DEFINING SUCCESS IN MULTIPLE SCLEROSIS: TREATMENT FAILURES AND NONRESPONDERS*

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ABSTRACT

Despite significant therapeutic advances in the treatment of multiple sclerosis (MS), the challenges facing neurologists are considerable. Because reliable predictors of sustained and progressive disability are lacking, there is a critical need for guidance regarding the definition and identification of treatment success and failure, breakthrough disease, and inadequate treatment response. Likewise, clinicians need practical treatment algorithms that focus on strategies for nonresponders, including the relative merits of drug dosage adjustment, switching therapies, and the use of combination therapies. This article identifies characteristics of patients with MS who are inadequate responders and discusses issues regarding treatment modification in these individuals.

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Although there have been significant advances in the management of patients with multiple sclerosis (MS) over the past decade, neurologists continue to face substantial challenges in the diagnosis, monitoring, and treatment of this disorder.

Disease onset and progression in MS is highly variable; this makes it challenging to predict its course for individual patients. The underlying mechanisms that lead to MS progression remain uncertain, which makes the timing of treatment initiation a significant challenge.

Initially, an unidentified factor triggers immune system inflammatory "attacks" on myelin sheaths, causing interference in the conduction of nerve impulses. These episodes of inflammation are sometimes clinically apparent, manifesting as a "relapse." The transition from relapsing to progressive disease typically represents a crossroads for treatment response; yet it is clear that axonal damage may be present at the earliest stage of disease or may occur at any time over the course of MS. The extent of axonal damage among patients with MS is highly variable, but it does appear that the accumulation of axonal destruction underlies clinical progression.[1,2] The benefits of early treatment are becoming increasingly apparent as evidence mounts to show that episodes of inflammation contribute to permanent axonal damage.

To date, no single drug has proven fully effective in halting disease progression or disability. Furthermore, there are limited comparative data among currently approved MS agents to assist clinicians in choosing an initial therapy. After therapy is initiated, it is equally hard to define what constitutes success and failure for an individual patient. Markers that are frequently used in assessing treatment efficacy in patients with MS, such as relapse frequency, acquired neurologic deficits, or new findings from magnetic resonance imaging (MRI) studies, are not absolute predictors of long-term prognosis.[3] Adverse effects of treatment, as well as treatment noncompliance, further confound clinical assessment and therapeutic modification. Nonetheless, it is recognized that currently approved agents are likely to reduce disease activity and improve quality of life for

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patients with relapsing MS. To achieve these benefits, treatment must be continued for years; stopping therapy can result in a return to pretreatment disease levels.[4]

In this article, we explore several key concepts that clinicians must grapple with in order to accurately identify nonresponders, including those exhibiting disease progression, breakthrough disease, treatment success, and treatment failure. When faced with a patient who fits the portrait of a nonresponder, the clinician has the latitude to choose among divergent strategies, including continuing current therapy, changing the dose of a current medication, switching therapies, or introducing combination therapy. To explore current views on these topics, we also present responses to survey questions posed to community neurologists during 2 recent conferences held in Dallas, TX, and Philadelphia, PA, on the topic of MS disease-modifying therapy nonresponders. In addition, we propose algorithms for treating this group of patients and provide guidance for clinical decision making.

Defining MS Nonresponders

Defining nonresponders is a challenge within the current environment of partially effective therapeutic options, in tandem with a disease that is highly variable both in its presentation and course. Typical presentations and the characteristics of disease progression in MS have been well described in several studies worldwide; however, grouped data provide little to help prognosticate in individual cases.[5] In its natural history, MS prognosis is determined by the frequency and features of relapses in the early years of disease, as well as by distinguishing between relapsing-remitting disease and progressive disease, which may overlap with relapses (Table 1). Approximately 85% of patients present with a relapsing-remitting (RRMS) pattern of disease that is characterized by an initial episode of acute disease-related symptoms followed, in most, by some residual deficits or a full recovery over a few weeks to months. Up to 20% of these patients may remain clinically stable for

