Clinical Management of Multiple Sclerosis: The Treatment Paradigm and Issues of Patient Management

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ABSTRACT

OBJECTIVE: To summarize the conclusions of an expert panel of neurologists specializing in multiple sclerosis (MS) convened for the purpose of creating a treatment algorithm with regard to the clinical management of MS. The panel was sponsored by the Health Science Center for Continuing Medical Education and the University of Medicine and Dentistry of New Jersey and supported by an educational grant from Biogen Idec, Inc.

SUMMARY: MS is a chronic demyelinating disease characterized by a variable clinical course. Currently, there is no cure for MS, and the management of MS requires lifelong treatment with disease-modifying agents. Some patients respond well to therapy for many years, whereas others may have aggressive disease that is more difficult to manage. Hence, given the variable nature in the course of MS and patients' response to treatment, neurologists must individualize care for their patients.

An MS treatment algorithm was recently developed by a panel of neurologists who are MS experts to provide community neurologists with best-practice protocols for treating and managing their MS patients. The panel of experts categorized MS into 3 different stages, with patients transitioning between the stages based on their response to therapy and disease progression. Stage I represents MS early in the progression of the disease, during which platform drug therapy is recommended (i.e., interferon beta-1b [IFNβ-1b], IFNβ-1a, or glatiramer acetate). The results of randomized, controlled clinical trials suggest that IFNβ is the optimal choice for platform therapy. Despite treatment with platform therapy, it is common for patients to experience some ongoing symptoms and periodic exacerbations of the disease (annual relapse rate of 0.59 to 0.84 on treatment); such relapses should not be considered treatment failures and are best managed with steroids. Stage II represents acute breakthrough disease (i.e., when the clinical activity becomes more frequent or severe). This stage is best managed by the addition of pulse corticosteroids to the platform drug. Stage III represents continued breakthrough disease and is best managed by the addition of immunosuppressants to the platform drug.

CONCLUSION: The MS treatment algorithm provides an educational resource for physicians. It should assist all health care professionals involved in the management of MS patients and enhance their ability to improve quality of life for these patients over the course of the disease.

KEYWORDS: Multiple sclerosis, Breakthrough disease, Treatment algorithm

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Four different clinical courses have been defined in multiple sclerosis (MS):

- a relapsing-remitting form (RRMS), which is the most common (85%) and generally the presenting form of the disease;
- a secondary progressive form that generally develops in patients suffering from RRMS;
- a primary progressive form (10%) characterized by steady decline in function; and
- a progressive-relapsing form (5%) that begins with a progressive course characterized by occasional attacks.[1,2]

Figure 1 depicts the typical progression of MS if untreated.

The first treatment for MS demonstrating clear medical benefit was reported in 1952 and involved the use of corticotropin, which enhanced recovery from relapse.[3] More recent developments have involved immunomodulatory agents such as interferon beta-1b (IFNβ-1b); 2 different formulations of IFNβ-1a; glatiramer acetate; and mitoxantrone, which is generally reserved for the more progressive forms of the disease because of toxic adverse effects. All of the agents approved for the treatment of RRMS have been shown to reduce relapse rates in large-scale, randomized, double-blind, placebo-controlled, prospective studies.[4-7] Additionally, both IFNβ-1a products have been shown to reduce sustained disability progression in relapsing MS[6,7] and decrease progression to clinically definite MS when administered during the early phases of the disease.[8,9]

Despite the availability of treatments with demonstrated efficacy, approximately 45% of patients with relapsing MS in the United States are not currently receiving disease-modifying therapies

FIGURE 1 Progression of Untreated Multiple Sclerosis
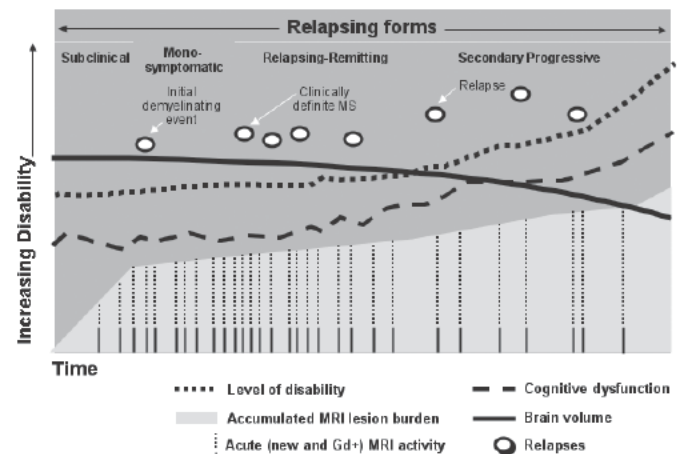
MRI = magnetic resonance imaging; Gd+ = gadolinium-enhanced.

