Meeting the Challenge of Incorporating Injectable Biologics Into Managed Care: Multiple Sclerosis and Psoriasis

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**FACULTY**

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**Terry Maves, RPh,** has been a community and pharmacy leader in northeast Wisconsin for more than 25 years. He is the pharmacy director for Touchpoint Health Plan, based in Appleton, Wisconsin, which, for the second consecutive year, has been named by the National Committee for Quality Assurance as the number one health plan in the nation in delivering preventive care and managing chronic diseases.

Maves has recognized the pharmacist's ability to intervene on the patient's behalf to improve patient therapies. He helped create the Everyone Teaching Compliance program, which helps health care providers coordinate care to improve medication utilization for 12 disease states. This program earned Maves recognition as the Innovative Pharmacist of the Year in 2000 for the state of Wisconsin. In addition to increasing pharmacists' involvement in the delivery of health care, he has created and implemented a cognitive reimbursement program and made this program available to all pharmacies in the Touchpoint Health Plan area. A leader in patient consultation and education, his role as a well-known preceptor, professional, and public speaker also demonstrates his commitment to the field of pharmacy.

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James R. Miller, MD, has recently retired after serving as director of the Multiple Sclerosis Center of Columbia-Presbyterian Medical Center in New York City for 20 years. He has lectured widely on the pathogenesis and treatment of multiple sclerosis and allied diseases as well as in the field of infections of the central nervous system. He has also written a variety of articles on these subjects and contributed chapters to several standard neurological textbooks. In retirement, Miller continues to lecture both to medical and patients groups concerning multiple sclerosis.

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Prior to starting his own consulting practice, Rich was director of pharmacy programs at SelectCare, Troy, Michigan, where he developed a nationally recognized, cost-effective pharmacy program and pharmacy network. He was responsible for development of drug utilization review programs, served as the chairperson of the pharmacy and therapeutics committee, and developed a comprehensive drug formulary. Rich earned his pharmacy degree from the University of Michigan. He also holds a doctorate in theocentric business ethics. He has held the position of clinical assistant professor at the University of Michigan since 1982 and has held a dual appointment as an adjunct assistant professor with the College of Pharmacy and Allied Health Professions at Wayne State University since 1994.

Rich has moderated more than 100 meetings and advisory boards, published numerous journal articles, and contributed to 2 textbooks. He served for 8 years on the Michigan Board of Pharmacy, 3 years as chairperson. Rich has received numerous professional awards and honors and is a member of several professional organizations.

Howard S. Rossman, DO, FACN, is a senior partner of the Michigan Institute of Neurological Disorders (MIND) in Farmington Hills, an organization with which he has been associated since 1978. He is medical director of the Multiple Sclerosis Center at MIND and has been involved in 10 major clinical trials for potential new MS therapeutics since 1999, 7 of which are currently ongoing. In addition, Rossmann is a clinical professor of neurology at Michigan State University and chairman of the neurology department at Botsford General Hospital, an affiliate of Michigan State University, where he directed the residency training program for 19 years until 2002. He is still actively involved in the training of medical students, interns, and neurology residents.

Rossman received his undergraduate degree from the University of Michigan and his medical training at the Michigan State University College of Osteopathic Medicine. He completed his residency in neurology at Botsford General Hospital, an affiliate of Michigan State University. Rossman is a member of the Consortium of MS Centers and a fellow of the American College of Neuropsychiatrists, where he served as president from 1994 to 1995.

William H. Stuart, MD, received his medical degree from Northwestern University Medical School and completed an internship at Cleveland Metropolitan General Hospital and a residency in internal medicine at Northwestern. He subsequently served as an epidemic intelligence service officer at the Communicable Disease Center (CDC) in Atlanta, Georgia, and completed a fellowship in neurology at Emory University Medical School. Upon completion of this training and serving at the National Institute of Neurological Disorders and Stroke, Rockville, Maryland, he entered private practice in the Atlanta area, forming the Atlanta Neurological Clinic, subsequently renamed the Peachtree Neurological Clinic in 1990.

One of the founding members of the American Society of Neuroimaging in 1975, Stuart served as its president in 1984 and 1985. In 1980, he became a member of the Practice Committee of the American Academy of Neurology (AAN), remaining active on that committee until 1991 and serving as its chairman from 1985 through 1991. He was a member of the Executive Committee of AAN for several years and served as treasurer. His most recent activity with AAN was aiding in the formation of the academy’s MS section and serving on the Long-Range Planning Committee.

Stuart began his focused interest in multiple sclerosis in 1988, developing the Multiple Sclerosis Comprehensive Care and Research Center at Shepherd Center, Atlanta, in 1991. In 2001, he became medical director of the MS Center of Atlanta and the MS Research Network of Georgia. His interest in MS has focused on early treatment and aggressive combination therapy for patients with breakthrough disease.

He has maintained a broad interest in education and served as a clinical professor of neurology at Emory University Medical School from 1987 to 2003. He was named Clinical Teacher of the Year at Piedmont Hospital in 1987 and 1988. He has lectured widely in evolving treatments in MS. Stuart’s board certification includes the American Board of Internal Medicine and the American Board of Psychiatry and Neurology. He serves on the boards of the National MS Society—Georgia Chapter (and its Medical Advisory Board) and Millennium Medical Communications, Inc.
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S42 Continuing Education*: Record of Completion, Posttest, and Program Evaluation

Target Audience:
This program has been designed to meet the educational needs of pharmacists and other health care practitioners in a managed care environment.

Learning Objectives
After completing this continuing education module, the pharmacist will be able to
1. verbalize the importance and long-term potential of injectable biologic therapies for the treatment of multiple sclerosis (MS) and psoriasis;
2. describe strategies and considerations that optimize treatment success and ensure appropriate resource utilization for biologic therapies in MS and psoriasis;
3. recognize the complexity of treating MS and the importance of individualizing therapy and planning for long-term management of the disease;
4. employ (a) treatment protocols developed by neurologists for appropriate use of biologics in MS and (b) interventions for managing MS symptoms and treatment side effects;
5. describe an MS treatment algorithm developed by managed care professionals that provides guidelines for long-term disease management, including treatment initiation, recommended evaluations, and disease progression;
6. understand current clinical data concerning alefacept’s use in the treatment of patients with moderate-to-severe psoriasis, including long-term benefits and safety and tolerability considerations; and
7. identify key considerations for evaluating the cost implications and drug utilization for biologic therapies in psoriasis.

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*A total of .20 CEUs (2 contact hours) will be awarded for successful completion of this continuing education program (Program No. 233-000-04-040-H04).

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The development of injectable biologic agents has revolutionized the treatment of numerous diseases, including multiple sclerosis (MS) and psoriasis. These agents have the potential for long-term benefits, including reduced disease activity, improved quality of life, and decreased utilization of total health care services. As newly approved biologics for the treatment of MS and psoriasis become available, managed care decision makers must determine the appropriate use of these agents based on long-term efficacy, safety, and cost. The goal of this supplement is to provide information from clinical trials and from the experience of renowned specialists to aid in this endeavor.

Multiple sclerosis is a chronic, multifocal, demyelinating disease of the central nervous system (CNS). The onset of MS typically occurs in early adulthood, and MS is the leading cause of nontraumatic CNS morbidity in young and middle-aged adults. In the United States, the annual per-patient cost of MS has been estimated at $34,000, with a total lifetime per-patient cost of $2.2 million; a conservative estimate of the national annual cost is $6.8 billion. MS is a complex and heterogeneous disease, with high intrapatient and interpatient variability in its clinical course and manifestations. Consequently, physicians who treat patients with MS must tailor treatment to individual patients and actively plan for the long-term management of the disease.

Four articles in this supplement focus on the role of biologics in the management of MS. The first article, by James R. Miller, MD, provides an overview of the 4 biologic agents that are available in the United States for the treatment of relapsing-remitting MS as well as the complexities involved in the diagnosis and clinical course of MS. Data supporting early treatment of patients at high risk for MS also are discussed. The second article, by Howard S. Rossman, DO, FACN, reviews data on the development of neutralizing antibodies (NAbs) to biologic agents used to treat MS. Studies show that differences exist among biologics regarding the risk of developing NAbs and that these NAbs reduce or abolish the therapeutic effects of biologics. The article also discusses the implications of NAbs for neurologists and managed care professionals.

The third article, by William H. Stuart, MD, presents an MS treatment algorithm recently developed by a panel of neurologists who are MS experts. This algorithm provides best-practice guidelines on choosing the appropriate biologic agent for initiating therapy, managing occasional relapses, and selecting agents that can be added to biologics in patients whose disease progresses while they are on treatment. The fourth article, by my colleagues and me, provides a model treatment algorithm for use in the managed care setting, which was developed by a group of managed care professionals. This model MS algorithm provides health care professionals with guidelines on the following disease management issues: when to initiate treatment, how to select a biologic agent as the initial therapy, the use of magnetic resonance imaging in the diagnosis and management of patients with MS, when to test for NAbs and how to manage patients who have positive test results for NAbs, and how to manage patients who experience progression during treatment. An algorithm for NAb testing also has been proposed that, while recognizing the authority of the physician to make ultimate prescribing decisions, can be incorporated into a patient’s care path to ensure the quality of care without placing a burden on the patient.

An estimated 4.5 million adults in the United States have psoriasis, and approximately one third (1.5 million) of these individuals have moderate-to-severe disease. The financial burden of psoriasis is substantial, with annual U.S. economic costs estimated at $4.3 billion. Patients with moderate-to-severe psoriasis typically require chronic treatment with systemic therapy or phototherapy. Although conventional systemic agents can be effective in producing short-term reductions in disease severity, the long-term, chronic use of these treatments is limited by safety and tolerability concerns. Novel injectable biologics, which have been developed based on an understanding of the role of T cells in the pathogenesis of psoriasis, have advanced the treatment of moderate-to-severe psoriasis.

Alefacept was the first biologic therapy approved for the treatment of moderate-to-severe chronic plaque psoriasis in the United States, and it has been available here for more than 1 year. Two articles in this supplement review the use of alefacept in the treatment of psoriasis. The article by Jay N. Gade, MD, PhD, provides an update on the clinical efficacy and safety of alefacept in patients with psoriasis. Alefacept has proven to be an effective intermittent therapy for psoriasis that offers patients extended treatment-free and disease-free periods. As a result of prolonged remissions, overall drug utilization may be reduced.

In the second article, I review key considerations for the long-term assessment of biologic therapies in psoriasis. These considerations establish the importance of efficacy, safety, and cost parameters measured over a longer course of therapy than the traditional 3-month or 6-month time period utilized to date.

It is hoped that the timeliness and clinical relevance of the information provided in this journal supplement will assist you in improving the care of your patients with MS or psoriasis and will ensure the use of biologic therapies in the most cost-efficient manner.

REFERENCES
The Importance of Early Diagnosis of Multiple Sclerosis

JAMES R. MILLER, MD

ABSTRACT

OBJECTIVE: To describe the current understanding of the diagnosis and treatment of multiple sclerosis (MS) and to explore the use of magnetic resonance imaging (MRI) assessment as a prognostic tool and an indicator in the diagnosis of MS.

SUMMARY: MS is a chronic, progressive, demyelinating disease of the central nervous system that is associated with a significant economic burden. At this time, immunomodulatory agents (interferon beta-1a [IFNβ-1a] [Avonex], IFNβ-1a [Rebif], IFNβ-1b [Betaseron], and glatiramer acetate [Copaxone]) are first-line agents, which are reported to reduce relapse rates.

The diagnostic criteria for MS have evolved over time to include MRI findings as an integral part of the diagnosis. However, the most recent criteria (McDonald) are focused on the diagnosis of definite MS and do not address the status of patients with a first demyelinating event (clinically isolated syndrome [CIS]). This is an important issue because a CIS is highly predictive of developing further inflammation and definite MS when the episode occurs in conjunction with lesions on the initial MRI. Many times, MRI findings do not correlate with clinical symptoms, and clinically silent lesions are identified. Therefore, the use of MRI is salient to the early diagnosis of high-risk patients.

The evolution of thought concerning early treatment in MS is based on an increased understanding of the pathology of the disease. Axonal loss occurs early in the disease process, and both white matter and gray matter are affected. Studies that have analyzed early treatment in patients highly likely to have MS (clinically isolated events with evidence of lesions on MRI) report significant benefits in delaying further changes on MRI and further attacks. Patients who begin treatment later do not reap the same benefits as those who begin treatment earlier during the disease course.

CONCLUSION: Patients with clinically isolated events should be referred promptly to a neurologist for assessment, including MRI scans. An early recognition of the inflammatory process enables patients to begin treatment with an immunomodulatory agent even before the technical diagnosis of definite MS so that the degenerative progression of MS can be retarded.

KEYWORDS: Magnetic resonance imaging, Interferon beta, Glatiramer acetate, Multiple sclerosis, Diagnosis

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MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system (CNS). This treatable but uncurable degenerative disease affects approximately 400,000 people in the United States. Common symptoms of MS include spasticity, fatigue, sexual dysfunction, bladder dysfunction, pain, cognitive dysfunction, depression, bowel dysfunction, and weakness. The average age of onset of MS is 30 years. Because this is the age when individuals may be beginning a family and workers have not typically reached their full earning potential, it has a particularly devastating impact on family, social, and professional relationships.

MS is associated with a considerable economic burden. National costs of MS are estimated to range from $6.8 to $11.9 billion annually (approximately $34,000 per patient). The major components of these costs include earnings loss (incurred by the patient with MS) and costs of informal care (unpaid personal assistance). According to a survey of MS patients, the annual loss in earnings was $17,900; this amount was even greater ($41,000) for men younger than 65 years.

In that same study, the annual expenditures for informal care were $6,452, which translated to about one fifth of the annual per-patient costs of MS. Other large expenditures included costs for hospitalization and physician visits.

In 90% of patients, MSs natural progression traditionally has been categorized in sequential stages, which include subclinical disease, monosymptomatic disease, relapsing-remitting disease (RRMS), and then secondary progressive MS (SPMS). Clinicians diagnose definite MS after a second attack occurs or evidence of new MS lesions are visualized on magnetic resonance imaging (MRI). The clinical course of RRMS is described as clearly defined relapses with at least partial recovery of deficits. Periods between relapses are characterized by a lack of disease progression. In contrast, SPMS occurs when some deficits begin to progress even between obvious relapses. Relapses occur less frequently than during the RRMS phase or do not occur at all.