Table 1. Disease Patterns in MS

Disease Pattern	Description of Disease Course	Comments
Clinically isolated syndrome	A clinically discrete demyelinating event involving the optic nerve, spinal cord, or brain stem/cerebellum	Subclinical demyelination seen on brain MRI. Multiple differential diagnoses must be considered.
Relapsing-remitting MS	Episodic onset followed by residual deficits or full recovery	Presentation in approximately 85% of cases. Presents most frequently in women aged 20–40. Approximately 20% remain clinically stable for 20 years after an initial episode.
Primary progressive MS	Aggressive progression is present from the outset without relapsing events	Occurs in about 15%–20% of cases. Affects men and women equally, occurs in older individuals, and is unresponsive to immunomodulatory agents.
Secondary progressive MS	Chronic, steady increases in symptoms and disability	Occurs almost universally in definite MS. Time framework varies greatly.
Progressive relapsing MS	Progressive disease from onset, along with acute relapses, with or without recovery	Rare
Benign MS	Patient remains fully functional in all neurologic systems 15 years after disease onset	Many will go on to develop progression after 15 years.
Clinically definite MS	Evidence of lesion in the CNS disseminated over time and space (>1 episode involving >1 area of the CNS)	Diagnosis according to 2005 McDonald criteria includes definite MRI lesions and may include other supportive evidence, such as CSF and visual evoked potentials.

CNS = central nervous system; CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; MS = multiple sclerosis.

up to 20 years without therapy, giving rise to the concept of "benign MS," which raises the clinical question of whether or not early treatment will alter the course of disease in this subset of patients. Benign disease is statistically more frequent in younger female patients with fewer functional symptoms and lower disability scores at onset.[6] However, recent data from longitudinal surveys of patients with benign MS show that many (if not most) of these patients will ultimately acquire significant disability.[7] With or without treatment, a large number of patients with MS progress to a secondary-progressive (SPMS) pattern over time. Evidence indicates that, once progressive disease develops, the rate of progression is influenced little by the pattern of disease onset.[5]

To further confound decision making for patients with MS, up to 15% follow a primary progressive pattern, in which progression persists with or without treatment; however, such patients may eventually develop relapses (designated as progressive relapsing MS), and therefore may benefit from therapy. Patients who present with a clinically isolated syndrome that cannot be definitively diagnosed at onset as MS are considered in a separate article in this monograph (see article by Bruce Cree, MD, PhD, MCR, and Timothy L. Vollmer, MD).

Clinical Definition of Disease Progression

In the clinical setting, measures of ongoing disease activity are determined by a composite of relapse rate, periodic MRI findings, the clinical neurologic examination, disability scores, neuropsychological functioning assessments, as well as the patient's assessment of his or her level of functioning (eg, activities of daily living [ADLs]) and quality of life. Disability has classically been quantified by sequential use of the Expanded Disability Status Scale (EDSS; Table 2).[8] The EDSS quantifies disability in the areas of pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, and cognitive functioning. However, this assessment is highly limited in its characterization of vitally important aspects of function, such as cognitive and intellectual capability, mood, and

Table 2. Expanded Disability Status Scale

Score	Description	Ambulation
0	No disability	Fully ambulatory
1	Minimal signs in 1 function	
1.5	Minimal signs in >1 function	
2	Minimal disability in 1 function	
2.5	Mild disability in 1 function or minimal disability in 2 functions	
3	Moderate disability in 1 function or mild disability in 3–4 functions	
3.5	Moderate disability in >1 function	
4	Severe disability but able to work, walks without aid 500 meters without rest	
4.5	Severe disability but able to work, walks without aid 300 meters without rest	
5	Severe disability, unable to work, walks without aid 200 meters without rest	Assisted ambulation
5.5	Severe disability, limited activities, walks without aid 100 meters without rest	
6	Above plus intermittent or unilateral walking aid (cane, crutch, or brace)	
6.5	Above plus constant bilateral walking aid (canes, crutches, or braces)	
7	Wheelchair bound, wheels self and transfers alone	Non-ambulatory
7.5	Wheelchair bound, may need aid for transfers and mobility in wheelchair	
8	Bed or chair bound, retains many self-care functions	
8.5	Bed bound, retains some self-care functions	
9	Bed bound, needs assistance with self-care, can communicate and eat	
9.5	Totally dependent, unable to communicate effectively or eat/swallow	
10	Death due to MS	