TABLE 1	Expanded Disability Status Scale[13]
Score	Description
0.0	Normal neurologic examination
1.0	No disability, minimal signs on 1 of 7 functional systems*
1.5	No disability, minimal signs on 2 functional systems
2.0	Minimal disability in 1 functional system
2.5	Minimal disability in 2 functional systems
3.0	Moderate disability in 1 functional system *or* Mild disability in 3–4 functional systems, although fully ambulatory
3.5	Fully ambulatory but with moderate disability in 1 functional system and mild disability in 1–2 functional systems *or* Moderate disability in 2 functional systems *or* Mild disability in 5 functional systems
4.0	Fully ambulatory without aid, up and about 12 hours a day despite relatively severe disability; able to walk 500 meters without aid
4.5	Fully ambulatory without aid, up and about much of day, able to work a full day, may otherwise have some limitations of full activity or require minimal assistance Relatively severe disability; able to walk 300 meters without aid
5.0	Ambulatory without aid for about 200 meters; disability impairs full daily activities
5.5	Ambulatory for 100 meters; disability precludes full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk 100 meters with or without resting
6.5	Constant bilateral support (canes, crutches, or braces) required to walk 20 meters without resting
7.0	Unable to walk beyond 5 meters even with aid; essentially restricted to wheelchair, wheels self, transfers alone; active in wheelchair about 12 hours a day
7.5	Unable to take more than a few steps, restricted to wheelchair, may need aid to transfer; wheels self, but may require motorized chair for full day's activities
8.0	Essentially restricted to bed, chair, or wheelchair but may be out of bed much of the day; retains self-care functions; generally effective use of arms
8.5	Essentially restricted to bed much of the day, some effective use of arms, retains some self-care functions
9.0	Helpless bed patient, can communicate and eat
9.5	Unable to communicate effectively or eat/swallow
10.0	Death

* *Functional systems are pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other.*

(DMTs).[10] This "treatment gap" could represent 180,000 individuals, based upon estimates that 400,000 people suffer from MS in the United States.[11] Although the American Academy of Neurology (AAN) and the National Multiple Sclerosis Society state the importance of treating MS early upon diagnosis, no comprehensive guidelines on the treatment of MS factor-in the variability of disease course. Consequently, a need exists for recommendations that will assist health care providers in the management of MS by providing a set of best-practice protocols.

A treatment algorithm has been developed based upon the consensus of a panel of 15 neurologists with extensive experience in treating MS patients (hereafter referred to as the expert panel). Sponsored by the Health Science Center for Continuing Medical Education and the University of Medicine and Dentistry of New Jersey and supported by an educational grant from Biogen Idec Inc., the expert panel's express purpose was to develop a treatment consensus for MS to be collated in the form of a treatment algorithm. The objective of this article is to summarize the conclusions

of this expert panel with regard to the clinical management of MS and to introduce the proposed treatment algorithm.

■ Evaluating Multiple Sclerosis Therapies

Two types of immunomodulatory therapies may be used as first-line treatment for patients with RRMS: IFNβ products (IFNβ-1b, intramuscular (IM) IFNβ-1a (IM IFNβ-1a [Avonex, Biogen Idec Inc., Cambridge, MA]), or subcutaneous (SC) IFNβ-1a (SC IFNβ-1a [Rebif, Serono, Inc., Rockland MA]), and glatiramer acetate. For treatment decisions, physicians must consider the efficacy of each agent in terms of sustained disability, relapse rate, lesion load, brain atrophy, and cognitive function.[12] In addition, the physician may consider that some therapies, such as IM IFNβ-1a and SC IFNβ-1a, may reduce the relative risk of progression to clinically definite MS when initiated during the early stages of MS.[8,9] Furthermore, the efficacy of each agent must be weighed against potential side effects, the risk for immunogenicity, and whether the dosing regimen fits into the patient's lifestyle (i.e., the likelihood that patients will be compliant with the medication). Individual variability in clinical course and symptoms further complicate treatment choice.