The progression of MS is discernible when the recovery between relapses is incomplete, with a sustained worsening on the Expanded Disability Status Scale (EDSS) or other rating scales; lesion burden assessed by MRI is increased; cognitive dysfunction accumulates; and brain atrophy advances. In some patients, the cognitive effects of MS may be more severe than the physical effects during the early stages of the disease. If MS is left untreated, patients with RRMS develop SPMS (50% by 10 years; 90% by 30 years).

Treatment of Multiple Sclerosis

Only a small subset of the medical community makes treatment decisions in patients with MS. Because MS is a chronic degenerative disease, treatment must be continuous, not intermittent. At this time, immunomodulatory agents (IMAs) are considered first-
line treatments for patients with RRMS, including the following: intramuscular (IM) interferon beta-1a (IM IFNβ-1a) [Avonex, Biogen Idec Inc, Cambridge, MA], subcutaneous (SC) IFNβ-1a (SC IFNβ-1a [Rebif, Serono, Rockland, MA], SC IFNβ-1b (Betaseron, Berlex Laboratories, Montville, NJ), and SC glatiramer acetate (Copaxone, Teva Pharmaceutical Industries, Kansas City, MO). Another agent, mitoxantrone (Novantrone, Immunex Corp., Seattle, WA), is indicated for reducing the progression of neurologic disability and the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or significantly worsening RRMS. IMA treatment goals include reducing inflammation, reducing the relapse rate, slowing disability, slowing the accumulation of cognitive dysfunction, reducing the progression of brain atrophy, and improving quality of life.

Several large randomized trials demonstrate that IMAs reduce attack rates.10,11 Direct comparisons among the trials are impossible, but these data suggest that all agents reduce relapse rates similarly. For example, the phase III trial of IM IFNβ-1a reported a 32% reduction in relapses among patients who were treated for 2 years.11 Similarly, the mean percentage reduction in relapse rates over 2 years was 33% in patients who received SC IFNβ-1a.12 Two-year data from the SC IFNβ-1a trial revealed a 34% reduction in patients who received treatment.10 Finally, in the glatiramer acetate study, the 2-year reduction in relapse rate was 29%.11 Although trial outcomes were similar, there may be important differences among these agents with regard to their demonstrated ability to slow disability progression. For example, both IM IFNβ-1a and SC IFNβ-1a (44 mcg) have been associated with a significant reduction in sustained disability progression.11,14

Of note, sustained progression of disability must have occurred for ≥3 months during the SC IFNβ-1a trial and ≥6 months during the IM IFNβ-1a trial; the 6-month requirement provided a more stringent measurement of efficacy.11 Sustained disability progression was not significantly affected during the IFNβ-1b study.10 Reduction in sustained disability with glatiramer acetate was not statistically significant.13 Sustained disability progression is the most important clinical measure in MS because the major proportion of clinical deficit is caused by clinically silent events not manifested by relapses.

### Diagnosis of Multiple Sclerosis

Over the last 40 years, an important evolution has occurred in the diagnostic rubric of MS: the diagnostic criteria progressed from being solely clinical symptom-based (Schumacher15 and Poser16) to integrating MRI assessments (McDonald4). This salient advance allows for a more timely diagnosis and earlier treatment in patients with MS.

In 1965, Schumacher et al. published the first criteria for diagnosing MS.15 These early guidelines required the presence of CNS lesions disseminated in time and space and the exclusion of alternative diagnoses. The 1983 Poser criteria updated the Schumacher criteria.16 The latter guidelines reflected detection technique advances, such as MRIs and spinal taps, which identify lesions and other paraclinical evidence.

Most recently, an international panel in association with the National Multiple Sclerosis Society of America recommended revised criteria, and the McDonald criteria were published. These new criteria make use of advances in MRI imaging techniques and include criteria for dissemination of MS lesions in time and space. Prior to the McDonald criteria, a diagnosis of clinically definite MS (CDMS) might have taken several years. Still, these criteria focus on the diagnosis of CDMS and analyze inflammatory processes conservatively. They do not address the importance of MRI changes for the patient with a clinically isolated syndrome (CIS). For example, patients with an initial demyelinating event (such as optic neuritis, cerebellar syndrome, or spinal cord syndrome) must display changes over time in order to be diagnosed with definite MS. Despite the cautionary approach of the McDonald criteria, nearly 90% of patients with CISs who have MRI lesions will develop definite MS over time.17

In patients with CISs as well as with definite MS, MRI results usually reveal subclinical lesions. Data from a number of studies demonstrate that the presence of MRI-assessed lesions is strongly

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**TABLE 1** Summary of Studies Reporting Development of Clinically Definite Multiple Sclerosis (CDMS) in Patients Who Have Clinically Isolated Demyelinating Events With Lesions Assessed by Magnetic Resonance Imaging at Baseline

<table>
<thead>
<tr>
<th>Reference</th>
<th>Follow-up (Years)</th>
<th>Baseline Findings Predictive of CDMS</th>
<th>Criteria for CDMS</th>
<th>Patients Who Developed CDMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pary et al.16</td>
<td>1</td>
<td>4 lesions, or 3 lesions with 1 periventricular lesion</td>
<td>Schumacher criteria15</td>
<td>93% (18/19)</td>
</tr>
<tr>
<td>Barkhof et al.19</td>
<td>≥2</td>
<td>9 lesions</td>
<td>Poser et al.16</td>
<td>80% PPV*</td>
</tr>
<tr>
<td><strong>Optic Neuritis Study Group</strong>20</td>
<td>5</td>
<td>≥3 lesions ≥3 mm in size</td>
<td>Second attack confirmed by examination, with new neurologic disability</td>
<td>51% cumulative probability</td>
</tr>
<tr>
<td>O’Roordan et al.21</td>
<td>5–10</td>
<td>≥1 asymptomatic lesion compatible with demyelination</td>
<td>Poser et al.16</td>
<td>83% (45/54)</td>
</tr>
<tr>
<td>Sailer et al.22</td>
<td>10</td>
<td>≥1 asymptomatic lesion compatible with demyelination</td>
<td>Poser et al.16</td>
<td>82% (37/45)</td>
</tr>
<tr>
<td>Brex et al.23</td>
<td>1</td>
<td>≥1 gadolinium-enhancing lesion at baseline and at 3 months</td>
<td>Poser et al.16</td>
<td>70% PPV</td>
</tr>
<tr>
<td>Brex et al.27</td>
<td>14</td>
<td>≥1 asymptomatic lesion compatible with demyelination</td>
<td>Poser et al.16</td>
<td>88% (44/50)</td>
</tr>
</tbody>
</table>

*PPV = positive predictive value.
predictive of developing CDMS in patients who experience a clinically isolated event (Table 1). The results of a prospective longitudinal study of patients with CISs demonstrated that 88% of patients with abnormal MRI findings at baseline had developed CDMS at 14 years (Figure 1). Furthermore, at 14 years, the EDSS score was correlated with the number of lesions on MRI at baseline, with higher EDSS scores in patients who had more lesions at baseline (Figure 2).

Our understanding of the pathophysiology of MS has caused our thinking about early treatment of MS to evolve. Current dogma states that MS is an episodic autoimmune disease. MS is largely T-cell–mediated and involves environmental factors. Immune cells, activated in the periphery, enter the CNS by migrating across the blood–brain barrier, where they attack myelin and oligodendroglia. Traditionally, researchers postulated that axonal loss occurs late in the disease, secondary to this process, and that MS is a disease of the white matter. However, the current dogma is being questioned.

For example, evidence exists that the pathology of MS may differ among patients, suggesting that several different diseases culminate in a final pathway: MS. Studies of brain biopsy specimens and autopsies of patients with MS reveal that about 20% of patients have a major anti-CNS antibody component during acute flare-ups. Other lesions are associated with inflammatory macrophages. It is unknown whether various subtypes of MS exist or if these processes are part of a disease continuum in which different processes are active at various time points.

Evidence now suggests that axonal loss occurs early during the disease course and that it is prominent from the onset of MS. Trapp et al. used autopsy findings from patients with MS to define changes in axons. Their findings demonstrated that irreversible axonal transection occurred in both active and chronic lesions of patients, some of whom had MS for as few as 2 weeks. Transected axons were commonly found in lesions, and their frequency was related to the degree of inflammation within the lesion. These findings are critical; historically, axonal loss was not considered important in MS’s pathology. Moreover, axonal loss appears in normal-appearing white matter. A study of a patient who had MS for 9 months reported that myelin was relatively preserved despite a 22% axonal loss in the ventral column.

Reliable imaging of normal-appearing white matter and normal-appearing gray matter is challenging. Results from magnetic transfer imaging and spectroscopy have demonstrated abnormalities in areas that appear normal on conventional scans. Studies in which gadolinium is administered to patients before MRI to enhance MS lesions suggest that these gadolinium-enhanced (Gd+) lesions are preceded by abnormal findings on spectroscopy or magnetic transfer imaging.

Extensive evidence reveals that lesions occur in MS patients’ gray matter. In fact, cortical lesions occur early and frequently. One recent study reported that metabolic changes could be detected in the cortical gray matter of patients early in the disease course (mean duration of disease, 1.7 years). Furthermore, metabolic changes in the cortical gray matter were related to disability as measured by the EDSS, Multiple Sclerosis Functional Composite, 9-Hole Peg Test, and Paced Auditory Serial Addition Task. Abnormalities in normal-appearing gray matter are reported to correlate with cognitive deficits. Detection of gray matter lesions by conventional MRI is difficult because the relaxation characteristics of these lesions result in a poor contrast between them and the surrounding normal gray matter because of partial volume effects with cerebrospinal fluid (CSF).
Role of Magnetic Resonance Imaging

MRI-based assessments briefly discussed in this section are important tools in the diagnosis and management of patients with MS. In fact, MRI-based assessments are the most important ancillary tests performed in patients with MS. Gd+ T1-weighted scans display areas of blood–brain barrier disruption and are indicative of active inflammation and, therefore, reflect active disease.43 Gd+ lesions display a spectrum of appearances (e.g., ringlike, homogeneous) and may be clinically silent (i.e., without symptoms). The sensitivity of these images may be increased with various techniques that are becoming more readily available.44-46

The most commonly used measure of disease burden is the presence and number (and, for research, volume) of hyperintense lesions on T2-weighted images.31 However, these images are relatively insensitive to the underlying pathology and show both active and inactive lesions.37 Modifications of T2-weighted scans can provide additional information. Fluid-attenuated inversion recovery (FLAIR) sequences, for example, can visualize 2 to 3 times the number of lesions seen on conventional T2-weighted imaging.47

Hypointense lesions on T1-weighted images are also called “black holes.” Persistent T1 lesions indicate axonal loss, gliosis, loss of intracellular matrix, and demyelination; these lesions are thought to be markers for areas of more destructive focal CNS damage in MS patients.48-50 T1 hypointense lesions are thought to have a greater correlation with the clinical features of MS than T2 lesions44; however, more studies are needed to explore this relationship.

Brain atrophy is the best MRI predictor of clinical status. In fact, the degree and rate of brain atrophy correlate with physical disability, quality of life, depression, and cognitive dysfunction.47,51-61 Therefore, the measurement of brain atrophy has become increasingly important. Several measures can be used to quantify brain atrophy, including whole-brain and regional measures.51-60 These techniques are still not ready for general clinical use and remain research tools. However, visual inspection of MRI images alone can provide a reasonable sense of the degree of atrophy and comparisons can be roughly made between scans at different times.

A correlation has been observed between clinical status of patients with MS and spinal cord lesions and atrophy.47,61 These findings have increased the role of spinal cord MRI in the management of MS.62-70 Spinal cord MRI scans reveal T2 lesions in approximately 50% to 90% of patients with MS.31 Spinal cord scans can provide additional information when brain scans and clinical status are equivocal and can correlate spinal symptoms (cervical and thoracic). The frequency at which spinal cord MRI should be performed has not been fully determined but is advisable for tracking lesion load or atrophy.

Interestingly, 5 to 10 times more lesions occur on MRI than are manifested clinically.71-75 Possible explanations for this discrepancy include inattention to cognitive aspects of the disease, lesions located in noneloquent areas of the brain, lack of histopathologic specificity, absence of spinal cord involvement, underestimation of the damage to normal-appearing white and gray matter, and masking effects of brain adaptation.76 Recent improvements in MRI measures and techniques have increased their predictive value and improved their correlation with clinical status.71

MRI findings are needed to support the diagnosis of MS and are useful in evaluating patients with MS for other pathology. The appearance of Gd+ lesions in the appropriate clinical circumstances is particularly helpful in supporting the diagnosis of an inflammatory process. Furthermore, baseline MRI findings are helpful in determining patient prognosis. Therefore, Gd+ scans are recommended at diagnosis because Gd+ lesions are an indicator of active disease and have predictive value regarding the short-term course of MS77,78. In patients with a CIS, MRI will support a diagnosis of MS if there are a significant number of lesions.4 In addition, the longitudinal management of MS is increasingly utilizing MRI-based assessments.

Effect of Early Treatment on Multiple Sclerosis

The presence of MS lesions in the brain or spinal cord as detected by MRI indicates that the disease is active in the nervous system. If treatment is delayed until MS manifests clinically, irreversible damage may occur. Subclinical disease activity and axonal loss occur early in the disease process; hence, MS should be treated as early as possible. The earliest stage that patients can be diagnosed and treated is after a first clinical demyelinating event. A number of trials have studied the effects of early treatment in patients with suspected MS.80-82 Data from these trials reveal important clinical and MRI benefits in patients with syndromes that are suggestive of early disease who are treated promptly.