MS = multiple sclerosis.
Data from Kurtzke.[8]

quality of life. Instead, the EDSS is principally weighted on ambulation, which severely limits its ability to fully represent all aspects of disability that are important to patients with MS and their families. Individuals with EDSS scores from 1 to 4.5 are fully ambulatory, whereas those with scores from 5 to 9.5 have increasing degrees of ambulatory dysfunction and dependency in ADLs. Both MRI changes over time and increasing MRI lesion volume are associated with worsening of EDSS scores[9]; however, clinical use of the EDSS is limited due to time and staffing constraints, particularly due to the 500-meter walk requirement. A modified functional assessment is provided by the MS Functional Composite (MSFC), which combines a 25-foot timed walk, the 9-hole peg test to assess upper extremity function, and the paced serial auditory addition test to assess information processing speed.[10] In spite of the importance of these tools in assessing disease progression, 92% of neurologists working in the community (48 out of 52) surveyed indicated that they did not perform an EDSS or MSFC at every clinic visit. Thus, it is probably unreasonable to assume that these tools could be used to determine whether patients are "nonresponders" in typical neurology practices.

Numerous clinical risk factors have traditionally been used to predict more rapid disease progression, including older age at onset, male gender, MRI status, shorter interval between first and second attack, high relapse rate during the first 2 years, and incomplete recovery following an attack. Patient risk is assessed according to the number of risk factors identified; individuals with 0 or 1 risk factor are classified as low risk, whereas those with 2 or 3 risk factors are classified as medium risk, and patients with 4 or more risk factors are classified as high risk. Yet, prospective studies stratifying patients into these arms and assessing its impact on therapeutic decision making are lacking.

Role of Imaging Studies in Predicting Disease Progression

Although the diagnosis of MS remains a clinical one, evidence from MRI studies has proven increasingly valuable in diagnosing and managing the disease and in predicting progression. Although MRI is currently the most sensitive tool for investigating MS, it is important to note that the appearance of multiple lesions on any single MRI study is not diagnostic or predictive of disease progression; conversely, serial studies have shown that clinical evidence of disease stability is not reflective of current disease activity as defined by MRI findings.[11] New lesions on MRI in a patient who is clinically stable are indicative of active disease, and are particularly useful in defining breakthrough disease in individual patients. Indeed, the 2005 revision of the McDonald criteria for diagnosis of MS accepts the appearance of new lesions on MRI as fulfilling the separation in time component of the diagnostic criteria (Table 3).[12,13]

Defining Treatment Success

It is important to be able to recognize when a current therapy should be maintained and when a therapeutic change is warranted. Ideally, a successful therapy would prevent all new symptoms and disabilities; however, no current therapies are fully successful in this fashion. At present, assessing treatment efficacy requires the use of all available markers and predictors of the future course of the disease. Signs of progression may include an increase in the rate of relapse, new MRI evidence of disease activity, progressive disability as measured on the EDSS, or the appearance of new brain stem/cerebellar or cognitive deficits. Signs of disease progression in a treatment-naïve patient signal the need to initiate therapy. In some cases, disease progression may be an indication of treatment failure. If a patient does not experience a reduction in progression or rate of relapses after initiating a therapy, then it could be argued that the patient is not deriving a significant benefit from the medication. When asked to assess the relationship between relapse rate as one measure of disease progression and the recognition of treatment failure, 44% and 56% of neurologists ($n = 27$) judged that treatment failure had occurred when the number of relapses taking place during a 12-month period was 1 or 2, respectively.

Defining Breakthrough Disease

Although disease progression can be considered treatment failure, in an individual patient it might be classified as breakthrough disease. Because of the variability of MS, it is necessary to define breakthrough disease on a case-by-case basis. Breakthrough is generally characterized as unacceptable clinical or radiographic evidence of disease activity that is not sufficiently controlled by current treatment intervention, assuming treatment compliance. In breakthrough disease, treatment efficacy that had been established over a period of time disappears, and there is further progression of disability, increased relapse frequency, increased MRI evidence of disease activity, and new cognitive or brain stem/cerebellar deficits. Breakthrough differs from treatment failure pri-

