity while on DMT. The criteria include no evidence of disease activity on MRI, no clinical relapses, and no disability worsening. Exhibit 6 compares the currently approved agents in terms of NEDA (if known). Achievement of NEDA with the approved agents is not optimal and is less than 50 percent even with the most effective agents.

Monitoring and Adjusting Therapy

Monitoring of therapy both clinically and with MRI is common, though there are no standards, defined targets, or published guidelines. Some MS specialty centers have developed their own care pathways for monitoring DMT. For example, the Cleveland Clinic utilizes a care pathway for therapy initiation and monitoring therapy (Exhibit 7).[68]

Response to a DMT should be systematically and consistently assessed in order to identify suboptimal response to therapy breakthrough disease activity and appropriate treatment strategies. Assessment will require attention both to traditional clinical endpoints such as relapses and disability and outcome measures (e.g., progression on EDSS, MRI parameters, safety, adherence). Most clinicians will assess the patient for medication tolerance three months after starting and then conduct a clinical exam and MRI at six months.

Strategies for Switching Therapy after Inadequate Response with DMT

According to treat to target principles, if someone has evidence of disease activity, therapy should be changed to a different mechanism of activity. Other considerations that may lead to a change in therapy include intolerable adverse effects, detection of antibodies, route of administration problems, comorbidities, and financial/insurance issues. Antibodies may include newly positive JCV antibody titers and significant persistently elevated neutralizing antibodies (NAbs).

A suboptimal treatment response would be indicated by clinical or neuroimaging activity. There is considerable variability in how suboptimal response has been defined in the literature, and there is no consensus. A recent meta-analysis found wide variability among the 75 criteria included in their analysis.[69] A recent panel recommended suboptimal response be considered if at least one of the following criteria was met: greater than one relapse OR one severe relapse in a year; two or more new Gd+ lesions OR two or more spinal cord lesions OR more than two new T2 lesions per year; and two points or more sustained EDSS increase AND/OR greater than 20 percent increase in timed 25-foot walk (T25FW) confirmed at six months.[70] A retrospective analysis of RRMS patients found MRI and disability worsening to be the most common reasons for switching DMTs.[71]

No formal guidelines exist for when to switch therapy and which order to use DMTs. Switches should be made to a new mechanism of action as opposed to a similar mechanism of action. Switches between interferons are not recommended when lack of efficacy is the issue. Switches would be appropriate for adherence issues or patient desire for less frequent administration. Risk of significant disability may negate risk of therapy-related events in selecting an agent for a switch.[72]

Uncertainties in MS Treatment

In addition to a lack of guidelines and which order to use DMT, there are other uncertainties in MS treatment. The available options and how they are used are continually evolving. The roles of new and emerging therapies are still being determined.

Every practitioner has patients in different phases of their disease and has treatment experience with well-established therapies. New MS therapeutic options increase demand on practitioners to achieve optimal Rx response. In the past, practitioners could tolerate a modest amount of disease activity and/or progression of the disease as the options were limited. Now clinicians are concerned about evidence of disease activity. The optimal response for each individual patient's treatment remains an issue for which an inadequate amount of data is available to assist in patient management. The doctor-patient relationship becomes of upmost importance. This is the area where a practitioner becomes an artist in the management of their patient.

Combination therapy has been investigated in the past without great success, but there may be a future for it with some of the newer therapies. Restrictions imposed by insurance coverage, including impact of generics and biosimilars, also impact treatment selection and lead to uncertainty. How to treat progressive MS is a major unresolved issue.

Emerging Therapies

One area of emerging therapy is targeting CD20, a transmembrane protein that functions as a calcium-permeable cation channel. It is present on greater

than 95 percent of B-cells (pre, immature, mature, activated, and memory B-cells) and also present on a small subset of T-cells. It is not present on plasma cells or the antibody producing cells. Targeting CD20+ B-cells depletes circulating B-cells for up to 10 months and may preserve B-cell reconstitution and long-term immune memory.