During the earliest randomized, placebo-controlled trial (the Controlled High Risk Subjects Avonex Multiple Sclerosis Prevention Study [CHAMPS]), patients with CISs were treated with IM IFNβ-1a to determine whether the time to the development of CDMS could be prolonged.80 CISs were defined as those that involved the optic nerve (unilateral optic neuritis), spinal cord (incomplete transverse myelitis), or brainstem or cerebellum (brainstem or cerebellar syndrome).80 Patients also must have had evidence of demyelination confirmed by MRI.80 Results from this study showed that early treatment delayed or prevented CDMS and reduced the frequency of new lesions that would have allowed the diagnosis of definite MS by McDonald criteria.80 The probability of developing CDMS was 44% lower in patients who received IM IFNβ-1a than in those who received placebo.80 Furthermore, changes in lesion volume were significantly different between groups, and, at 18 months, there were 58% fewer new or enlarging lesions and 71% fewer Gd+ lesions in patients who received treatment than in those who received placebo.80

Results from a subsequent study (Early Treatment of Multiple Sclerosis [ETOMS]) were consistent with the findings of the CHAMPS trial.81 During ETOMS, the effects of SC IFNβ-1a were studied in patients who had unifocal or multifocal neurologic syndromes and ≥2 T2 lesions (or 3 white-matter lesions if 1 lesion was infratentorial or Gd+).81 Over 2 years, 24% fewer patients who
PRISMS-4’s results are further supported by those of the CHAMPIONS study, an extension of the CHAMPS trial.83 In CHAMPS, patients who experienced a first clinical demyelinating event immediately began treatment with IM IFNβ-1a or had treatment delayed for a median of 29.9 months (placebo group). In CHAMPIONS, all patients were offered IM IFNβ-1a and followed for up to 5 years. The rate ratio for the development of CDMS over 5 years was reduced by 35% in the group of patients who received immediate treatment. Relapse rates and MRI results also significantly favored immediate treatment. Based on these findings, it is apparent that early treatment initiation can reduce disease activity and can slow the progression of disability (Figure 3).

Identifying Patients at High Risk for Multiple Sclerosis

One of the most important questions is how to identify patients at risk for MS who should be referred to a neurologist to reap the benefits of IMA treatment. A key reason to refer patients to a neurologist is the sudden appearance of a focal neurologic event such as paresthesias, numbness, visual changes, or aphasia. The most important determinant of high risk for the development of CDMS is the confirmation of a first, well-defined neurologic event that is consistent with demyelination associated with MRI scan abnormalities. These types of events involve the optic nerve (unilateral optic neuritis), spinal cord (incomplete transverse myelitis), or brainstem or cerebellum (brainstem or cerebellum syndrome).86 MRI findings should reveal lesions in the brain that are ≥3 mm in diameter, at least one of which is ovoid or periventricular.

Patients with a CIS who have ≥1 lesion on MRI are at a significantly higher risk for the development of CDMS.84 In the Optic Neuritis Treatment Trial, the 10-year risk of developing MS after an initial episode of optic neuritis was 38%.84 However, in the subgroup of patients with ≥1 lesion, the risk increased to 56%, while the risk in those with no lesions at baseline was 22%. Over 2 years, 86% of untreated patients with ≥1 new or enlarging lesion went on to develop MS compared with 38% of untreated patients without lesions.84

MS lesions typically are >5 mm in diameter and ovoid or oval. These lesions are usually in the periventricular, perivenular (Dawson’s fingers), juxtacortical, and infratentorial regions. MS lesions are visualized in the corpus callosum and spinal cord. The morphology of Gd+ lesions may be ringlike or homogeneous. The duration of ringlike lesions is longer than that of homogeneously enhancing lesions, and ringlike lesions are thought to be related to aggressive disease activity and a higher level of tissue damage.85-90 T1 black holes, a marker for considerable matrix destruction and axonal loss, are found most often in patients who have SPMS and higher EDSS scores.85

A number of diseases can cause MRI-signal hyperintensities of the white matter.91 However, the signal abnormality patterns associated with these disorders usually differ from those associated with MS such that the potential for misdiagnosis is low. In the diagnosis of MS, the physician should evaluate MRI scans to rule
out other illnesses such as demyelinating or hypoxic-ischemic disorders, immune-mediated vasculopathies, infectious and inflammatory diseases, and leukodystrophies and toxic metabolic diseases (very rare). For example, normal aging is associated with punctuate or patchy white matter signal hyperintensities, and hypertension and migraine are associated with a higher frequency of lesions randomly distributed throughout the deep and subcortical white matter; the intratentorial regions are usually not affected. Patients with subcortical arteriosclerotic encephalopathy have irregular and sometimes extensive periventricular hyperintensities on MRI, with confluent signal changes that usually spare subcortical U-fibers. However, in contrast with lesions, the center of a lacune appears isointense to CSF on all sequences because of complete tissue destruction.

Primary care physicians should refer patients to a neurologist for further assessment, including an MRI, after the suggestion of a first clinical demyelinating event. In patients with spinal cord symptoms, MRI along the entire spinal cord is suggested. Moreover, it is important to educate patients regarding the signs and symptoms of MS and to gain their full cooperation to optimize disease management. Patients should be able to recognize the symptoms of MS so that they are able to better inform their physician about their status.

### Conclusions

Early diagnosis and early treatment are critical to prevent irreversible long-term sequelae in patients with MS. Prior to the use of MRI, patients with a first clinical demyelinating event may have had to wait several years before receiving a diagnosis of CDMS. However, the use of MRI is emerging as one of the most important tools in the management of MS. The presence of ≥1 lesion is highly prognostic in the development of CDMS in patients who have experienced a clinically isolated neurologic event. In fact, the number of baseline lesions predicts the severity of future disability in patients who do not receive treatment. MRI data show that there can be significant subclinical disease activity, including axonal loss and brain atrophy, prior to a diagnosis of CDMS, and, many times, the number of lesions visualized on MRI does not correlate well with clinical symptoms. Importantly, it has been shown that axonal loss occurs very early in the disease process. Hence, MRI assessments are recommended after a first demyelinating event to allow for the identification of patients who are at high risk of CDMS (newer diagnostic criteria include MRI).

Several studies demonstrate that early treatment significantly reduces the risk of developing CDMS; this benefit is more pronounced in patients who have a high burden of disease at baseline. Thus, all patients with a clinically isolated demyelinating event should be referred to a neurologist for a more thorough examination and MRI testing. The effects of disease-modifying agents are greater in patients who begin treatment early.

### DISCLOSURES

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### REFERENCES


Neutralizing Antibodies to Multiple Sclerosis Treatments

HOWARD S. ROSSMAN, DO, FACN

ABSTRACT

OBJECTIVE: This article reviews the incidence and clinical significance of neutralizing antibodies (NAbs) in patients with multiple sclerosis (MS) undergoing treatment with interferon beta (IFNβ). Implications for practice are also discussed in light of the currently available data on the clinical consequences of NAbs in patients with MS.

SUMMARY: As with other recombinant protein drugs used for the treatment of a number of diseases, antibodies commonly develop to IFNβ products during the treatment of patients with MS. Neutralizing antibodies (NAbs) are a subset of antibodies that reduce or diminish the biologic activity of IFNβ. Three formulations of IFNβ are currently available for the treatment of relapsing-remitting MS: IFNβ-1b (Betaseron), intramuscular (IM) IFNβ-1a (Avonex), and subcutaneous (SC) IFNβ-1a (Rebif). Individual phase III clinical trials and direct comparison studies have shown that NAbs develop more frequently during treatment with IFNβ-1b than IFNβ-1a and that between the 2 IFNβ-1a products, NAbs develop more frequently during treatment with SC IFNβ-1a than IM IFNβ-1a. Data from clinical trials of IFNβ products indicate that clinical efficacy of IFNβ is reduced in NAb-positive patients.

CONCLUSION: In light of these data, the immunogenicity of IFNβ products should be considered prior to initiating treatment with IFNβ. Also, ongoing laboratory monitoring of patients treated with higher-dose IFNβ is recommended for early detection of NAbs.

KEYWORDS: Interferon-beta, Neutralizing antibodies, Multiple sclerosis

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Therapeutic use of protein products is frequently associated with antibody development. Antibodies develop, albeit at a reduced rate, even with the widespread use of recombinant DNA technology to produce protein drugs that are nearly identical to their endogenous human counterparts. Antibodies to biotherapeutic agents are broadly classified into binding antibodies and neutralizing antibodies (NAbs). Binding antibodies include all antibodies that can bind to the drug (and may or may not inhibit the drug), whereas NAbs are a subset of binding antibodies that can inhibit or neutralize the biologic activity of the protein drug.1

NAbs have been shown to develop following treatment with a variety of recombinant human protein drugs, including insulin, erythropoietin, and coagulation factor VIII (Table 1).1-6 In most cases, the main clinical outcome of NAbs is loss of efficacy of the protein drug. For example, the use of interferon alpha (IFNα) for the treatment of hepatitis or cancer has been associated with NAb development resulting in nonresponsiveness to treatment, disease reactivation, and decreased response duration.7-10 Similarly, in patients treated for cervical dystonia with botulinum toxin type A, the development of NAbs rendered the treatment ineffective.11

In addition to reduced efficacy, more severe clinical effects may be observed when NAbs form against a protein that has an impor-

<table>
<thead>
<tr>
<th>Disease/Condition</th>
<th>Consequence of Antibody</th>
<th>Biotherapeutic Agent</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Loss of efficacy</td>
<td>Insulin</td>
<td>Meager; Fineberg et al.2</td>
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<td>Acute myocardial infarction</td>
<td>Streptokinase</td>
<td>Rosenechim et al.14</td>
<td>Vanderschueren et al.15</td>
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<td>Adenosine deaminase deficiency</td>
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<td>Chaffee et al.16</td>
<td></td>
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<tr>
<td>Cervical dystonia</td>
<td>Botulinum toxin</td>
<td>Rollnik et al.11</td>
<td></td>
</tr>
<tr>
<td>Hemophilia A</td>
<td>Factor VIII</td>
<td>Lusher; 2000.5</td>
<td></td>
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<tr>
<td>Malignant carcinoid tumors</td>
<td>Interferon alpha-2</td>
<td>Freund et al.17; Quesada et al.10</td>
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<tr>
<td>Multiple sclerosis</td>
<td>Interferon beta</td>
<td>IFNB MS Study Group; PRISMS Study Group; Sorensen et al.11</td>
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<tr>
<td>Cancer</td>
<td>Interleukin-2 (IL-2)</td>
<td>Prümmer 18</td>
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<td>Hypogonadotropic azoospermic men</td>
<td>Gonadotropin-releasing hormone</td>
<td>Blumenfeld et al.19</td>
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<tr>
<td>Cutaneous T-cell lymphoma</td>
<td>Denileukin diftitox</td>
<td>Olsen et al.20</td>
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<td>Hypogonadotropic hypogonadism</td>
<td>Human chomic gonadotropin</td>
<td>Clausrat et al.21</td>
<td></td>
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<tr>
<td>Carcinoma</td>
<td>GM-CSF/IL-3</td>
<td>Raghunathan and Wadhia 82</td>
<td></td>
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<tr>
<td>Anemia</td>
<td>Neutalization of native protein</td>
<td>Erythropoietin</td>
<td>Casadevall et al.23; Prabhakar and Muhlfeild.19</td>
</tr>
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</table>

* GM-CSF = granulocyte-macrophage colony-stimulating factor.
Neutralizing Antibodies to Multiple Sclerosis Treatments

The incidence of NAb to IFN-β among IFN-β products varies widely, as reported in phase III trials (Table 2). In the pivotal phase III trial of IFN-β, 47% of patients who received IFN-β 1.6 million international units (MIU) and 45% of patients who received 8 MIU SC every other day developed NAb. In a study conducted by the European Study Group on IFN-β in secondary progressive MS, approximately 28% of patients (100 of 360) who received SC IFN-β 8 MIU every other day tested positive for NAb at some time during the study, with most patients becoming NAb positive in the first 6 months of treatment.

Phase III studies with IM IFN-β-1a have shown consistently lower levels of immunogenicity, with incidences of NAb ranging from 2% to 5.8%. Interestingly, in the earlier pivotal phase III trial of IM IFN-β-1a, NAb were detected in 14% of patients treated with IM IFN-β-1a 30 mcg once weekly at week 52, 21% at week 78, and 22% at week 104. The reduction in immunogenicity of IM IFN-β-1a after the pivotal phase III trial is thought to be due to improvements in manufacturing, purification, and storage processes of the now commercially available IM IFN-β-1a product. In the pivotal phase III trial of SC IFN-β-1a (Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis [PRISMS] study), NAb were observed in 23.8% of patients who received SC IFN-β-1a 22 mcg and 12.5% of patients who received SC IFN-β-1a 44 mcg. In PRISMS-4, which was the extension study of the phase III trial, 23.7% of patients who received SC IFN-β-1a 22 mcg and 14.3% of patients who received SC IFN-β-1a 44 mcg had a positive test result for NAb. However, in patients who had been on placebo during the first 2 years of the trial and received SC IFN-β-1a 22 mcg or 44 mcg during years 3 and 4, the incidence of NAb was 27.7% and 24.4%, respectively.