Table 3. McDonald Criteria for the Diagnosis of MS Using MRI

MRI Criteria for Lesion Dissemination in Time	MRI Criteria for Lesion Dissemination in Space
• Detection of Gd enhancement at least 3 months after the onset of the initial clinical event, if not at the site corresponding to the initial event OR • Detection of a new T2 lesion if it appears at any time compared with a reference scan done at least 30 days after the onset of the initial clinical event	Three of the following: • At least 1 Gd-enhancing lesion or 9 T2 hyperintense lesions if there is no Gd-enhancing lesion • At least 1 infratentorial lesion • At least 1 juxtacortical lesion • At least 3 periventricular lesions Regarding spinal cord lesions: • A spinal cord lesion can be considered equivalent to a brain infratentorial lesion • An enhancing spinal cord lesion is considered equivalent to an enhancing brain lesion • Individual spinal cord lesions can contribute together with individual brain lesions to reach the required number of T2 lesions

Gd = gadolinium; MRI = magnetic resonance imaging; MS = multiple sclerosis.
Data from Nielsen et al.[11]

marily in the timing of worsening of disease activity and manifestations. Breakthrough activity is not necessarily a reason for discontinuation of current therapy, although modification should be considered. Hopefully, the use of newer imaging techniques, including magnetic resonance spectroscopy, magnetization transfer, and diffusion tensor imaging, will lead to improvements in the ability to assess disease burden.[1,2]

Distinguishing treatment failure from breakthrough disease depends a great deal on a collaborative interpretation of objective and subjective findings by the clinician and patient. Treatment failure in one patient may be viewed as breakthrough disease in another. In order to help patients with MS differentiate between treatment failure and breakthrough disease, they should be made aware early in the course of treatment that disease activity is expected even with therapy. Thus, before initiation of therapy, patients should be educated regarding available treatment options, the time course for evaluating a treatment, and realistic expectations while on therapy. The patient's tolerance for ongoing disease activity should be explored, and the patient should undergo regular evaluation of disease activity with ongoing discussion of the benefits and risks of therapy modification. Regular evaluations should include sequential neurologic examination and patient assessment of his or her quality of life and ability to perform ADLs. For patients receiving interferon (IFN) β therapies, some argue that it is also prudent to evaluate levels of neutralizing antibodies (NAbs) to IFN (to differentiate between breakthrough disease and treatment failure). NAbs have been shown to decrease the biologic response to treatment with IFNβ after 18 to 24 months of therapy, and MRI lesions are increased in NAb-positive patients.[1,2,14,15] It is important to note that clinical stability does not preclude the need to investigate for development of NAbs, as occult disease is more common in NAb-positive patients. The development of NAbs is more likely seen with high doses of IFN, versus low-dose IFN, but can be seen with either. Although the European community recommends regular screening for NAbs, the recommendation has not been recreated in America. Indeed, a single positive NAb test in a patient who is doing well is not justification to withdraw therapy. It has also been noted that 5% to 10% of patients undergoing therapy with natalizumab can develop NAbs that diminish or negate treatment effects. Of the US Food and Drug Administration (FDA)-approved medications currently available, only glatiramer acetate (GA) has not been associated with clinically significant antibody formation.

Treatment Algorithms

Several treatment strategies are employed over the course of MS to achieve the best possible patient outcomes. Current therapies for MS are summarized in Table 4.[1,2,16-29] Optimal therapies should demonstrate long-term benefit to patients with regard to physical, MRI, and cognitive outcome measures and a favorable side-effect pro-

file. Although current therapies do not cure MS, several medications are currently approved by the US FDA as disease-modifying agents (DMAs) that demonstrate at least some of the above capabilities. Primary approved therapies, including IFNβ (intramuscular IFNβ-1a, subcutaneous IFNβ-1b, and subcutaneous IFNβ-1a) and GA, have been shown to alter the natural history of MS by preventing or delaying disease progression. At 18 to 24 months, IFNβ agents appear to be more effective than GA in controlling the formation of new MRI lesions, but relapse rate reductions are very similar. Among the IFNβ agents, intramuscular IFNβ-1a and subcutaneous IFNβ-1a are the only agents approved by the US FDA to reduce disability progression in RRMS. Natalizumab is recom-