Rituximab (Rituxan®) is an anti-CD20 monoclonal antibody that is not currently FDA approved for MS treatment but is frequently used for this purpose off-label. It is approved for treatment of non-Hodgkin lymphoma and rheumatoid arthritis (RA) and is given intravenously every six months. There have been no major safety issues even when it has been used in combination with immunosuppressive therapy in RA. The risk of PML with rituximab in RA is 1 in 25,000; the risk in MS in unknown.[73]

Ofatumumab (Arzerra®) is another anti-CD20 monoclonal antibody that is FDA approved for chronic lymphocytic leukemia treatment. This agent has enhanced complement-dependent cytotoxicity (CDC) compared with antibody-dependent-cellular cytotoxicity (ADCC) activity and binds to a unique CD20 epitope. It is given intravenously and subcutaneously and is being investigated in Phase II trials for RRMS treatment against teriflunomide.

Ocrelizumab (Ocrevus®) is an investigational anti-CD20 monoclonal antibody that will likely be FDA approved in 2017. The FDA requested additional information on the manufacturing process in late 2016. It selectively depletes B-cells via ADCC, CDC, and apoptosis and is given by infusion every six months. Ocrelizumab is similar to rituximab (>90% epitope overlap) but is humanized instead of chimeric, has a different though overlapping antigen site, and more potent effect on ADCC and apoptosis and less potent effect on CDC. The higher percentage of human component should lead to fewer infusion reactions.

Compared with IFNβ-1a, ocrelizumab reduced ARR (46-47%), 12- and 24-week confirmed disability progression (CDP, by 40%),T1 Gd+ lesions (by 94–95%), and new and/or enlarging T2 lesions (by 77–83%).[74] The NEDA was 47 percent with ocrelizumab and 29.2 percent with IFNβ-1a. The safety profile of ocrelizumab is similar to IFNβ-1a with first dose infusion-related reactions being the most common adverse effect.

Ocrelizumab showed some efficacy over placebo in one trial in PPMS but that efficacy appears to have been driven by the 25 percent subset of patients with an inflammatory component as indicated by new or active lesions on MRI.[75] This trial was different from other PPMS studies in that the subjects were younger and more had the inflammatory component. In a post hoc analysis of this study, no evidence of progression (NEP) at 120 weeks was 42.7 percent versus 29.1 percent in the placebo group (p=0.0006). NEP was no deterioration on the EDSS, T25FW, and 9-hole peg test (a measure of hand function).

Ocrelizumab was granted breakthrough therapy designation for PPMS in mid-2016. If approved as the first agent with an indication for PPMS, most clinicians will likely start this agent in the patients who have demonstrated active lesions on MRI who are most likely to benefit.

The most common adverse effects of anti-CD20 agents involve infusion-related reactions (fever, headache, rigors, flushing, nausea, rash). Strategies to reduce infusion-related reactions involve slowing infusion and premedication.

Before being given an anti-CD20 agent, patients need to be screened for hepatitis B and C and tuberculosis which would be worsened by B-cell suppression. Immune globulin levels can also be altered with anti-CD20 therapy, which will increase risk of infection. Human anti-globulin antibodies and human anti- chimeric antibodies have not been an issue so far with the investigational anti-CD20 .There were a few more cases of breast cancer than would have been expected in the ocrelizumab treatment groups compared with placebo in one trial (2.3% vs. 0.8%) but not in the other (0.5% vs. 0.2%).[74,75] There are concerns that long-term suppression of B-cells may lead to cancers or other unanticipated adverse effects.

The American College of Rheumatology recommends certain vaccines before rituximab is started in rheumatoid arthritis.[76] It is likely similar recommendations would be made for anti-CD20 therapy in MS. Prior to therapy, appropriate killed vaccines (pneumococcal, influenza, hepatitis B); recombinant vaccine (human papilloma) and live attenuated vaccine (zoster) in those 50 years or older should be considered. On therapy, appropriate killed and recombinant vaccines can be considered, but not live vaccines.