An evaluation of the relative immunogenicity of the different IFN-β products by comparing incidences among phase III trials is not ideal because of differences in the methods used for detecting and reporting NAb. However, results from individual phase III trials have shown consistently lower immunogenicity for IM IFN-β-1a compared to SC IFN-β-1a. The ability of a biologic protein product to trigger formation of antibodies is influenced by its structural properties as well as other factors, including formulation, presence of contaminants and impurities, route of administration, length of treatment, and dose. Source: Adapted with permission from Schellekens H. Bioequivalence and the immunogenicity of biopharmaceuticals. Nat Rev Drug Discov. 2002;1:457-62.1

### Incidence of Neutralizing Antibodies to Interferon Beta

<table>
<thead>
<tr>
<th>IFNβ Product</th>
<th>Dose and Frequency of Administration</th>
<th>Incidence of NAb (% of Patients)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNβ-1b (Betaseron)</td>
<td>SC* 3.5 times weekly 1.6 MIU†</td>
<td>47.0</td>
<td>IFNβ MS Study Group12</td>
</tr>
<tr>
<td>IFNβ-1b (Betaseron)</td>
<td>8 MIU</td>
<td>45.0</td>
<td>European Study Group15</td>
</tr>
<tr>
<td>SC IFNβ-1a (Rebif)</td>
<td>SC 3 times weekly 22 mcg</td>
<td>23.8</td>
<td>PRISMS Study Group14</td>
</tr>
<tr>
<td>SC IFNβ-1a (Rebif)</td>
<td>44 mcg</td>
<td>12.5</td>
<td>SPECTRIMS Study Group10</td>
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<tr>
<td>IM IFNβ-1a (Avonex)</td>
<td>IM once weekly 30 mcg</td>
<td>22.0</td>
<td>Jacobs et al.13</td>
</tr>
<tr>
<td>IM IFNβ-1a (Avonex)</td>
<td>30 mcg</td>
<td>2.0</td>
<td>Jacobs et al.18</td>
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<tr>
<td>IM IFNβ-1a (Avonex)</td>
<td>30 mcg</td>
<td>2.3</td>
<td>Clanet et al.17</td>
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<tr>
<td>IM IFNβ-1a (Avonex)</td>
<td>60 mcg</td>
<td>5.8</td>
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<td>IM IFNβ-1a (Avonex)</td>
<td>60 mcg</td>
<td>3.3</td>
<td>Panitch et al.21</td>
</tr>
<tr>
<td>IM IFNβ-1a (Avonex)</td>
<td>30 mcg</td>
<td>2.1</td>
<td>Panitch et al.21</td>
</tr>
</tbody>
</table>

* SC = subcutaneously, † MIU = million international units, ‡ IM = intramuscularly.

The ability of a biologic protein product to trigger formation of antibodies is influenced by its structural properties as well as other factors, including formulation, presence of contaminants and impurities, route of administration, length of treatment, and dose. Source: Adapted with permission from Schellekens H. Bioequivalence and the immunogenicity of biopharmaceuticals. Nat Rev Drug Discov. 2002;1:457-62.1


Impact of Neutralizing Antibodies on Biologic Activity and Clinical Efficacy of Interferon Beta Products

Biologic Activity

In general, NAb s are detected based on their ability to diminish the biologic activity of IFNβ in vitro. The ability of NAbs to interfere with the in vivo biologic activity of IFNβ has also been demonstrated. 21,22,23 Typically, the biologic activity of IFNβ is determined by measuring levels of biologic markers of IFNβ activity, such as neopterin, myxovirus resistance protein A (MxA), and β2-microglobulin.

Measurements of serum neopterin and β2-microglobulin levels before and 48 hours after IM IFNβ-1a injection were conducted in the trials of each IFNβ product are consistent with data from studies that have directly compared IFNβ products using the same criteria and methods. 22-25

For example, Bertolotto et al. conducted a study to directly compare the immunogenicity of the 3 IFNβ products. 22 Patients with relapsing-remitting MS were treated with SC IFNβ-1b 8 MIU every other day (n = 29), IM IFNβ-1a 30 mcg once weekly (n = 44), or SC IFNβ-1a 22 mcg 3 times weekly (n = 36). 22 Patients were screened for the presence of NAbs at baseline and every 3 months for up to 18 months. The risk of becoming persistent NAb-positive (i.e., ≥2 consecutive NAb samples with a titer ≥20) during 18 months of treatment was 31% for patients who received IFNβ-1b, 15% for patients who received SC IFNβ-1a, and 2% for patients who received IM IFNβ-1a (IM IFNβ-1a versus IFNβ-1b, P = 0.001; IM versus SC IFNβ-1a, P = 0.04); no significant difference in the incidence of NAbs was noted between SC IFNβ-1a and IFNβ-1b. 22

The European North American Comparative Efficacy study, EVIDence of Interferon Dose-response (EVIDENCE), compared SC IFNβ-1a (prefilled syringe) 44 mcg 3 times weekly with IM IFNβ-1a 30 mcg once weekly in patients with relapsing-remitting MS. 24 NAbs were measured in sera collected after 48 weeks of treatment. Results showed that 25% of patients (84 of 335) who received SC IFNβ-1a were positive for NAbs (titer ≥20), compared with 2% in the IM IFNβ-1a group.

In summary, available data show that there are differences in immunogenicity among IFNβ products. Individual phase III clinical studies and direct comparison studies have shown that 28% to 47% of patients develop NAbs to IFNβ-1b, 12% to 25% to SC IFNβ-1a, and 2% to 6% to the commercially available formulation of IM IFNβ-1a. The incidence of NAbs in the U.S. Food and Drug Administration-approved package insert for each product is 45% for IFNβ-1b, 24% for SC IFNβ-1a, and 5% for IM IFNβ-1a. 20-26

Factors Affecting Immunogenicity of Interferon Beta Products

All 3 IFNβ products are recombinant protein drugs. Some factors affecting the immunogenicity of IFNβ products are shown in Figure 1. 1 These include the protein sequence and molecular structure of the drug, manufacturing and storage conditions, and route and frequency of administration. Unlike IFNβ-1a formulations, which are both identical in protein sequence to the natural human IFNβ, IFNβ-1b has a serine-to-cysteine substitution at position 17 and a deletion of the N-terminal methionine residue. 20 Also, IFNβ-1b is produced in Escherichia coli bacteria, whereas IM IFNβ-1a and SC IFNβ-1a are produced in mammalian cells (Chinese hamster ovarian cells). Because it is produced in bacterial cells, IFNβ-1b is not glycosylated. The lack of glycosylation is thought to result in an increased tendency of IFNβ-1b to form aggregates that can trigger the formation of antibodies. 21 The differences in protein sequence and molecular structure between IFNβ-1b and IFNβ-1a likely account for the observed greater incidence of NAbs with IFNβ-1b compared with either of the IFNβ-1a products.

Given that the 2 IFNβ-1a formulations have an identical protein sequence, differences in their immunogenicity are likely due to manufacturing, purification, and storage conditions. It is conceivable that differences in these conditions can lead to the production of recombinant proteins with different glycosylation patterns. Also, under differing conditions, oxidation and deamidation of amino acids may vary. Indeed, in the case of IM IFNβ-1a, improving the manufacturing process resulted in a less immunogenic product. Other factors affecting the immunogenicity of IFNβ may include dose, route of administration, length of treatment, and frequency of administration. Both IFNβ-1b and SC IFNβ-1a are administered 3 to 3.5 times weekly by SC injection. In contrast, IM IFNβ-1a is administered once weekly by IM injection.

Although Ross et al. showed that SC administration of IFNβ is more immunogenic than IM administration, 22 Bertolotto et al. showed no differences in immunogenicity between SC and IM administration of IFNβ. 25 Hence, the route of administration is a potential factor influencing immunogenicity.
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the open-label, safety-extension study of the pivotal phase III trial of IM IFNβ-1a. The levels of serum NAb titers correlated with measurements of neopterin levels (Figure 2), such that the mean increase in neopterin level after IFNβ-1a injection was significantly lower in NAb-positive patients (titer 5 to 19 and titer ≥20) compared with NAb-negative patients (P = 0.012 and P = 0.001, respectively). Similar results were also observed with serum levels of β-microglobulin.

Another study used MxA as a marker for the biologic activity of IFNβ in patients with MS who received IFNβ-1b and a healthy control group. MxA levels were significantly lower in NAb-positive patients compared with NAb-negative patients (P<0.001). Furthermore, the levels of MxA in NAb-positive patients were similar to those of the untreated healthy control group, suggesting that the biologic activity of IFNβ-1b in these patients was completely inhibited by NAbs. Inhibition of MxA expression by NAbs has also been reported at the level of messenger ribonucleic acid (mRNA), with MxA mRNA levels being significantly lower in persistent NAb-positive (22 consecutive positive samples titer ≥20) patients compared with NAb-negative (P<0.001) and isolated NAb-positive (1 positive titer ≥20) patients (P<0.005).

### Clinical Efficacy

NAbs have been shown to reduce the clinical efficacy of IFNβ in MS patients, based on increased relapse rate and lesion activity on magnetic resonance imaging (MRI). In the pivotal phase III trial of IFNβ-1b, the mean relapse rate during 18 to 36 months of treatment was significantly greater in NAb-positive patients (1.16 per year) compared with NAb-negative patients (0.50 per year) (Figure 3). In fact, the relapse rate in NAb-negative patients was similar to that observed in patients given placebo (1.02 per year, P < 0.05). Similarly, in the 2-year extension study of the phase III trial of SC IFNβ-1a (PRISMS-4), in patients treated with SC IFNβ-1a 44 mcg, NAb-positive patients experienced a significantly higher mean relapse rate during years 3 and 4 (0.81) compared with NAb-negative patients (0.50, P = 0.002).

In addition to data from phase III studies of IFNβ, a recent study by the Danish Multiple Sclerosis Study Group also provides evidence of diminished clinical efficacy of IFNβ in NAb-positive patients. The study involved 541 patients randomly selected from all patients in Denmark who started treatment with IFNβ between 1996 and 1999. Yearly measurements of NAbs in these patients revealed that relapse rates were significantly higher during NAb-positive periods (0.64 to 0.70) than they were during NAb-negative periods (0.43 to 0.46, P<0.03). Furthermore, the proportion of relapse-free patients was significantly lower (P = 0.0064), and the median time to first relapse was significantly reduced (by 244 days; Kaplan-Meier analysis, log rank test 6.83, P = 0.009) in NAb-positive patients compared with NAb-negative patients.

Decreased efficacy of IFNβ due to NAbs has also been noted using MRI measures. Patients who developed NAbs to IFNβ-1b had significantly more enlarging T2 lesions than NAb-negative patients (0.41 versus 0.19 between years 1 and 2 [P≤0.05], 0.589 versus 0.26 between years 3 and 4 [P = 0.011]). Furthermore, NAb-positive patients also showed an increased tendency to form new lesions (mean values of 1.03 in NAb-positive patients versus 0.40 in NAb-negative patients, P = 0.067).

Data from the open-label extension study of the pivotal phase III trial of SC IFNβ-1a (PRISMS-4) provide even stronger evidence of diminished therapeutic effects of IFNβ on MRI due to NAbs (Table 3). After 4 years of treatment with SC IFNβ-1a, disease burden on MRI was decreased by 8.5% from baseline in NAb-negative patients compared with a 17.6% increase in disease burden in NAb-positive patients (P<0.001). The values in NAb-positive patients approached those of patients treated with placebo during the first 2 years of the study. Furthermore, the median number of T2 active lesions was 1.4 in NAb-positive patients compared with 0.3 in NAb-negative patients (P<0.001). Although only a small number of patients develop NAbs to IM IFNβ-1a, results in these patients are similar to those noted with IFNβ-1b and SC IFNβ-1a. Patients who developed NAbs to IM IFNβ-1a have
Neutralizing Antibodies to Multiple Sclerosis Treatments

The time course of the development of NAbs is an important facet of monitoring and assessing the clinical effects of NAbs during treatment with IFNβ. In general, NAbs become detectable at any time between 3 and 18 months following initiation of treatment with IFNβ (Figure 4). An 18-month study that compared the immunogenicity of the 3 IFNβ products showed that, although patients continued to develop NAbs to each of the 3 products throughout the study period, 76% developed NAbs during the first 9 months and a further 14% developed NAbs by 12 months. Thus, 90% of the NAb-positive patients in the study developed NAbs during the first year of treatment with IFNβ.

Results from clinical trials indicate that in NAb-positive patients undergoing treatment with IFNβ, the effects of NAbs on MRI measures of disease burden become apparent at approximately 1 year and effects on clinical outcomes after 18 to 24 months of treatment. Thus, short-term studies (≤2 years) cannot adequately assess the impact of NAbs on the clinical efficacy of IFNβ.

An unresolved question with regard to the clinical relevance of NAbs is how long NAbs persist once they are formed. Available data indicate that once formed, NAbs can persist for several years. In a recent study by the Danish Multiple Sclerosis Study Group, 45% of patients were NAb-positive to IFNβ-1b at 1 year, 35% at 3 years, and 28% at 4 years. Thus, approximately 80% of patients who were NAb-positive to IFNβ-1b remained positive over 3 years and approximately 70% remained NAb-positive over 4 years. However, these data are difficult to interpret because a large proportion of patients dropped out of the study, and no information was provided regarding the numbers of NAb-positive and NAb-negative patients who discontinued the study. There is evidence that the persistence of NAbs is dependent on both NAb titer (higher-titer NAbs persist longer) and IFNβ product.

Implications for Practice

The Consortium of Multiple Sclerosis Centers recently published a list of consensus statements (>70% agreement) regarding the issue of NAbs to IFNβ in patients with MS; this list was developed based on the opinions of 33 researchers in the area of NAbs. Of note, this group of experts believes that NAbs should be one of the factors that clinicians consider in the ongoing management of MS patients and that future studies should be conducted to determine how best to counteract NAbs. Specific recommendations for NAb testing and the management of NAb-positive patients are provided in the article in this supplement by Sheldon J. Rich et al.

As discussed in the preceding sections, data from a number of clinical studies have shown that NAbs can develop in MS patients undergoing treatment with IFNβ, but there is no way to predict which patients will develop NAbs. Key evidence from these studies that should be considered when making treatment decisions relating to IFNβ treatment in MS patients include the following:

- NAbs (titers ≥20) can reduce the bioavailability and clinical efficacy of IFNβ.
- The incidence of NAbs varies with the 3 IFNβ preparations. IFNβ-1b treatment is more immunogenic than IFNβ-1a treatment, and between the 2 IFNβ-1a products, SC IFNβ-1a treatment is more immunogenic than IM IFNβ-1a treatment. Prior to initiating treatment with an IFNβ product, these differences in immunogenicity of IFNβ products should be considered.
- IFNβ-treated patients who experience worsening in clinical status should be tested for the presence of NAbs. For patients who have a positive test result for NAbs, switching to another IFNβ product is not recommended because antibodies are cross-reactive among IFNβs.
- Given that the clinical effects of NAbs are manifested several months after they develop, ongoing monitoring and early detection of NAbs in patients at higher risk (i.e., those on higher-dosing, more frequently administered, SC IFNβs) will likely improve the quality of treatment received by MS patients undergoing treatment with IFNβ.