In order to assist physicians with MS therapy selection, the expert panel developed a treatment algorithm using evidence-based evaluations of the results of pivotal studies assessing each DMT as a treatment for relapsing MS. The results of these trials, each of which was a randomized, double-blind, placebo-controlled multicenter study, are briefly summarized in the following sections.

Sustained Disability

In the pivotal phase III studies of each DMT, sustained disability was defined as a worsening of ≥1.0 point on the Expanded Disability Status Scale (EDSS)[13] either for a period of 6 months (IM IFNβ-1a) or a less stringent, 3 months (all other agents) (Table 1). In the pivotal phase III trial of IFNβ-1b, performed by the IFNB Multiple Sclerosis Study Group, treatment with IFNβ-1b 8 million international units subcutaneously every other day produced a 29% reduction in the progression of sustained disability at 3 years compared with placebo; however, this benefit was not statistically significant.[4] In contrast, both formulations of IFNβ-1a have been shown to significantly reduce the progression of sustained disability in patients with MS. In the pivotal phase III trial of IM IFNβ-1, which was conducted by the Multiple Sclerosis Collaborative Research Group, 30 mcg of IM IFNβ-1a once weekly significantly reduced disability progression by 37% compared with placebo after 2 years of treatment ($P = 0.02$).[6] The pivotal phase III trial of SC IFNβ-1a, performed by the Prevention of Relapses and Disability by Interferon-β-1a Subcutaneously in Multiple Sclerosis (PRISMS) group, evaluated the efficacy of 2 different dosages of SC IFNβ-1a (22 or 44 mcg 3 times weekly). At 2 years, significant reductions in the progression of sustained disability were observed for both SC IFNβ-1a 22 mcg (22%) and 44 mcg (30%) compared with placebo ($P<0.005$).[7]

The results of the 2-year pivotal study of glatiramer acetate were published in 1995,[5] with a follow-up report describing results of an 11-month extension period published in 1998.[14] The initial study indicated that there was no significant effect on progression to sustained disability.[5] Post hoc analysis of the extension trial results revealed a significant decrease in the EDSS score with glatiramer acetate treatment.[14] However, these latter data should be interpreted with caution because post hoc analyses are subject to bias and the investigators used atypical statistical analysis methods and the less stringent definition of sustained disability (≥1.5-point worsening of the EDSS score for 3 months).

Relapse Rate

Pivotal trials have demonstrated that treatment with each DMT significantly reduces annual relapse rates in MS. The magnitude of reduction has been shown to be very similar (approximately 30%) among DMTs.[4-7] A significant effect of IFNβ was apparent in the first year of therapy in several studies.[7,15]

Lesion Load

Historically, there has been a lack of guidelines and consensus on the role of magnetic resonance imaging (MRI) in MS. Its use in evaluating the progression of MS is attractive because MRI allows a direct examination of a pathological process in the central nervous system indicative of disease that can potentially be followed serially over a period of time.[16] Serial MRI detection of disease activity in relapsing forms of MS seems to be significantly more sensitive than clinical evidence of disease progression.[17-19] A report of the Therapeutics and Technology Assessment Subcommittee of AAN has recommended the use of MRI for the diagnosis of MS.[20] This recommendation was based upon prospective studies indicating that the finding of ≥3 T2 lesions at baseline is a very sensitive predictor of subsequent development of MS. Additionally, the committee concluded that the presence of ≥2 gadolinium-enhancing (Gd+) lesions at baseline or the appearance of new T2 or Gd+ lesions on follow-up MRI scans is also predictive of the development of clinically definite MS. For more details on the role of MRI assessments in the management of patients with MS, see the article by James R. Miller in this supplement.

Several MRI end points, including the number and volume of Gd+ lesions, the number and volume of T2 lesions, the number of new or enlarging T2 lesions, and the volume of T1 hypointense lesions, have been studied in multiple trials of DMTs.[6, 21-26] The major difference between treatments was that, although IFNβ and glatiramer acetate reduce Gd+ lesions, which is a marker of active inflammation and breakdown of the blood–brain barrier, IFNβ products have a more profound effect (82% to 89% reductions) compared with glatiramer acetate (29% to 35% reductions).[27] Additionally, the benefit of IFNβ on Gd+ MRI activity is evident within 2 weeks, whereas the effect of glatiramer acetate is considerably less rapid.[28]