There is speculation on what role the various anti-CD20 agents will have when approved. They may be used as initial therapy for RRMS in those with high disease activity and a poor prognosis profile or as switch therapy for RRMS in those with breakthrough disease activity, for guaranteed adherence, for convenience (Q6 months therapy), or for favorable adverse effect profile. Approval for PPMS would likely enhance use in RRMS. It is a question to be answered whether off-label rituximab will be a more cost-effective alternative.

Other agents under study for RRMS include

ublituximab, another anti-CD20 monoclonal antibody, selective S1P receptor modulators like fingolimod (ponesimod, siponimod, ozanimod) and oral α4β–integrin antagonists. Firategrast is an anti-α4β-integrin small molecule with a similar mechanism of action to natalizumab, but its faster elimination could provide an improved safety profile and oral administration would improve ease of use.

High-dose immunosuppressive therapy and autologous hematopoietic stem cell transplantation is under study for RRMS.[77-79] The goal of this therapy is to reprogram or reboot the adaptive immune system. In one study that used autologous CD34+ selected peripheral blood stem cell grafts, the overall event-free survival was 78.4 percent at three years. Progression-free survival and clinical relapse-free survival were 90.9 percent and 86.3 percent respectively, at three years. Adverse events were consistent with expected toxic effects associated with the high- dose chemotherapy regimen used to wipe out the immune system. Studies to date in MS have utilized various regimens, small cohorts, and variable follow-up periods. A recent meta-analysis (N=887) found a 1.9 percent mortality with stem cell transplantation for MS.[80] The post 2009 studies had a zero percent mortality versus 3 percent in earlier studies. Mortality was associated with progressive MS, increased age, and increased EDSS. The NEDA after stem cell transplantation was 67 percent at five years.

Additional treatments for progressive MS under investigation include comorbidity management, high-dose biotin, and repair and neuroprotective strategies such as blockers of neurite outgrowth inhibitor to promote axonal sprouting, blockers of LINGO-1 which promote oligodendrocyte differentiation, growth factors to promote neuronal survival, and anti-apoptosis factors to promote survival of neurons and oligodendrocytes.

Vitamin D Supplementation
Given the association of vitamin D levels and the development of MS, clinicians have wondered whether vitamin D supplementation would alter the MS disease process. In a small double-blind, placebo-controlled trial of MS patients, vitamin D2 6000 IU/day provided no therapeutic advantage in RRMS over low dose D2.[81] In a one-year trial of escalating vitamin D doses, patients who were supplemented appeared to have fewer relapses and persistent reduction in T-cell proliferation. This trial gave doses up to 40,000 IU/day over 28 weeks, followed by 10,000 IU/day over 12 weeks and then no vitamin D for 12 weeks.[82] For some patients, it may be difficult to increase their levels adequately. In one study of vitamin D supplementation, MS pa-

tients had a significantly lower increase in vitamin D levels compared with controls.[83]

In a small trial of pregnant women with MS with low vitamin D levels, 50,000 IU/week of D3 was compared to routine care.[84] During pregnancy, the immune system automatically downgrades, so MS tends to improve. The average serum level at the end of the trial (6 months after delivery) was greater in the supplemented group (33.7 ng/ml vs. 14.6 ng/ml, p<0.050). The EDSS score did not change in the supplemented group six months post-partum versus an increase in EDSS score in the non-supplemented group (p<0.07). Those with vitamin D supplementation had fewer relapses during pregnancy and six months post-partum.

There are not a lot of good sources that take all the studies and come together to make a recommendation for vitamin D supplementation in MS. The Canadian Agency for Drugs and Technologies in Health did a systematic review that found there was limited evidence suggesting potential benefit of vitamin D supplementation for prevention of MS and no evidence to support treatment benefits, but more studies are needed.[85] The review noted that high-dose vitamin D is well tolerated and associated with minimal risk.