Conclusions

Data from a number of clinical trials indicate that NAbs can reduce the therapeutic benefits of IFNβ treatment in patients with MS. Loss of clinical efficacy has been observed in these studies in the form of increased relapse rates and disease burden on MRI in NAb-positive patients. Another important issue is the persistence of NAbs once they are formed. Available data indicate that once
formed, NABs tend to persist for several years. In light of these data, the immunogenicity of IFNβ products should be considered prior to initiating treatment with IFNβ. Also, ongoing laboratory monitoring of patients treated with higher-dose IFNβ is recommended for early detection of NABs.

DISCLOSURES

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Neutralizing Antibodies to Multiple Sclerosis Treatments


39. Goelz SE. The persistence of neutralizing antibodies to interferon beta (IFNβ) over 6 years of treatment in MS patients is dependent on titer and IFNβ product. Neurology. 2004;62(suppl 5):A156.


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.

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. 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. Additionally, both IFNβ-1a products have been shown to reduce sustained disability progression in relapsing MS and decrease progression to clinically definite MS when administered during the early phases of the disease.

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.
Evaluating Multiple Sclerosis Therapies

Two types of immunomodulatory therapies may be used as first-line treatment for patients with RMS: 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. 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. 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) 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. 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). 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).
The results of the 2-year pivotal study of glatiramer acetate were published in 1995, with a follow-up report describing results of an 11-month extension period published in 1998. The initial study indicated that there was no significant effect on progression to sustained disability. Post hoc analysis of the extension trial results revealed a significant decrease in the EDSS score with glatiramer acetate treatment. 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. A significant effect of IFNβ was apparent in the first year of therapy in several studies.

**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. Serial MRI detection of disease activity in relapsing forms of MS seems to be significantly more sensitive than clinical evidence of disease progression. A report of the Therapeutics and Technology Assessment Subcommittee of the AAN has recommended the use of MRI for the diagnosis of MS. 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. 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). Additionally, the benefit of IFNβ on Gd+ MRI activity is evident within 2 weeks, whereas the effect of glatiramer acetate is considerably less rapid.

In the MS treatment algorithm, MRI scans are recommended to 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. 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. The results of a recent open-label study found that IFNβ-1b slowed brain atrophy progression during the second and third years of treatment. 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.

**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. The incidence of NAbs is higher with IFNβ-1b treatment (45% of patients) compared with IFNβ-1a products. In addition, the incidence of NAbs is higher

### Table 2

**Immunomodulatory Adverse Events That May Compromise Compliance**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>IFNβ-1b</th>
<th>IFNβ-1a-1Avonex 351/333</th>
<th>IFNβ-1a-Rebif 44 mcg 184/187</th>
<th>Glatiramer Acetate 201/206</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection-site reactions</td>
<td>85%/29%</td>
<td>3%/1%</td>
<td>92%/39%</td>
<td>66%/19%†</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>60%/41%</td>
<td>49%/29%</td>
<td>59%/51%</td>
<td>19%/17%</td>
</tr>
<tr>
<td>Depression</td>
<td>NA</td>
<td>18%/14%</td>
<td>25%/25%</td>
<td>NA</td>
</tr>
<tr>
<td>Fatigue</td>
<td>NA</td>
<td>NA</td>
<td>41%/36%</td>
<td>NA</td>
</tr>
<tr>
<td>Chest pain</td>
<td>11%/7%</td>
<td>5%/2%</td>
<td>8%/5%</td>
<td>21%/11%</td>
</tr>
<tr>
<td>Pain</td>
<td>51%/42%</td>
<td>23%/21%</td>
<td>NA</td>
<td>28%/25%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>NA</td>
<td>NA</td>
<td>36%/14%</td>
<td>NA</td>
</tr>
<tr>
<td>SGPT increased</td>
<td>10%/4%</td>
<td>NA</td>
<td>27%/4%</td>
<td>NA</td>
</tr>
<tr>
<td>SGOT increased</td>
<td>3%/1%</td>
<td>NA</td>
<td>17%/4%</td>
<td>NA</td>
</tr>
</tbody>
</table>

IFNβ = interferon beta; SGOT = serum glutamate oxaloacetate transaminase; SGPT = serum glutamate pyruvate transaminase.

† Injection site erythema.
with SC IFNβ-1a (24%) compared with IM IFNβ-1a (5%) treatment. 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). 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. Glatiramer acetate product labeling does not contain such a warning.

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%). 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%). 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 panels' 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; 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. 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.

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. Patients on IFNB 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 IFNB may not provide additional benefit and may lead to increased side effects and a higher incidence of NABs.

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.

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.

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. 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.

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. Some of the more commonly used agents that have been combined with IFNB 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-
pies selected must be tailored to suit the current status of the patient and should be initiated during specific treatment “windows.” These treatment windows represent stages in the disease during which appropriate therapy has the greatest chance to significantly alter the course of the disease.

In order to develop the physician treatment algorithm, the MS disease process was categorized into 3 different stages. Patients will transition between stages depending upon their response to therapy and disease progression (Figure 2). Stage I represents MS early in the progression of the disease. Management is recommended using a platform drug (IM IFNβ-1a, SC IFNβ-1a, IFNβ-1b, or glatiramer acetate). Based on the results of pivotal studies, IFNβ is the optimal choice for platform therapy. The ideal IFNβ platform therapy would have the following characteristics: ability to significantly slow disability progression; ability to reduce relapse rate, MRI lesion activity, and brain atrophy; low immunogenicity; a low incidence of side effects, including injection-site reactions; and a convenient dosing schedule. Relapses should be treated with corticosteroids. Stage II represents acute breakthrough disease that is managed by the addition of pulse corticosteroids to the platform drug. Stage III represents continued breakthrough disease that is managed by the addition of immunosuppressants to the platform drug. It is hoped that this new treatment algorithm assists physicians in the management of patients with MS and enhances physicians’ ability to improve patient quality of life over the course of the disease.

DISCLOSURES

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REFERENCES


Stepped-Care Approach to Treating MS: A Managed Care Treatment Algorithm

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ABSTRACT

OBJECTIVE: To introduce a model treatment algorithm for use in the managed care setting as a strategy to provide ongoing disease management and long-term care for patients with multiple sclerosis (MS), with the goal of delaying disease progression and the associated disability and cognitive dysfunction.

SUMMARY: MS is a chronic inflammatory disorder of the central nervous system that is associated with progressive disability and cognitive dysfunction. Currently, management of MS involves planning an effective long-term treatment strategy that can delay the progression of the disease. This article reviews a typical stepped-care approach to treating MS that is based on the concept of a platform drug, which is an agent that provides baseline immunomodulatory action throughout the course of the disease.

Considerations for selecting a platform therapy include the effect on the full spectrum of MS (disability, relapses, lesion load, and atrophy as well as patient compliance and the potential impact of neutralizing antibodies [NAbs]). Currently, 4 first-line therapies are approved for relapsing MS: the 3 interferon beta (IFNβ) products and glatiramer acetate. Of these, the IFNβs are generally recommended as platform therapy because all have shown significant effects on relapses, magnetic resonance imaging parameters of the disease, and because intramuscular (IM) IFNβ-1a (Avonex, Biogen Idec Inc., Cambridge, MA); subcutaneous (SC) IFNβ-1a (SC IFNβ-1a [Rebif, Serono, Inc., Rockland, MA]); and IFNβ-1b (Betaseron, Berlex Laboratories, Montville, NJ) and glatiramer acetate (Copaxone, Teva Neuroscience, Inc., Kansas City, MO). Consequently, these drugs are used as baseline immunomodulatory agents (platform drugs) in the treatment of MS. These treatments are proven to slow various aspects of MS; however, most patients will experi-
Diagnosis and Therapy Selection

Diagnosis

A single clinical event indicative of demyelination is often the earliest symptom detected in patients with MS. Typically, patients present to their primary care physician with an isolated clinical event, for example, optic neuritis in one eye or numbness on one side of the body. Once a patient is referred to a neurologist, a diagnosis of clinically isolated syndrome (CIS) is made based on a neurologic or ophthalmologic examination, or both, confirming the clinical event consistent with demyelination involving the optic nerve (optic neuritis), spinal cord (incomplete transverse myelitis), or brainstem or cerebellum (brainstem or cerebellar syndrome).‡

Following a diagnosis of CIS and exclusion of alternate diagnoses, the patient’s risk of developing clinically definite MS (CDMS) is evaluated. Historically, a diagnosis of CDMS was made following the occurrence of a second clinical demyelinating event.† However, because the time between the first and second attacks varies considerably, diagnosis and therapy initiation could take several years. Many studies have therefore evaluated the risk of developing CDMS in patients diagnosed with CIS using paraclinical measures, such as MRI, evoked potentials, and examination of cerebrospinal fluid (CSF) for the presence of oligoclonal bands. Of these measures, MRI has been shown to be the most sensitive method for predicting the development of CDMS in patients with suspected MS.§ Further, the prognostic value of MRI in MS has been demonstrated in prospective follow-up studies of patients with CIS.¶ Diagnostic criteria for MS now include MRI as a paraclinical diagnostic tool∥ because the presence of characteristic MS lesions on MRI is associated with a high risk of developing CDMS.¶∥

Therapeutic Plan Development and Selection of a Platform Therapy

The National Multiple Sclerosis Society recommends initiation of treatment as soon as possible after a definitive diagnosis of MS is made and also recommends that treatment be initiated in patients at high risk of developing MS.∥∥

Following the decision to initiate therapy, one of the first steps is selection of an appropriate platform drug (Figure 1), which is defined as an agent that can provide baseline immunomodulatory action throughout the course of the disease. Platform treatment may be adequate treatment for many patients for years; however, for patients with aggressive disease, additional agents can be added to the platform drug, based on symptoms and disease progression. Platform therapy options are the 4 drugs that are approved by the U.S. Food and Drug Administration (FDA) for use in relapsing MS: IFNβ-1a, IM IFNβ-1a, SC IFNβ-1a, and glatiramer acetate. The relative efficacy, side effects, convenience, and compliance issues relating to these drugs (discussed in the article by William H. Stuart in this supplement) should be considered when evaluating the different platform drugs. IFNβs are recommended as platform therapy because they have an impact on relapses and lesions on MRI. In addition, IM and SC IFNβ-1a have been shown to slow the progression of sustained disability¶¶ and IM and SC IFNβ-1b therapies have been shown to significantly decrease brain atrophy¶∥.

Given the long-term nature of MS treatment, the clinical aspects of the available platform drugs should be given careful consideration before initiating treatment. The complications that may arise due to the generation of NAbs to IFNβ also should be taken into account (for a detailed discussion, see the article by Howard S. Rossman in this supplement). These complications include reduced efficacy of the drug and cross-reactivity of NAbs that make switching between IFNβ products impractical. The neurologist must consider these factors and assist individual patients in selecting the appropriate agent rather than simply providing general information to patients and having them select a drug.

Ongoing patient education sets realistic expectations for agent effectiveness. For instance, after treatment initiation, a patient may experience exacerbations or relapses for some time. Generally, the IFNs require 3 to 6 months of treatment to become fully effective, and glatiramer acetate may take up to 9 months to become fully effective. Patients must also be aware of the potential side effects of the chosen platform therapy. Some of the common side effects associated with IFNβ treatment are injection-site reactions (mostly SC formulations), flu-like symptoms, and headache.¶∥∥ These side

<table>
<thead>
<tr>
<th>Figure 1</th>
<th>Diagnosis and Therapy Selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically isolated syndrome + MRI to support diagnosis</td>
<td>Patient meets diagnostic criteria for MS</td>
</tr>
<tr>
<td>Develop therapeutic plan and select platform therapy</td>
<td>Neurologist recommends appropriate therapy based on:</td>
</tr>
<tr>
<td>IFNβ-1a (Avonex)</td>
<td>• Evidence-based efficacy</td>
</tr>
<tr>
<td>IFNβ-1a (Rebif)</td>
<td>• Patient lifestyle: likelihood patient will comply with dosing and administration regimen</td>
</tr>
<tr>
<td>IFNβ-1b (Betaseron)</td>
<td>• Low immunogenicity</td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone)</td>
<td>• Ability for long-term treatment (suitability and tolerability)</td>
</tr>
</tbody>
</table>

The decision to initiate treatment for multiple sclerosis (MS) is followed by careful consideration of the available first-line or “platform” therapies. Educating patients and setting realistic treatment expectations are also important factors in designing an effective long-term treatment plan. IFNβ = interferon beta; MRI = magnetic resonance imaging.
**Ongoing Disease Management**

Effective, dynamic treatment strategies require initiation of platform therapy followed by regular, ongoing monitoring of patients for MS symptoms and disease activity. Ongoing monitoring of patients with MS can aid early detection of breakthrough disease. Occurrence of breakthrough disease is identified on an individual basis on unacceptable disease progression. Possible criteria to assist in this determination include disability progression (e.g., increase of ≥1 point on the Expanded Disability Status Scale), multiple relapses in a short time span (e.g., ≥2 relapses in 6 months after 1 year of IFNβ therapy), development of new urologic deficits, or deterioration evident on MRI. Factors such as poor patient adherence and development of NAbs can contribute to the occurrence of breakthrough disease in patients on a platform drug and should therefore be monitored as well (Figure 2).

**Symptom Management**

The most common symptoms of MS are spasticity, fatigue, sexual dysfunction, bladder dysfunction, pain, and cognitive dysfunction. Other frequently noted symptoms include depression, bowel dysfunction, paroxysmal symptoms, and weakness. Many MS symptoms can be interrelated such that one untreated symptom aggravates or leads to other symptoms, causing a cycle of interdependent symptoms. Disease progression also can lead to a wide range of complicating symptoms requiring additional treatments. Educating primary care physicians and nurses to identify symptoms that the patient is experiencing, and encouraging patients to avoid using multiple over-the-counter medications, vitamins, and herbal preparations are important symptom management tools. Not all drugs listed in the following section are approved by the FDA for use in MS. These drugs are discussed to educate pharmacists about medications that neurologists empirically have found useful and commonly prescribe for patients with MS.

**Spasticity.** Impairment of muscle function is one of the most common symptoms of MS, affecting an estimated 40% to 75% of patients, and spasticity accounts for most of the physical disability seen in MS patients. Nonpharmacologic treatment options for spasticity include carefully planned, physician recommended exercise regimens (including aerobic exercise, stretching exercises to improve flexibility, and both active and passive movements that incorporate the full range of motion) and relaxation techniques (such as yoga, meditation, biofeedback, and tai chi). Pharmacologic treatments include baclofen (GABAB-receptor stimulator [Lioresal]), tizanidine (α-adrenergic receptor agonist [Zanaflex]), and benzodiazepines.