Table 4. MS Treatments

Treatment	Status	Suggested Mechanism of Action	Efficacy
IFNβ by SC injection	3 US FDA-approved agents: • IFNβ-1a (IM and SC) • IFNβ-1b (SC)	• Inhibits adhesion • Inhibits synthesis and transport of MMPs • Blocks antigen presentation • May show loss of efficacy after 2 years if neutralizing antibodies are present	• All 3 reduced relapses and disability, but only modestly • All 3 significantly reduced Gd+ and T2 lesions on MRI • IM IFNβ-1a and SC IFNβ-1b improved cognitive dysfunction
GA by daily SC injection	1 US FDA-approved agent	• Increases regulatory T cells • Suppresses cytokines • Blocks antigen presentation	• Reduced relapses and disability • Reduced Gd+ and T2 lesions on MRI
Natalizumab	1 US FDA-approved agent	• Selective adhesion molecule inhibitor	• Dramatic reduction in relapse rate, MRI lesion formation, and disability over 2-year study • Safety, with respect to development of PML, needs to be verified in post-marketing surveillance
Mitoxantrone	1 US FDA-approved agent	• Antineoplastic agent • Reduces cytokines • Eliminates lymphocytes • Potential cardiotoxic effects • Increased risk of leukemia	• Used primarily in secondary progressive MS • Reduced lesions seen on MRI • Slows progression • Platform for combination therapy
Corticosteroids (usually IV methylprednisolone)	Adjuvant therapy used over the past 2 decades	• Inhibits synthesis and transport of MMPs • Alters cytokine profile • Reduces CNS edema	• Hastens recovery from relapses • Reduces tissue damage • Promotes lesion recovery
Azathioprine	Adjuvant therapy first proposed for MS therapy 30 years ago	• Inhibits purine synthesis	• Slows secondary progression • Potential for bone marrow toxicity
Methotrexate	Adjuvant therapy	• Folate antagonist	• Slows secondary progression • Currently being studied in combination with IM IFNβ-1a and corticosteroids
Plasma exchange	Adjuvant therapy	• Removes deleterious antibodies	• Short-term treatment for acute inflammatory demyelinating polyneuropathy
Intravenous immunoglobulin	Adjuvant therapy	• Anti-idiotypic effects • Blocks Fc receptors • Alters cytokine profile	• Treatment and prevention of relapses in patients with treatment failures

CNS = central nervous system; FDA = Food and Drug Administration; GA = glatiramer acetate; Gd = gadolinium; IFN = interferon; IM = intramuscular; IV = intravenous; MMP = matrix metalloproteinase; MRI = magnetic resonance imaging; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy; SC = subcutaneous.

mended for patients who have had an inadequate response to, or are unable to tolerate, other primary MS therapies. In addition, mitoxantrone may be considered for worsening disease in selected relapsing patients or patients with SPMS with or without relapse. With any of these therapies (with the exception of mitoxantrone), treatment must be sustained for years.

When asked to choose between IFN, natalizumab, combination glatiramer and IFN, cyclophosphamide, and monthly steroids as a therapy change for a patient currently receiving glatiramer, 46% of surveyed neurologists selected IFN, 42% selected natalizumab, and 12% indicated combination glatiramer and IFN (n = 26). Discussions indicated that as safety data for natalizumab become clearer, it may become the preferred second-line drug for most patients. Although DMAs reduce the number of RRMS relapses, they appear to be less effective (or ineffective) in purely progressive disease, and seem to have limited effect once the disease enters a secondary-progressive phase.[11] Current data indicate that mitoxantrone is the most favorable SPMS treatment option; however, GA has not yet been studied in SPMS.

There are 3 strategies to consider when breakthrough disease is encountered on a current therapy: (1) change the dose; (2) switch therapies; or (3) add a therapy to the current regimen (combination therapy). A review of open-label, prospective studies ranging in duration from 63 weeks to 6 years, and involving nearly 5000 patients, revealed no advantage to increasing the dose of an ongoing primary therapy.[30,31] For example, an evaluation of extended intramuscular IFNβ-1a treatment conducted by Clanet et al found equal efficacy over 4 years among patients with MS treated with either 30 or 60 µg intramuscular IFNβ-1a.[32]