Iran has published a consensus statement on use of vitamin D in patients with MS.[86] These guidelines recommend vitamin D supplementation in MS and CIS patients with vitamin D levels less than 40 ng/ml with 50,000 IU per week for eight to 12 weeks as a loading dose; then a maintenance dose of 1500 to 2000 IU per day is suggested. The guidelines recommend checking serum vitamin D twice a year (beginning of spring and autumn) in MS patients. Additional recommendations include checking vitamin D levels for first-degree relatives of MS patients at high-risk age and supplementing for levels less than 40 ng/ml. For women considering pregnancy, vitamin D deficiency should be corrected before pregnancy. The guidelines suggest that 1500 to 2000 IU per day be given during the second and third trimesters. Many American clinicians routinely check vitamin D levels in their MS patients and supplement those who have low levels.

Several large-scale, methodologically rigorous trials of vitamin D in MS are underway. It is hoped that results of these trials will help to clarify some of the uncertainty surrounding the effectiveness of vitamin D supplementation for the treatment of MS.[84]

Overcoming Barriers to Treatment
There are numerous barriers which prevent optimal treatment of MS. One is access to MS specialists, which is an issue in many parts of the country where

there are just not enough neurologists who specialize in MS. Few general neurologists are comfortable in prescribing oral DMT or infusion therapies. They are comfortable with interferon and glatiramer.

Another barrier is medication cost. DMT costs average $65,000 per year. Costs have increased annually at rates five to seven times higher than prescription drug inflation. Newer DMTs commonly enter the market with a cost 25 to 60 percent higher than existing DMTs. DMT costs in the U.S. are two to three times higher than in other comparable countries.[87]

The high cost of these agents has led to insurance restrictions which can make prescribing DMT burdensome for clinicians and patients and limit access. Many of the restrictions require a patient to fail one or more prior therapies, which is not always the appropriate medical decision to gain early aggressive control over inflammation. Practices of U.S. health insurance companies concerning MS therapies have been noted to interfere with shared decision-making and to harm patients.[88] In a North American Research Committee on Multiple Sclerosis (NARCOMS) survey regarding health insurance coverage sent to MS patients, 98.5 percent of respondents had health coverage, but 22.1 percent reported a negative insurance change in the past year.[89] Among those not taking DMT, 6.1 percent cited insurance or financial issues as the only cause. Twenty- five percent on DMT relied on support from free or discounted drug programs. For those with RRMS, negative insurance change increased their odds of not taking a DMT or using free/discounted programs to get a DMT. Generics/biosimilars for many of the already approved agents will likely be coming to market in the near future which will help ease some of the cost pressure.

Adverse effects with DMTs are another barrier. Some are better tolerated than others. In addition to adverse effects, administration method can be another barrier. It can include shot fatigue with self-injectables and time commitment with the infusion therapies. Patients can also have issues with skin and intravenous access. A barrier with the infusion therapies is the need to have transportation to the infusion center.

The self-injectable DMTs are now easier to give than in the past. They now come in prefilled syringes (PFS) with or without automatic injection devices, preloaded one-time use automatic injection devices, or electronic auto-injector. Injection devices and auto-injectors were favored over administration with a needle and syringe, particularly with respect to ergonomics, convenience, and portability.[90,91] Auto-injectors have several advantages, including reduced pre-shot anxiety, maintenance of patient autonomy, and fewer injection site reactions. It is also easier to individualize injection depth for different shot locations, they are easy to use with one hand, and electronic versions include tracking and provide the ability to alter the speed of injection. It appears that electronic auto-injectors help improve medication tolerance, adherence, and patient satisfaction, but the data are limited.[92,93]

Because treatment of MS is a lifetime endeavor, adherence and persistence with DMT treatment can be a major barrier. A retrospective cohort study using enrollment/claims data used a medication possession ratio (MPR) greater than 80 percent to define adherent.[94] Those individuals more likely to be adherent were over 45 years old or male. Factors that made patients less likely to be adherent included depression and injection site reactions from self-injected DMTs. Compared with injectables, oral agents appear to increase adherence. A study looking at fingolimod adherence found that the discontinuation rate was higher for glatiramer, interferon, and natalizumab than for fingolimod.[95] One study did find that adherence was better with glatiramer compared with the oral therapies.[96] A big barrier to adherence is changing in insurance coverage frequently. This leads to significant confusion and treatment lapses in getting regimens approved.