**Fatigue.** Fatigue is reported by 80% to 97% of patients with MS and is characterized by a lack of energy, an overwhelming sense of tiredness, or a feeling of exhaustion. Nonpharmacologic management of fatigue involves treating symptoms in patients that lead to fatigue, such as depression and sleep disturbances, and improving patient mobility through exercise. Pharmacologic treatments include the off-label use of modafinil (Provigil), The N-methyl-D-aspartate antagonist amantadine (Symmetrel), methylphenidate (Ritalin), and amphetamines also are used off-label to treat fatigue.

**Depression.** The lifetime prevalence of depression among patients with MS is 47% to 54%. Nonpharmacologic treatment consists of psychotherapy and pharmacologic agents used to treat depression include selective serotonin reuptake inhibitors (SSRIs [e.g., fluoxetine, sertraline, paroxetine, escitalopram, and citalopram]), tricyclic antidepressants (e.g., amitriptyline and nortriptyline), and atypical antidepressants (e.g., bupropion and venlafaxine).

**Bladder dysfunction.** Bladder symptoms are experienced by 80% to 96% of patients with MS and include overactive bladder (detrusor hyperreflexia) and urinary retention (overactive sphincter). Treatment for overactive bladder consists of anticholinergics (e.g., oxybutynin and tolterodine), and treatment for urinary retention involves the off-label use of α-adrenergic antagonists (e.g., tamsulosin, doxazosin, and terazosin).

**Pain.** Approximately 65% of patients with MS experience acute and subacute painful syndromes, the extent and impact of which are often underestimated. Paroxysmal neuropathic pain is acute and intense; may worsen with age and disease progression; and includes trigeminal neuralgia, which is triggered by sensory stimuli at various points on the face or head, Lhermitte’s
phenomenon caused by cervical cord lesions, and dystonic spasms from paroxysmal dystonia. Treatment options for such pain include anticonvulsants, antispasmodics, and surgery. Constant neuropathic pain also can occur and may require the use of anticonvulsants, nonsteroidal anti-inflammatory drugs, opioid narcotics, nerve blocks, or tricyclic antidepressants. 

**Sexual dysfunction.** Approximately 48% to 75% of patients with MS may experience sexual dysfunction. In men with MS, symptoms include erectile dysfunction, ejaculatory disorders, and difficulty achieving orgasm. In women with MS, symptoms include reduced libido; reduced, altered, or painful sensations; reduced lubrication; difficulty achieving orgasm; and anxiety about incontinence. Nonpharmacologic treatment options include addressing psychophysiological issues that can contribute to sexual dysfunction; pharmacologic treatments include drugs for erectile dysfunction and lubricants. Discontinuation of SSRIs associated with sexual side effects also may be considered. Alternatives to SSRIs include tricyclic antidepressants and monoamine oxidase inhibitors.

**Cognitive dysfunction.** Impairment of cognitive processes is reported by 45% to 65% of patients with MS and is the symptom that is of greatest concern to patients. Cognitive dysfunction most often includes impairment in learning and memory, attention, and information processing. Nonpharmacologic cognitive rehabilitation is the main treatment option because, currently, no medications are approved for the treatment of cognitive impairment in MS. Because the occurrence or progression of cognitive dysfunction is an indicator of active disease, treatment options for this symptom are the same as those used to delay the progression of the physical symptoms of MS (i.e., IFNβ and glatiramer acetate). IM IFNβ-1a has been shown to delay progression of cognitive dysfunction in patients with MS. 

**Use of MRI to Monitor Disease Activity**

Subclinical disease activity detected using MRI plays an important role in the longitudinal management of MS. Typically, lesions seen on MRI and used to assess disease activity include hyperintense lesions on T2-weighted images, hypointense lesions on T1-weighted images, and gadolinium-enhanced lesions on postcontrast images. Another measure that is being increasingly accepted as an important MS outcome is MRI measurement of CNS atrophy. Increase in lesion load and progressive atrophy on MRI often may be clinically silent. Because brain MRI can detect disease activity that is subclinical, it is considered a more sensitive measure of disease activity than clinical findings.

Generally, insurance coverage for MRI is available for the purpose of diagnosis but not necessarily for ongoing disease monitoring. Given that MRI measures can detect asymptomatic worsening of disease and thus help in making preemptive alterations to the treatment plan, it is recommended that MRI be performed periodically in patients with MS. Ideally, MRI should be performed every 12 months in patients with MS who are asymptomatic and more often (every 6 months) in patients who are symptomatic. Recommended MRI protocols are shown in Table 1.

**Testing for Neutralizing Antibodies**

In patients with MS undergoing treatment with IFNβ, formation of NAbbs to IFNβ can lead to a loss of efficacy of the drug and subsequent occurrence of breakthrough disease. Antibodies also form against glatiramer acetate, although their clinical significance needs to be elucidated. Early detection of NAbbs through periodic testing can make the neurologist aware of the potential for recurrence of symptoms in patients who are NAbbs-positive.

The 3 different formulations of IFNβ are associated with varying incidences of NAbbs: IM IFNβ-1a, 5%; SC IFNβ-1a, 24%; IFNb-1b, 45%. (For a detailed discussion, see the article by Howard S. Rossman in this supplement.) Consequently, the guidelines for NAb testing depend on which IFNβ product is being used as the platform drug. For patients using the more immunogenic IFNβ products (IFNβ-1b and SC IFNβ-1a), testing for NAbbs should be done at 12 months or if breakthrough disease occurs. Patients who are being treated with the less immunogenic IM IFNβ-1a only need to be tested if breakthrough disease occurs.

The NAbFeron (IFNβ) antibody test (Athena Diagnostics) is the most commonly used, commercially available assay for NAbbs. The cytopathic effect assay for NAbbs, recommended by the World Health Organization, is based on the ability of NAbbs in serum to interfere with the antiviral effects of IFNβ on human lung carcinoma cells. NAbbs are quantitatively expressed in neutralizing titers (a neutralizing titer is defined by a 50% inhibition of the activity of 10 IU/ml IFNβ). The threshold for NAbbs-positivity is defined by the presence in patient serum of NAb titers ≥20. The NAb titer appears to influence the persistence of NAbbs. Patients with NAb titers >100 are more likely to remain NAbbs-positive for years. Patients treated with corticosteroids should not be tested for NAbbs until 30 days after the last corticosteroid dose because corticosteroid treatment can temporarily suppress NAbbs.

For symptomatic patients with high NAb titers (≥20), therapy alteration is recommended. For those with high titers who are asymptomatic, the NAb test may be repeated in 6 months. If NAbbs are persistent, then therapy should be altered. For patients with low

<table>
<thead>
<tr>
<th>TABLE 1 Recommended Magnetic Resonance Imaging Protocol</th>
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</thead>
<tbody>
<tr>
<td><strong>Brain, axial</strong></td>
</tr>
<tr>
<td>T1 noncontrast</td>
</tr>
<tr>
<td>T1 postcontrast</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
<td>Fluid-attenuated inversion recovery (FLAIR)*</td>
</tr>
<tr>
<td><strong>Brain, sagittal</strong></td>
</tr>
<tr>
<td>T1 noncontrast</td>
</tr>
<tr>
<td>FLAIR</td>
</tr>
<tr>
<td><strong>Spinal</strong></td>
</tr>
<tr>
<td>T1 sagittal</td>
</tr>
<tr>
<td>T2 sagittal</td>
</tr>
<tr>
<td>T2 axial</td>
</tr>
<tr>
<td>Postcontrast (T1 axial, T1 sagittal)</td>
</tr>
</tbody>
</table>

*FLAIR is recommended to increase the sensitivity and specificity of hyperintense MS lesions.
Management of Breakthrough Disease

In general, for the purpose of designing a treatment plan, the MS disease process can be categorized into 3 stages. Stage I is the early part of the disease, Stage II involves acute breakthrough disease on treatment, and Stage III is characterized by continued breakthrough disease despite treatment. Depending on their response to therapy, and disease fluctuations and progression, patients may move from one stage to another and back.

Acute Breakthrough Disease

Management of breakthrough disease in Stage II involves the use of pulse corticosteroids. Typically, intravenous (IV) methylprednisolone 1 g/day is administered over 1 to 4 hours for 3 to 5 days. The platform drug is continued during the management of breakthrough disease.

Continued Breakthrough Disease and Combination Therapy

Continued breakthrough disease requires addition of either maintenance pulse corticosteroids or a secondary agent to the platform drug.

Continued breakthrough

Continue platform therapy plus
Maintenance pulse corticosteroids and/or
Stage IIIA: oral immunosuppressant and/or
Stage IIIB: IV immunosuppressant

Management of Breakthrough Disease

One of the concerns regarding testing for NABs is expense. The cost of the NABFeron test is estimated at $600. However, given that yearly costs of IFNβ therapy may exceed $15,000, the benefit of identifying NAB-positive patients and switching them to alternate treatments is likely to be economically viable in the long term.

Conclusion

One of the fundamental treatment goals in MS is to delay the progression of disease and the associated disability and cognitive impairment. A stepped-care approach is an effective method for achieving this treatment objective and consists of the following: (a) initiating therapy with a platform drug in patients diagnosed with CDMS or patients with a CIS and at high risk of developing CDMS; (b) monitoring disease progression by assessing the severity of MS symptoms, noting the presence and number of lesions on MRI, and testing for NABs; (c) identifying breakthrough disease early based on ongoing monitoring of disease activity; and (d) managing breakthrough disease.

Disclosures

Funding for this paper was provided by Biogen Idec Inc. All authors received an honorarium from Biogen. Author Ben Johnson has also previously received an honorarium from Berlex. Author Sheldon J. Rich does consulting work for Biogen and participates in the Biogen and Berlex speakers bureaus; author James R. Miller participates in the Biogen lecture bureau; author Howard S. Rossman is a consultant and speaker for Biogen, Teva Neuroscience, and Serono, Inc.; and has received compensation for clinical research from these companies.
TABLE 2  Novel Immunomodulatory Agents for Use in Combination Therapy for Multiple Sclerosis

<table>
<thead>
<tr>
<th>Immunomodulatory Agent</th>
<th>Characteristics</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalizumab (Antegen)</td>
<td>Humanized monoclonal antibody to α4β1 integrin; inhibition of leukocyte adhesion and extravasation</td>
<td>Miller et al. 2003.63</td>
</tr>
<tr>
<td>BX-471</td>
<td>Nonpeptide chemokine receptor (CCR1) antagonist</td>
<td>Elices; 2002.66</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Matrix metalloproteinase inhibition</td>
<td>Brundula et al. 2002.67</td>
</tr>
<tr>
<td>Simvastatin (Zocor)</td>
<td>Immunomodulation, Th2 cytokine promotion</td>
<td>Stuve et al. 2003.69</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>Phosphodiesterase inhibition, suppression of TNFα and IFNγ production</td>
<td>Weber et al. 1998.75</td>
</tr>
<tr>
<td>Estril</td>
<td>Immunomodulation, Th2 shift</td>
<td>Sicotte et al. 2002.72</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>Chimeric murine/human anti-CD20 monoclonal antibody</td>
<td>Saleh et al. 2000.71</td>
</tr>
<tr>
<td>TCR peptide (NeuroVax)</td>
<td>Combination of 3 different TCR peptides</td>
<td>Chou et al. 1994.74</td>
</tr>
<tr>
<td>T-cell vaccination</td>
<td>Attenuation of myelin-specific immune responses</td>
<td>Correale et al. 2000.73</td>
</tr>
<tr>
<td>Stem cell transplantation</td>
<td>Immunoablation followed by infusion of autologous hematopoietic stem cells</td>
<td>Muraro et al. 2003.76</td>
</tr>
<tr>
<td>All-trans retinoic acid</td>
<td>Potentiation of T suppressor cell function</td>
<td>Qu et al. 1998.77</td>
</tr>
</tbody>
</table>

REFERENCES


Author Sheldon J. Rich served as principal author of the study. Study concept and design were contributed primarily by Rich and authors Howard S. Rosenman and William H. Stuart. Analysis and interpretation of data were contributed by all authors. Drafting of the manuscript was primarily the work of Rich, and its critical revision was the work of all authors. Administrative, technical, and/or material support was provided by Biogen Idec Inc.
Stepped-Care Approach to Treating MS: A Managed Care Treatment Algorithm

Clinical Update on Alefacept:
Consideration for Use in Patients With Psoriasis

JAY N. GADE, MD, PhD

ABSTRACT

OBJECTIVE: Alefacept was the first of the biologic agents to be approved for the treatment of adult patients with moderate-to-severe chronic plaque psoriasis, who are candidates for systemic therapy or phototherapy. This fully human fusion protein inhibits the activation of and reduces levels of memory (CD45RO+) T cells, a subpopulation of lymphocytes that plays a critical role in the pathogenesis of psoriasis. The purpose of this article is to provide a clinical update on the use of this agent in patients with psoriasis.

SUMMARY: A single course of alefacept, defined as 12 weekly injections followed by 12 treatment-free weeks, provides clinically meaningful improvements in the symptoms of psoriasis for a majority of patients. Patients who achieved a response have been shown to maintain the benefit for a median duration of about 7 months, without the need for systemic therapy or phototherapy. With each additional course of alefacept, the percentage of patients responding increases, confirming the incremental benefit of repeated administration. More than 1,300 patients have received alefacept in controlled clinical trials. Over multiple courses of therapy, alefacept-induced reductions in circulating lymphocyte counts were consistent and not cumulative.

The incidences of serious adverse events, discontinuations, malignancies, and anti-alefacept antibodies were low and did not increase with subsequent courses. No relationship was observed between decreases in lymphocyte counts and incidences of infections or malignancies. No cases of opportunistic infections, including tuberculosis, have been reported. The favorable safety profile of alefacept was maintained in patients who received concomitant or prior immunosuppressants. Alefacept did not cause reactivation of tuberculosis in case studies of patients who showed a purified protein derivative reaction prior to the initiation of therapy. Immune responses to a neoantigen and recall antigen remained intact in alefacept-treated patients, suggesting that vaccinations may be possible during therapy.