In the MS treatment algorithm, MRI scans are recommended to

TABLE 2	Immunomodulatory Adverse Events* That May Compromise Compliance[34 37]			
	Therapy, n (Drug/Placebo)			
Adverse Event	IFNβ-1b 1,115/789	IFNβ-1a- Avonex 351/333	IFNβ-1a- Rebif 44 mcg 184/187	Glatiramer Acetate 201/206
Injection-site reactions	85%/29%	3%/1%	92%/39%	66%†/19%†
Flu-like symptoms	60%/41%	49%/29%	59%/51%	19%/17%
Depression	NA	18%/14%	25%/25%	NA
Fatigue	NA	NA	41%/36%	NA
Chest pain	11%/7%	5%/2%	8%/5%	21%/11%
Pain	51%/42%	23%/21%	NA	28%/25%
Leukopenia	NA	NA	36%/14%	NA
SGPT increased	10%/4%	NA	27%/4%	NA
SGOT increased	3%/1%	NA	17%/4%	NA

IFNβ = interferon beta; SGOT = serum glutamate oxaloacetate transaminase; SGPT = serum glutamate pyruvate transaminase.
* Incidence of ≥2% higher frequency in drug-treated patients than placebo.
† Injection site erythema.

confirm diagnosis and rule out other pathologies. Annual MRI scans are also recommended for the management of ongoing MS to monitor disease progression and reveal underlying pathology. MRI may provide valuable information leading to therapy modification. Additionally, periodic MRI to monitor spinal cord lesions should also be considered. Increasing evidence suggests that MRI for monitoring of spinal cord lesions, especially spinal cord atrophy, is useful for the evaluation of primary disease and may correlate with progression of disability.[29] Given the value of MRI in the management of MS, the expert panel strongly recommended that insurance coverage be provided for follow-up MRI scans.
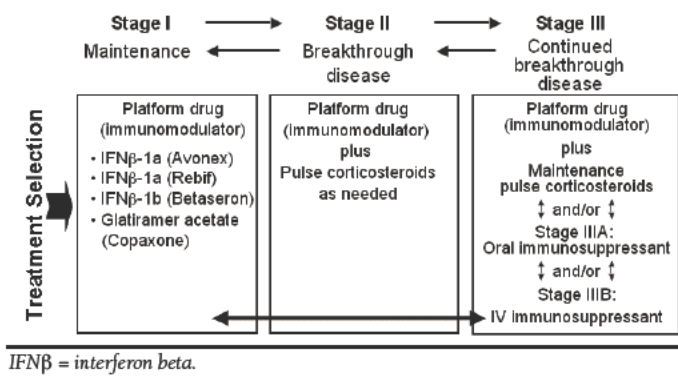
Brain Atrophy

Brain atrophy has been examined using MRI scans in patients who received IFNβ. A post hoc analysis of data from the pivotal phase III trial of IM IFNβ-1a found a significant reduction in brain atrophy during the second year of treatment.[30] The results of a recent open-label study found that IFNβ-1b slowed brain atrophy progression during the second and third years of treatment.[31] However, an examination of MRI scans from a trial using SC IFNβ-1a did not find a significant effect on brain atrophy, despite improvements in other MRI and clinical parameters.[32]

Neutralizing Antibodies

IFNβs have been shown to have similar incidences of neutralizing antibodies (NAbs) in numerous studies. NAbs have been shown to reduce the clinical efficacy of IFNβ.[33] The incidence of NAbs is higher with IFNβ-1b treatment (45% of patients)[34] compared with IFNβ-1a products. In addition, the incidence of NAbs is higher

FIGURE 2 Treatment Outline for Multiple Sclerosis

Stage I →	Stage II →	Stage III
Maintenance ←	Breakthrough disease ←	Continued breakthrough disease

Platform drug (immunomodulator)	Platform drug (immunomodulator) plus	Platform drug (immunomodulator) plus
• IFNβ-1a (Avonex) • IFNβ-1a (Rebif) • IFNβ-1b (Betaseron) • Glatiramer acetate (Copaxone)	Pulse corticosteroids as needed	Maintenance pulse corticosteroids ↕ and/or ↕ Stage IIIA: Oral immunosuppressant ↕ and/or ↕ Stage IIIB: IV immunosuppressant

IFNβ = interferon beta.

with SC IFNβ-1a (24%)[35] compared with IM IFNβ-1a (5%) treatment.[36] More details on the development of NAbs to DMTs and the implications for clinical practice are provided by Howard S. Rossman in this supplement.