Another barrier to effective outcomes is patients stopping DMT on their own. The National MS Society notes five main reasons why patients stop DMT. These include not feeling any better, adverse effects that feel worse than the disease, relapses despite therapy, insurance coverage issues, and inability to afford co-pays.[97] Education on the importance of continuing therapy and how to deal with adverse effects can help patients remain on therapy.

Discontinuing Therapy
Older patients without current activity can have DMT therapy stopped, but many patients are reluctant to stop. There is a current trial looking at this issue. Providers can suggest a trial off medication with monitoring, especially if a patient is having adverse effects. Age appears to be the biggest factor predicting that stopping medication can be effective. Those older than 65 are more likely to have success in discontinuing treatment.

Payer Management of MS Care
There is currently insufficient Class I evidence for a detailed MS treatment algorithm, and there are still no national guidelines that can be used (unlike for many other diseases). The lack of definitive clinical evidence to guide MS treatment decisions has become increasingly important as the number of thera-

peutic options continues to increase annually. Payers struggle with which drug is right for which patient and how to balance costs, outcomes and access. It is important that payers ensure access to all DMT categories for appropriate patients. Therefore, plans must conduct their own assessments of literature and data, consider the newer agents and their roles in therapy, and work with physicians to assess the role of newer therapeutic agents. Plans should consider establishing quality metrics to improve outcomes in MS. Patient education and support programs can be used to improve outcomes.

As noted before, adherence and persistence are issues in MS management. Payers should look to actively manage medication adherence because of their large fiscal investment in MS treatments. DMT that is not taken is wasted money. Nurse case managers and specialty pharmacists can be utilized to help patients manage adverse effects, understand the need for continuing DMT even when MS is controlled, maintain adherence by understanding the directions for use, be persistent with therapy for the long-term, and complete any post-treatment monitoring.

Adherence with DMT can have an impact on costs. In a retrospective analysis of 2,407 natalizumab patients, those who were consistently persistent had the lowest relapse rate and lowest one-year relapse cost.[98] Those who were not persistent had significantly higher relapse rates and one-year relapse costs compared with those who were persistent.

Site of service management is one option for managed care to control MS costs. In a retrospective analysis on the impact of site of care on natalizumab utilization and cost in four geographic areas, hospital outpatient department administration was more expensive than physician office administration. [99] Hospital outpatient department administrations accounted for 40 percent of claims but 50 percent of cost. Physician office administration accounted for 50 percent of claims and 43 percent of cost. Home infusion accounted for 10 percent of claims and 8 percent of cost. This analysis concluded that managing the site of service of infused agents can a have substantial cost impact.

Conclusion

MS is a lifelong and disabling disease with an unpredictable course. Clinicians are increasingly categorizing patients as having active or inactive and progressive or non-progressive disease to accurately know what is going on with the patient. The goal of treatment in RRMS is to prevent relapses to avoid disability accumulation. This will help patients continue to be functioning, contributing members of society. There is a window of opportunity to impact development of irreversible damage and disability with early DMT which impacts the natural history of the disease. There is a new emphasis on strategies targeting B-cells. The current focus is on anti-CD20 monoclonal antibodies which are poised to be a significant treatment choice in RRMS and possibly in progressive MS. There are many barriers to successful MS treatment, but managed care can have an impact with patient support programs. It is all about taking care of patients early in the disease process so this generation of MS patients will have limited disability and will maintain the ability to work, raise their families, and have health insurance. They will be different from previous generations of MS patients who were very disabled.

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