CONCLUSION: Alefacept is an effective intermittent therapy for psoriasis that can provide extended treatment-free and disease-free periods, which may lessen the need for treatment over time. The incremental efficacy seen with each subsequent course of alefacept suggests that physicians should administer 2 courses to determine efficacy before altering therapeutic interventions. The selective mechanism of action of alefacept affords multiple safety advantages and no apparent increased risk of infections or malignancies.

KEYWORDS: Alefacept, Psoriasis, Biologic therapy, Lymphocyte/T cell

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Psoriasis is a chronic, immune-mediated dermatologic disease in which memory T cells play a central role. Approximately 80% of individuals afflicted with this disease have chronic plaque psoriasis, which is characterized by the presence of well-defined, erythematous, scaling plaques. These lesions typically affect the elbows, knees, scalp, and intergluteal cleft, but can occur anywhere on the body. According to the National Psoriasis Foundation, an estimated 4.5 million adults in the United States have psoriasis and, of these, about one third (1.5 million) have moderate-to-severe psoriasis. The worldwide prevalence of psoriasis may be as high as 2.5%. The significant negative impact of psoriasis on health-related quality of life is well recognized. In fact, the burden of psoriasis on both physical and mental functioning has been found to be comparable to that of other major medical diseases such as cancer, depression, diabetes, heart disease, and hypertension. The lesions of psoriasis are often itchy and painful, and individuals may suffer from a variety of psychological effects, including embarrassment, depression, difficulties at work, and, in social situations, fear of worsening disease, sexual problems, and sleep disturbances. The financial burden of psoriasis is also considerable, with estimates of up to $4.3 billion per year in the United States alone.

Patients with psoriasis seek safe, effective, and aggressive therapies and are searching for new therapeutic options. The conventional treatments for moderate-to-severe disease comprise systemic agents (e.g., cyclosporine, methotrexate, and acitretin) and phototherapy (i.e., ultraviolet B and psoralen plus ultraviolet A light). Although these treatments demonstrate varying degrees of efficacy, the vast majority do not provide long-lasting improvement of symptoms. In addition, serious adverse effects, including major organ system toxicities, may limit or contraindicate their use.

An increased understanding of the role of T cells in the pathogenesis of psoriasis has led to the development of biologic agents that more specifically interfere with various aspects of the immunologic cascade of psoriasis. Alefacept, the first of the biologics to be approved in the United States for the treatment of moderate-to-severe chronic plaque psoriasis, has now been available for more than 1 year. Alefacept selectively targets the T cells implicated in the pathogenesis of psoriasis (i.e., skin-homing memory T cells) by inhibiting their activation and reducing their numbers. The objective of this article is to provide a clinical update on the use of this fully human fusion protein in patients with psoriasis.

Efficacy of Alefacept

As summarized in the following sections, alefacept is a remittive therapy for chronic plaque psoriasis, which means that it provides sustained disease improvement in the absence of continuous treatment. Thus, alefacept is administered on an intermittent basis,
and, with each subsequent treatment course, incremental benefits in efficacy have been achieved. Importantly, patients who respond to a given course of alefacept are highly likely to respond to subsequent treatment courses.

### Efficacy Following 1 and 2 Courses of Alefacept

The clinical program of alefacept included 2 phase III, randomized, placebo-controlled, double-blind studies in which 1,060 patients with moderate-to-severe chronic plaque psoriasis were treated for up to 2 courses. Each course was defined as 12 weeks of once-weekly injections (intramuscular [IM] in 1 trial, intravenous [IV] in the other) followed by ≥12 weeks of observation.

The Psoriasis Area and Severity Index (PASI) is considered by regulatory authorities to be the standard for evaluating antipsoriatic efficacy in clinical trials and thus was used in these trials. PASI is a composite measurement of body surface area affected, erythema, induration, and desquamation. The U.S. Food and Drug Administration has established PASI 75 (i.e., the percentage of patients who achieved a ≥75% reduction from baseline PASI) as the rigorous end point for clinical trials of drugs to treat psoriasis. A PASI 50 is regarded by patients and physicians to be a clinically meaningful end point. Although the primary end point was initially set at 2 weeks after the last dose of alefacept, results of the phase II clinical trial showed that patients responded to alefacept at different times and that many patients continued to respond long after the 12-week treatment was completed. Thus, the use of a single time point to determine the efficacy of alefacept is likely to underestimate the overall efficacy of therapy. In the 2 phase III trials, a key efficacy outcome was the overall response rate, defined as the percentage of patients who achieved a PASI 75 or PASI 50 at any time during the treatment and follow-up periods.

In course 1 of the trial with IM alefacept, PASI 75 and PASI 50 were achieved by 33% and 57%, respectively, of patients who received alefacept 15 mg (P<0.001 versus placebo). A postdosing effect with alefacept was clearly apparent. The mean reduction from baseline PASI reached a maximum of 46% in the alefacept 15-mg group at 6 weeks after the last dose of the first course. The clinical response to a single course of alefacept was durable. Patients who achieved a PASI 75 at any time after the first dose of alefacept 15 mg in course 1 maintained a PASI 50 response for a median of 209 days (~7 months), without the need for systemic therapy or phototherapy.

A second course of alefacept 15 mg resulted in incremental benefit, with 43% and 69% of patients achieving a PASI 75 and PASI 50, respectively. Among patients who did not achieve a PASI 50 in the first course, 35% did achieve this level of efficacy with a second course. The duration of response following a second course of alefacept was longer. The estimated median duration of response following the second course could not be determined because >50% of patients had maintained a PASI 50 response at the final study end point, which was nearly 1 year after the start of the study. Over the course of the study, no alefacept-treated patient experienced rebound or flare of disease activity after the cessation of treatment.

The other phase III study evaluated the clinical effects of up to 2 courses of alefacept 7.5 mg when administered by weekly IV injection. The efficacy results obtained with this regimen were comparable to those described for alefacept 15 mg IM.

### Multiple-Course Use

Given the chronic and relapsing nature of psoriasis, repeated courses of treatment are often necessary to maintain adequate control of the disease. New long-term data on the efficacy of a multiple course of alefacept were recently presented at the 62nd Annual Meeting of the American Academy of Dermatology in Washington, DC.

Patients who completed phase II studies of alefacept were eligible to participate in an ongoing, multicenter, open-label extension provided they had received ≥8 doses of study medication and had completed the final 12-week postdosing assessment in the previous trial, were in need of systemic therapy for psoriasis, and had CD4+ T-cell counts at or above the lower limit of normal. Patients were either naive to alefacept (i.e., received placebo in phase II) or had received up to 2 courses of alefacept in previous studies.

The initial treatment course in the open-label extension is referred to as course A; subsequent courses are labeled course B, C, and so on. In each course, patients received alefacept 7.5 mg IV once weekly for 12 weeks followed by 12 weeks of treatment-free follow-up. Retreatment courses were administered provided patients met the same criteria mentioned previously. For course C and subsequent courses, lymphocyte counts were required to be ≥75% of the count recorded at the screening visit of the open-label extension. In course A, PASI was evaluated at weeks 1, 3, 5, 7, 9, 11, and 12 during treatment and at 2, 4, 6, 8, and 12 weeks after treatment. For subsequent courses, PASI assessments were performed at weeks 1 and 7 during treatment and at 2 and 12 weeks after treatment.

At the time of the analysis, 175 patients had received ≥1 course of alefacept, 126 received ≥2 courses, 96 received ≥3 courses, and 71 received ≥4 courses. As shown in Figure 1, the percentages of patients who achieved a PASI 50 at 2 or 12 weeks after the last dose of alefacept increased with each subsequent course (range, 61% in course A to 79% in course D). For courses A through D, the incremental benefit and repeat response of additional courses of alefacept are shown in Figure 2. For patients who achieved a PASI 50 in course A and who received additional courses of alefacept, the percentages of patients who achieved a PASI 50 increased with each subsequent course (incremental benefit). In general, patients continued to respond to repeat treatment with alefacept, with no evidence of tachyphylaxis (Figure 2). Of those who achieved a PASI 50 in a given course, 75% to 90% of patients achieved a PASI 50 in subsequent alefacept courses (repeat response).

### Safety of Alefacept

In phase II and III clinical studies, alefacept has demonstrated excellent safety and tolerability. As described subsequently, this safety profile is maintained over multiple courses of therapy.
and is not altered by concomitant or prior use of immunosuppressants. Opportunistic infections, including tuberculosis, have not been observed among alefacept-treated patients. In case studies, alefacept did not cause reactivation of tuberculosis in patients who showed a purified protein derivative (PPD) reaction prior to treatment initiation. In addition, the results of an immune function study suggest that vaccinations may be possible while undergoing treatment with alefacept.

### Pooled Safety Analysis Over Multiple Courses

Data from all studies in the alefacept clinical program were pooled to better evaluate safety and tolerability. As shown in Table 1, the incidences of serious adverse events, discontinuations because of adverse events, malignancies, and antialefacept antibodies were low and did not increase over up to 4 courses of treatment. Accidental injury and cholelithiasis were the most frequent serious adverse events; headache, nausea, and herpes zoster were the most common events that led to withdrawal. Each of these events occurred in <1% of patients in any course. No relationship was observed between the incidence of infections and CD4+ or CD8+ T-cell counts (Table 2). Most infections were common colds. Serious infections were rare (0.7%, 0.6%, 0.7%, and 0% during the first through fourth courses, respectively). There were no cases of opportunistic or unusual infections, tuberculosis, or deaths related to infections. The incidence of malignancies also was not related to CD4+ and CD8+ T-cell counts. Skin carcinoma (basal and squamous cell carcinomas) was the most frequently diagnosed malignancy. The overall malignancy rate among patients who received alefacept was 25.6 per 1,000 person-years of exposure, which is less than that in the general psoriasis population (29.0 per 1,000 person-years)\(^2\).

### Effects on T Lymphocytes

In the phase III studies, alefacept reduced circulating CD4+ and CD8+ T-cell counts, the magnitude of which was similar after 1 or 2 courses.\(^2\) In the open-label extension described previously (see “Multiple-Course Use”), alefacept-induced reductions in CD4+ T-cell counts were consistent and not cumulative over up to 4 courses of therapy (Figure 3).\(^2\) Mean CD4+ T-cell counts remained above the lower limit of normal (404 cells/mm\(^3\)) for all courses and did not decrease with multiple-course exposure to alefacept.

Consistent with the phase III clinical trial protocols, the prescribing information for alefacept recommends weekly monitoring of CD4+ T-cell counts during treatment.\(^2\) Based on the safety of alefacept, the consistency of the T-cell response in the phase III studies, and the lack of adverse events reported that could be associated with a reduction in T cells, a biweekly monitoring schedule for T-cell counts was evaluated in subsequent open-label extension trials.\(^2\) Patients were eligible to receive up to 3 additional courses of alefacept (IM or IV), consistent with what they had received in the phase III studies. During the first open-label course (course A), lymphocyte and lymphocyte subset counts were obtained weekly during treatment and at 2, 6, and 12 weeks after treatment. In courses B and C, counts were obtained biweekly during treatment and at 2 and 12 weeks after treatment. Mean CD4+ T-cell counts remained above the lower limit of normal (approximately 4000 cells/mm\(^3\)) for all courses.

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**FIGURE 1** Percentages of Patients in Courses A Through D Achieving a ≥50% Reduction From Baseline Psoriasis Area and Severity Index (PASI 50) at 2 or 12 Weeks After Alefacept Treatment

<table>
<thead>
<tr>
<th>Course</th>
<th>Percentage of Patients Responding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>61</td>
</tr>
<tr>
<td>B</td>
<td>63</td>
</tr>
<tr>
<td>C</td>
<td>74</td>
</tr>
<tr>
<td>D</td>
<td>79</td>
</tr>
</tbody>
</table>

**FIGURE 2** Percentages of Patients Achieving a ≥50% Reduction From Baseline Psoriasis Area and Severity Index (PASI 50) in Courses B Through D Relative to Course A (Incremental Benefit) and Prior Course (Repeat Response)

<table>
<thead>
<tr>
<th>Course</th>
<th>Percentage of Patients Responding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>75</td>
</tr>
<tr>
<td>C</td>
<td>82</td>
</tr>
<tr>
<td>D</td>
<td>83</td>
</tr>
</tbody>
</table>

**FIGURE 3** Percentages of Patients Achieving a ≥50% Reduction From Baseline Psoriasis Area and Severity Index (PASI 50) at 2 or 12 Weeks After Alefacept Treatment

<table>
<thead>
<tr>
<th>Course</th>
<th>Percentage of Patients Responding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>61</td>
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<tr>
<td>B</td>
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<tr>
<td>C</td>
<td>74</td>
</tr>
<tr>
<td>D</td>
<td>79</td>
</tr>
</tbody>
</table>
Use of Alefacept in Special Populations

Concomitant and Prior Use of Immunosuppressants

The incidence and nature of adverse events reported in the phase III studies were examined in patients who received alefacept and any of the following immunosuppressants: methotrexate, cyclosporine, prednisone, etanercept, leflunomide, infliximab, and mycophenolate mofetil. Use of these therapies during the study resulted in disqualification from the efficacy analysis. One or more of these drugs were used concomitantly by 21 (6%) patients in the alefacept 7.5 mg IV group, 4 (2%) in the alefacept 15 mg IM group, and 22 (6%) in the placebo group. The frequency and spectrum of adverse events, including infections, were not altered by concomitant use of immunosuppressants in patients treated with alefacept. Similar results were found for patients who had used an immunosuppressant within 60 days before alefacept.

Positive Tuberculin Reaction

The latest guidelines for targeted tuberculin testing for latent tuberculosis infection have been published. Tuberculin testing is not a prerequisite for alefacept therapy. However, some investigators chose to test for tuberculosis before initiating any of the biologic therapies. Menter et al. reported that none of the 4 patients who showed a PPD reaction before beginning alefacept therapy experienced a reactivation of tuberculosis after receiving a 12-week course of alefacept 15 mg IM.