The expert panel recommended that patients at high risk for NAbs (i.e., those on a more immunogenic product) be tested for NAbs after the first year of treatment, and, if the test results are positive, these patients should be retested after another 6 months of treatment to confirm NAb status. Patients on a less immunogenic product should be tested if they experience disease progression. In patients who are NAb-positive, physicians may choose to switch the patient to an alternative therapy or to continue with the same treatment and have the patient undergo retesting in another 6 months.

Side Effects and Compliance

Successful long-term treatment of MS requires patient compliance throughout the course of the patient's life. Compliance is affected by multiple issues, including side effects, frequency of administration, perceived efficacy, self-esteem, level of disability, treatment convenience, and the support provided by family and health care providers.

DMTs have several side effects that can have a negative impact on compliance. For example, injection-site reactions, flu-like symptoms, fatigue, chest pain, leukopenia, and elevated hepatic enzyme levels occur to varying degrees with these agents (Table 2).[34-37] The most common events are injection-site reactions, which occur more frequently with the SC route of administration. Local injection-site reactions are a significant issue because necrotizing lesions can occur following SC delivery; patients may be unable or unwilling to take therapy on a regular basis. Flu-like symptoms also occur frequently and are more common during treatment with IFNβ versus glatiramer acetate. Approximately 10% of patients treated with glatiramer acetate experience a postinjection reaction. The symptoms are generally transient and self-limiting and may include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. The product labeling for all 3 IFNβ products includes a warning that IFNβ should be

used with caution in patients with depression or severe psychiatric symptoms because depression, suicide ideation, and suicide attempts have been reported to occur with increased frequency in patients receiving IFNβs.[34-36] Glatiramer acetate product labeling does not contain such a warning.[37]

One study that directly compared the 2 formulations of IFNβ-1a found that IM IFNβ-1a was associated with a significantly lower rate of side effects compared with SC IFNβ-1a. These side effects included injection-site disorders (28% versus 83%), liver function abnormalities (9% versus 18%), white blood cell abnormalities (5% versus 11%), and lymphopenia (<1% versus 4%).[38] In another comparative study, IFNβ-1b and IM IFNβ-1a were similarly well tolerated, with the exception of a higher incidence of injection-site reactions in IFNβ-1b patients compared with IM IFNβ-1a patients (37% versus 8%).[39] Physicians and patients should be aware of and aggressively manage side effects of DMTs. This will help to improve compliance with the MS therapy.

■ The Physician Treatment Algorithm

Because there is no cure for MS to date, patients and physicians need realistic expectations concerning the efficacy of MS therapies. Given the multifactorial and heterogeneous nature of MS, each patient will respond differently to treatment. Many patients respond well to treatment for years, while others may have aggressive disease, and although initially responsive to therapy, the disease eventually progresses. Furthermore, there is no way to predict in advance which patients will respond to treatment and for how long, highlighting the importance of patient monitoring. The following sections summarize the expert panel's recommendations for the management of MS throughout the course of the disease, categorized into 3 different stages (Figure 2).

Stage I: Maintenance

Selection of platform therapy. In the development of the MS treatment algorithm, a platform therapy has been defined as an agent that will provide baseline immunomodulatory action. The agent should be a first-line treatment of choice that can be administered for an extended period because of the chronic nature of MS. The physician's choice should be based on a balance between several factors, including efficacy; incidence of NAbs (in the case of IFNβ therapy); side effects; the potential for combination therapy with other agents should the clinical course dictate; and patient compliance, which can be influenced by the agent's suitability to the patient's lifestyle.

The MS treatment algorithm recommends IFNβ therapy as the optimal choice for platform therapy (i.e., the agent to be used when initiating treatment in patients presenting with RRMS). This recommendation is based upon the efficacy, tolerability, and immunogenicity data previously reviewed (see "Evaluating Multiple Sclerosis Therapies"). The ideal IFNβ platform therapy would be one that has been shown to significantly slow the progression of sustained disability, reduce the relapse rate and MRI

lesion activity, and reduce brain atrophy. In addition, the platform therapy should be associated with a low risk for developing NAbs, a low incidence of side effects, including injection-site reactions, and a convenient dosing schedule.