Switching Therapies

There are no current data from controlled, prospective, direct-comparison clinical trials to support switching therapies in the event of treatment failure with a primary DMA in MS. Furthermore, there is little evidence to direct when we should discontinue a therapy in the event of breakthrough disease.[33,34] Recent data from the retrospective QUASIMS (Quality Assessment in MS Therapy) study compared IFNβ therapies in RRMS and found no clinical benefit as a result of switching between IFNs.[35] In QUASIMS, 4754 patients with RRMS who were enrolled in open-label studies of intramuscular IFNβ-1a, subcutaneous IFNβ-1b, and subcutaneous IFNβ-1a (at 2 doses) were analyzed retrospectively. Evaluated outcomes included disability progression, percent of progression-free patients, percent of relapse-free patients, annualized relapse rate, and reasons for changing therapies. Investigators concluded that switching between different IFNβ agents provided no clinical benefits; however, findings based on aggregate data do not preclude a benefit for individual patients. Furthermore, the study found that NAbs had no observable impact on clinical efficacy until 2 years after the initiation of IFN therapy. In summary, unless side effects are significant, toxicity is unacceptable, or NAbs are present after 2 years of therapy, there is currently no tried and true algorithm for changing therapies between IFNβ agents or between an IFNβ agent and GA. Yet, these data did not track the outcomes for patients switching from an injectable medication to natalizumab.

Combination Therapy

Compared with the limited benefits of dose changes with a current agent or switching agents when breakthrough disease is encountered in patients with RRMS, combination therapy has some potential distinct advantages.[36,37] The current strategy for designing a combination regimen has been developed in anticipation of encountering 3 disease stages. During the first stage, a patient is stabilized on a platform DMA, such as an IFNβ or GA.

Therapy is escalated to stage 2 when breakthrough disease occurs. In general, this would involve maintaining platform therapy at the same dose and adding pulsed corticosteroids intermittently as needed to control relapses and symptoms. If breakthrough disease persists, stage 3 is implemented by continuing the platform agent along with pulsed corticosteroids and/or the addition of another agent or changing the platform agent. There are no large-scale trials that identify the efficacy of long-term combination therapies in MS, thus first-line consideration should be given to switching therapies altogether. Potential stage 3 agents include oral immunosuppressant drugs (stage 3A) and intravenous immunosuppressant agents (stage 3B). In addition to disease-modifying combination therapies, several adjunctive medications are also used in MS to alleviate symptoms such as spasticity, neuropathic pain, fatigue, and bladder dysfunction.

As noted, pulsed corticosteroids are frequently used in combination with platform therapies during relapses. Corticosteroids have both anti-inflammatory and immunosuppressive effects, and are not toxic to bone

marrow. They have been shown to provide rapid response and symptom improvement, as well as an increase in the time to sustained worsening on the EDSS.[11,38-41] Using steroids as a DMA has also been studied with varying schedules, including 1 g of methylprednisilone once every 4 months with oral taper, or 1 g daily for 1 to 3 days at 1- to 3-month intervals. Frequent use of corticosteroids must be monitored carefully, and precautions appropriate to long-term steroid use should be observed, including blood glucose monitoring and bone density measurements.

In addition to immunomodulatory agents, cytotoxic agents have potential uses in combination with platform therapies. Agents that have been used in treating MS include azathioprine, cyclophosphamide, mitoxantrone, methotrexate, cladribine, and mycophenolate mofetil.[30,42-46] Other potential candidates include anti-infectious agents, antioxidants, T-cell activation inhibitors, matrix metalloproteinase inhibitors, statins, and neuroprotective agents.

Some combination therapies are currently being evaluated in clinical trials involving patients with RRMS, including studies of intramuscular IFNβ-1a plus GA compared with either agent plus placebo,[47] investigations of intramuscular IFNβ-1a in combination with azathioprine and/or prednisone,[48] and comparisons of intramuscular IFNβ-1a combined with methotrexate plus placebo, intramuscular IFNβ-1a combined with intravenous steroids plus placebo, and all 3 active agents.[49] Additional ongoing research includes a small study of cyclophosphamide plus intravenous steroids in RRMS not responsive to IFNβ agents or GA, and a safety and mechanistic study of intramuscular IFNβ-1a plus mycophenolate mofetil compared with intramuscular IFNβ-1a plus placebo in patients with early RRMS.[30,31,50]

Clinical Decision Making

As a general rule, most compliant and noncompliant patients with MS have a positive opinion of the effectiveness of their MS therapy. Nonetheless, it is critical to assess medication compliance in all patients with MS as a precondition for assessing treatment success or failure, or for confirming disease breakthrough. Medication-taking behavior must be assessed for long- and short-term compliance and for persistence of adherence. Noncompliance is a term used to describe failure to take medication as prescribed in a general sense, whereas nonadherence generally refers to short-term discontinuation of a medication. A lack of persistence signifies loss of adherence or compliance after a significant period of compliance. Noncompliant patients may forget to take medications or lack an understanding of how to take them, or may have unrealistic expectations and beliefs about their medications. Nonadherent patients may have a temporary inability to access their medications, complex life events that interfere in self-care, depression or cognitive lapses, or a temporary perception of adverse effects. Lack of persistence may occur for many reasons, but typically occurs in patients who are feeling well and do not understand the long-term benefits of maintaining their medical regimen. In all cases, a therapeutic alliance between the patient and provider underlies successful medication compliance. The provider must set the stage for realistic expectations regarding disease progression and benefits of therapy, and stay in close contact with patients, particularly during therapeutic initiation or adjustment. In addition, providers must inquire about, monitor, and manage adverse effects, and employ a multidisciplinary approach to patient care, ensuring that patients have access to therapies, social workers, nurses, and other providers who have a good understanding of MS.

In making therapeutic decisions, it is important to track progressive disability over time, using sufficient scales and tools at regular intervals in order to make appropriate treatment decisions. The patient's impression of his or her ability to perform ADLs and the patient's quality of life are important subjective measures of disease activity. Serial inquiries about exercise tolerance and generalized symptoms, such as fatigue, sleep disturbances, depression, and confusion, should be conducted. The patient can be observed for gait mechanics and cognitive function during routine visits. In patients with fatigue and exercise intolerance, deconditioning from lack of activity should be considered as a possible contributor. Furthermore, many patients with MS have unrecognized poor sleep schedules that dramatically impact fatigue scales.

Because current therapies do not offer a cure for MS, it is important to ensure that patients are counseled to expect some disease activity while on therapy. Patients should further be aware that breakthrough disease is a manageable stage in MS progression. The stage should be set for the addition of therapies over time by explaining that combination therapies may have a synergistic therapeutic effect and are used successfully in many other chronic diseases.

In addition, clinicians must incorporate non-clinical information in order to make appropriate treatment deci-

sions. Imaging studies should be conducted at regular intervals and interpreted in light of the overall clinical portrait. In patients who have been on IFNβ agents for more than 18 months, clinicians can consider obtaining tests for NAbs and interpreting the results based on clinical findings, as well as imaging study results. It should be stressed that MRI findings are 5 to 10 times more active than clinical events; thus, clinically stable patients who demonstrate new MRI activity have active disease and should be considered for a change in therapeutic approach. A majority of the neurologists surveyed (n = 49) appreciated the importance of MRI findings, with 84% indicating that they would consider changing therapies in a clinically stable patient based purely on MRI lesions. When asked to select between enhancing lesions, increasing T2 lesion numbers, increasing T2 lesion volumes, increasing T1 black hole numbers, or any of the above, 83% of respondents (n = 46) supported the use of any of these categories of MRI changes as criteria for therapy modification. A minority of neurologists identified a single MRI lesion type as criterion for changing therapies, with 9%, 7%, and 2% selecting enhancing lesions, increasing T2 lesion numbers, and increasing T1 black hole numbers, respectively.

Clinicians should keep in mind that current data do not support switching therapies or dose increases, yet these data did not consider the potential to switch to natalizumab. In those with recurrent severe exacerbations not controlled by more conservative measures, changing therapies to immunosuppression with azathioprine, methotrexate, mycophenolate, or chemotherapy with mitoxantrone or cyclophosphamide should be considered.

Conclusions

Multiple sclerosis is a lifelong disease that requires effective and persistent therapy. MS most often presents as a relapsing-remitting disease, in which it is difficult to predict an individual's course of disease progression. Although some patients may have few relapses and mild disability over many years, almost all patients with MS will eventually progress to severe disability. Early treatment is the only way to interfere with disease progression, because every episode of inflammation is likely to contribute to the accumulation of permanent axonal damage. Current data indicate that patients receiving early treatment derive greater benefit than those receiving delayed treatment. Treating MS successfully requires defining breakthrough disease for each patient and considering altering therapy early in the course of disease.

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