Relapse management. The use of platform therapies reduces but does not eliminate relapses in RRMS.[4-7] Regardless of the treatment, patients are apt to have relapses or acute exacerbations of the disease. This does not signify treatment failure. In the pivotal studies, annual relapse rates were significantly lower among patients treated with DMTs relative to placebo-treated patients but still ranged from 0.59 to 0.84 relapses per year on treatment.[4-6]

Several factors are important to consider in relapse management. First, relapses may be the result of poor compliance with the MS therapy, underscoring the need for physicians to carefully monitor patient adherence. Second, it is essential to distinguish between disease worsening and a pseudo-relapse because of the symptoms of MS, which may mimic a relapse when not adequately managed. Physicians must monitor patients for symptoms and must educate them to self-monitor and communicate with their physician and nurse team on an ongoing basis. Aggressively managing the symptoms of MS should enhance patient compliance with therapy and reduce unnecessary switching of medications.

Physicians should consider managing these initial relapses (while on a platform therapy) with corticosteroids. For example, intravenous (IV) methylprednisolone 1 g/day may be administered over 3 to 5 days. Some physicians may prefer an oral taper after IV methylprednisolone (e.g., prednisone or oral methylprednisolone over 6 to 12 days). IV dexamethasone 160 to 180 mg/day may also be used followed by an oral taper. Corticosteroid use should be adjusted based on patient tolerance.

Stage II: Acute Breakthrough Disease

Breakthrough disease represents MS in its more progressive stages. There is variability among physicians on the precise definition of breakthrough disease; however, in clinical trials of MS therapies, breakthrough has been defined based upon the following criteria: progression of disability, multiple relapses in a short time span, further neurologic deterioration, increased disease burden or activity detected by MRI, or newly identified cognitive defects.[40-43] Patients on IFNβ who experience breakthrough disease should first be tested for NAbs to make sure that the medication is still working. Patients who are NAb-positive should be retested in 6 months; if test results remain positive on retesting, patients then should be switched to a less immunogenic DMT. Patients who are NAb-negative should continue treatment with the platform therapy and consider the addition of another therapeutic agent.

Management
Switching and dose escalation. Once breakthrough occurs, one option is to switch to a different agent as the platform therapy. However, the rationale for switching to a different agent is lacking because no adequately controlled studies have been conducted to examine its potential benefits and limitations. Despite the ongoing debate on the potential benefits of increasing the dose of the platform therapy, there are no clinical trials reporting the efficacy of increasing the dose of an immunomodulatory agent following breakthrough disease. Furthermore, there is evidence that increasing the dose of IFNβ may not provide additional benefit and may lead to increased side effects and a higher incidence of NAbs.[44-47]

Combination therapy. Breakthrough disease in MS could represent a shift to a more neurodegenerative phase of the disease, beyond the inflammatory component that platform therapies have been targeting. Another option for treating patients with breakthrough disease is to add another agent to the platform therapy (i.e., combination therapy). Combination therapy has been effective for the treatment of cancer, infectious diseases, and rheumatoid arthritis, with dramatically better outcomes than monotherapy.[48] Given these considerations and the heterogeneous nature of MS, it is likely that the use of a combination of therapies that complement one another will have beneficial effects in patients with MS.[48,49]

Patients who are NAb-negative should continue treatment with the platform therapy in addition to initiating a pulse treatment schedule of corticosteroids (1 g/month or 1 g/day for 5 days every 4 months), followed by an oral steroid taper.[19] Issues to be considered in the use of high-dose pulse corticosteroids include short-term indigestion, heartburn, exacerbation of peptic ulcers, gastroesophageal reflux, fluid retention, weight gain, and a metallic taste in the mouth. In the long term, osteoporosis, diabetes, and hypertension must be considered.[50-52]

Stage III: Continued Breakthrough Disease

In the face of continued breakthrough disease in patients who are NAb-negative, the potential agents for use in combination with platform therapy can be separated into 2 general categories: cytotoxic agents and immunomodulatory agents. The rationale for using these agents stems from the fact that MS is considered an autoimmune disease, and as such, they may slow autoimmune destruction. Cytotoxic agents include methotrexate, azathioprine, mitoxantrone, cyclophosphamide, mycophenolate mofetil, and cladribine; immunomodulatory agents include pulse corticosteroids, IV immunoglobulins, and glatiramer acetate. Some additional agents that are currently under investigation for their efficacy in MS include anti-infectious agents, antioxidants, inhibitors of T-cell activation, natalizumab, and statin drugs.

Although the use of combination therapy for the treatment of MS is still in its infancy, there are numerous recently completed and ongoing clinical trials exploring various treatment combinations.[53] Some of the more commonly used agents that have been combined with IFNβ include mitoxantrone, cyclophosphamide, and azathioprine.

■ Conclusions

While there is no cure for the chronic progressive disease of MS, current therapies can modify the course of the disease. The thera-

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