Immunizations

Gottlieb et al. evaluated the effect of alefacept on immune responses to a neoantigen (φX174) and recall antigen (tetanus toxoid) in patients with psoriasis randomized to alefacept (7.5 mg IV weekly x 12) or control groups. Mean anti-φX174 titers were similar in both groups at all time points after the first and second immunizations (P = NS) and comparable to those reported for healthy volunteers. Two weeks after the second immunization, the percentage of patients with anti-φX174 immunoglobulin G (IgG) of ≥30% of the total anti-φX174 response was similar in the alefacept (86%) and control (82%) groups (P = NS). IgG titers after the third and fourth exposures in the alefacept group showed durability of memory responses. Response to tetanus also was similar between the 2 groups, with 89% of alefacept recipients and 91% of controls having antitetanus toxoid titer increases ≥2 times baseline at 3 weeks after immunization. These data demonstrate that alefacept-treated patients maintain their ability to mount an immune response to new or previously encountered antigens.

Pregnancy

Alefacept has a pregnancy category B rating. The results of preclinical studies have not demonstrated a risk to the fetus, but there are no adequate and well-controlled studies in pregnant women.
Clinical Update on Alefacept: Consideration for Use in Patients With Psoriasis

During pregnancy, alefacept should be used only if clearly needed. If pregnancy occurs while receiving alefacept, its continued use should be assessed.

Conclusions

Alefacept offers patients with psoriasis an effective intermittent therapy that can provide extended treatment-free and disease-free periods. Given the incremental benefits of alefacept, additional courses of alefacept therapy increase the likelihood for patients to achieve a clinically meaningful response. Thus, it seems reasonable to attempt 2 courses of therapy before concluding that treatment is ineffective. Because of prolonged remissions, the potential exists that a lesser amount of drug will be needed over time and that the use of alefacept may reduce overall drug and health care utilization.

The once-weekly dosing schedule of alefacept is convenient, and because it is administered in a doctor’s office, physicians can easily monitor compliance. The selective mechanism of action of alefacept affords multiple safety advantages in terms of no apparent increased risk of infections or malignancies, the potential to use it concomitantly with other drugs and vaccines, and safe use in special patient populations. The excellent safety profile of alefacept may reduce the overall use of health care services to manage untoward effects in patients who have chronic plaque psoriasis.

DISCLOSURES

Funding for this paper was provided by Biogen Idec Inc. Author Jay N. Gade is a consultant to Biogen.

REFERENCES

Considerations for Assessing the Cost of Biologic Agents in the Treatment of Psoriasis

SHELDON J. RICH, RPh, PhD

ABSTRACT

OBJECTIVE: This paper will establish the rationale for developing a long-term cost model to assess the utilization and associated economics of biologic agents in the treatment of moderate-to-severe psoriasis. This information should assist with defining the total cost of drug treatment when using biologic therapy to treat psoriasis.

SUMMARY: The development of biologic therapies has effected the treatment of many chronic diseases, including psoriasis. Managed care organizations are debating the appropriate use of these injectable drugs because of the associated acquisition costs and administration requirements. Important considerations for evaluating these agents include the ability to produce off-treatment remissions, the ability to improve patients’ quality of life, and safety and tolerability profiles. A remittive therapy may be a good early treatment for these patients because it offers the chance to avoid lifelong therapy. In addition, the safety and tolerability profiles of all biologic agents are substantially improved compared with conventional systemic psoriasis treatments. However, therapy must be individualized because risks vary with each agent. Thus, these differences in the biologic agents should be considered in the assessment of the economic impact and drug utilization of biologics for patients with psoriasis.

CONCLUSION: The biologic agents currently used in the treatment of psoriasis offer new hope for safe and effective therapy. Comparison of these agents by managed care decision makers requires consideration of characteristics that differentiate the agents, including efficacy, duration of off-treatment response, and safety and tolerability.

KEYWORDS: Alefacept, Psoriasis, Biologic therapy, Remittive, Off-treatment response, Cost model

J Manag Care Pharm. 2004;10(3)(suppl S-b):S38-S41

Biologic therapies are changing the treatment of many chronic diseases, including psoriasis. The number of these naturally occurring molecules or modifications thereof is steadily increasing, with more than 350 agents in various stages of development. Currently, 3 biologic agents have been approved for the treatment of patients with moderate-to-severe psoriasis: alefacept, efalizumab, and etanercept. These agents target several key inflammatory mediators linked to the pathogenesis of psoriasis. As a result of their selective action, these emerging therapies promise the potential for efficacy without the toxicities associated with conventional treatments such as skin cancer from phototherapy, liver and hematologic toxicity from methotrexate, and nephrotoxicity from cyclosporine.

With the expected market penetration of these products and the influx of new products over the next several years, managed care decision makers are centering efforts on determining the appropriate use of these agents. Evaluations focus on the long-term efficacy and safety as well as the costs of biologic agents used to treat psoriasis. Many health plans have debated the use of biologic therapies since their introduction in 2003, primarily because these drugs require in-office or at-home administration and have higher acquisition costs.

Recently, several short-term cost analyses (6 to 12 months) have been presented at major dermatology meetings that provide direct cost comparisons and cost-efficacy comparisons for the biologic therapies. Because no head-to-head comparative trials are available, the analyses were based on individual clinical trial data and product labeling. This approach is limited because clinical trial data may not be reflective of what happens in clinical practice, and outcomes deemed important for regulatory approval may be too stringent for clinical practice or may underestimate the clinical benefit. In addition, short-term cost analyses fail to consider the implications of long-term efficacy and the potential for some products to produce remissions that continue after treatment has been completed. This paper reviews key considerations for the long-term assessment of the biologic therapies.

Characteristics That Differentiate Biologic Therapies’ Remittive Versus Suppressive Mode of Action

Depending on their mechanisms of action and the clinical outcomes after treatment has been completed, psoriasis treatments can be classified as suppressive or remittive. Suppressive therapies require continuous treatment to maintain a response. Most conventional agents used in the treatment of psoriasis are suppressive, including cyclosporine, methotrexate, and retinoids. The average response duration for these treatments is approximately 1 to 2.5 months.
Suppressive agents also can be associated with disease rebound or flare on discontinuation.

Remittive therapies provide long-term management of psoriasis by controlling symptoms without the need for continuous treatment. These therapies can offer patients extended periods of time free of psoriasis and its treatment. Therapy with psoralen plus ultraviolet A (PUVA) light is associated with periods of time free of psoriasis and its treatment. Remittive effect is associated with the ability of PUVA to eliminate intraepidermal T cells, in contrast with suppressive agents that typically act by inactivating or inhibiting T-cell effects.

Alefacept has a dual mechanism of action that inhibits T-cell activation and induces T-cell apoptosis. The latter mechanism results in the reduction of T cells both in the peripheral circulation and in lesional skin. Alefacept-induced reductions in circulating CD4+ T-cell counts have been shown to correlate with clinical improvement in large cohorts of patients with psoriasis. However, T-cell changes in individual patients are not necessarily predictive of response. Importantly, the effects of alefacept are selective for memory T cells, which have been specifically implicated in the pathogenesis of psoriasis. As a result of this selective action, alefacept eliminates pathogenic T cells while preserving immune function.

Thus, alefacept was expected to be remittive in its effect, and phase II and III clinical studies measured the duration of response after completion of therapy. The phase II study used a subjective determination for the duration of off-treatment response by measuring the time between the last dose of alefacept and the need for retreatment in an open-label follow-up study. The time to retreatment was evaluated in patients who responded to alefacept by achieving an assessment of “clear” or “almost clear” by their physician (or Physician Global Assessment [PGA]). The median time to retreatment was 10 months, with a range of 6 to 18 months.

In subsequent phase III studies, the duration of response was defined using objective measures of disease activity, specifically the Psoriasis Area and Severity Index (PASI). Two pre-specified measures for duration of response were defined as shown schematically in Figure 1. The length of time during which patients were able to maintain a 75% reduction from baseline PASI (PASI 75) was determined for 2 sets of patients: (1) patients who achieved PASI 75 at any time during the study, and (2) patients who achieved a PGA of “clear” or “almost clear” at any time during the study. The use of PASI 50 as an evaluation criterion was based on data that support achievement of PASI 50 as clinically relevant and meaningful to patients.

In both phase III studies of alefacept, the median duration of response exceeded 7 months, regardless of the definition of response. Some patients who have received additional courses of alefacept have reported longer durations of response, up to 24 months. These data are unique to alefacept. Efalizumab and etanercept are clearly suppressive in their mode of action and require continuous therapy to maintain a response. Alefacept’s remittive action suggests that it is a good early treatment for patients with moderate-to-severe psoriasis, offering time free of the disease and its treatment.

**Treatment Selection**

Typically, drug utilization and cost analyses are based on a stepwise treatment approach. However, treatment algorithms for moderate-to-severe psoriasis are difficult to create because of the potential risks of treatment and the unpredictable nature of disease progression. The placement of a particular drug in a patient’s therapeutic options must be individualized for risk. For example, a patient with a history of liver disease or alcohol abuse is not a good candidate for either cyclosporine or etanercept, whereas a patient with a history of liver disease or alcohol abuse is not a good candidate for methotrexate or retinoids. In addition to these medical contraindications, personal factors must be considered, such as the frequency of dosing and office visits, convenience of and expected compliance with administration, and cost.

Although no comparative trials exist for the biologic agents, differences are evident among the products. These differences can significantly influence therapy selection and its administration frequency and subsequent cost (Table 1). The need for continuous therapy versus intermittent therapy could substantially impact cost, particularly for a chronic and incurable disease such as psoriasis. Not only is actual drug administration reduced with an intermittent therapy that provides off-treatment remissions, but also the potential for adverse events...
is reduced because patients are not continuously receiving medication. The associated frequency and cost of adverse events are other factors in the overall cost of care for patients receiving biologic therapy for psoriasis.

### Safety and Tolerability

Safety and tolerability profiles of the various biologic therapies are substantially improved compared with generalized immunosuppressants used to treat psoriasis, such as methotrexate and cyclosporine. However, safety warnings also exist for the various approved biologic therapies. Because the biologic agents affect the immune system, they all have warnings about the risk of serious infection and malignancy (Table 1). Key differences in safety warnings include the following: etanercept has a warning about serious infections, including tuberculosis; efalizumab has warnings about thrombocytopenia and worsening of psoriasis on discontinuation of treatment; and alefacept is associated with decreased CD4+ T-cell counts, requiring routine patient monitoring.

### Designing a Cost Model

An approach for comparing the costs of the approved biologic therapies and quantifying the potential cost savings associated with off-treatment remissions would be to investigate the costs for achieving symptom-free and side effect–free days in patients with psoriasis. Key elements for such an analysis would include side effect/adverse event frequencies, duration of therapy, and total cost of care, inclusive of concomitant therapies. The objective would be to capture the cost per day of remission with no side effects for each therapy and compare the costs of maintaining a remission for patients with psoriasis for up to 2 years.

A basic equation for such a model is as follows:

$$\text{Cost per side effect–free remission day} = \frac{\text{Cost of care}}{\text{Side effect–free days in remission}}$$

Cost of care includes the costs of product acquisition for all therapies (including systemic agents used concomitantly), delivery, and monitoring (including T-cell counts, platelet counts, liver function tests, and purified protein derivative tests for tuberculosis, as appropriate) for all patients started on treatment over periods of 12, 18, and 24 months. The duration of observation is another key variable because it examines the long-term costs for this chronic disease. Side effect–free days in remission represent the total number of days achieved by all patients with symptoms in “adequate control” or “remission” and also without side effects of treatment for each of the 3 observation periods. Cost per side effect–free remission day represents the output of the equation.

Using clinical trial data, the total number of days that patients are free of symptoms and have no side effects could be estimated. The goals of this approach would be to differentiate biologic therapies regarding efficacy and duration of off-treatment response, examine the economic impact of side effects/adverse events; and investigate the costs associated with individual products for up to 2 years. Using these key attributes of the various products, this type of analysis could identify an agent with lower overall costs because it possesses several key characteristics, including a low incidence of side effects; good tolerability; compliance, such that patients achieve clinically meaningful responses; and a long duration of symptom control without the need for new or additional treatments.

### Conclusions

As rationally designed biologic therapies assume a larger role in the treatment of diseases including psoriasis, managed care organizations need effective means of assessing the overall effect and costs of these agents. It is important to consider all relevant factors in drug utilization and cost analyses because these new agents redefine efficacy, safety, and mode of drug delivery. In the case of psoriasis, a long-term cost model is necessary to meet these needs and compare the various products with consideration of their differences.

### DISCLOSURES

Funding for this paper was provided by Biogen Idec Inc. Author Sheldon J. Rich does consulting work for Biogen and participates in the Biogen and Berlex speakers bureaus.

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Continuing Education
Meeting the Challenge of Incorporating Injectable Biologics Into Managed Care: Multiple Sclerosis and Psoriasis

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In order to receive CE credit for this program, you must complete this form and the Program Evaluation form in addition to completing the posttest with a score of at least 70% (forms may be photocopied). Please mail all materials to the Academy of Managed Care Pharmacy, 100 N. Pitt St., Suite 400, Alexandria, VA 22314. To receive credit, these forms must reach the Academy of Managed Care Pharmacy by March 1, 2007. CE certificates will be mailed to your address (below) as soon as possible after receipt of the Record of Completion and Program Evaluation forms and the posttest is graded and successful completion is determined.

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The Academy of Managed Care Pharmacy is approved by the American Council on Pharmaceutical Education (ACPE) as a provider of continuing pharmaceutical education. A total of 20 CEUs (2 contact hours) will be awarded to pharmacists for successful completion of this continuing education program. Successful completion is defined as receiving a minimum score of 70% on the posttest and completion of the Program Evaluation form. Continuing education statements will be mailed to pharmacists within 6-8 weeks of receipt of the Record of Completion, Posttest, and Program Evaluation forms. Universal Program No. 233-000-04-040-H04. (Expiration date: 6/1/07).
Please indicate the correct answers on the Record of Completion.

1. Which of the following agents is not considered a platform drug?
   a. Interferon beta-1a
   b. Interferon beta-1b
   c. Methylprednisolone
   d. Glatiramer acetate

2. Optic neuritis may be the first clinical sign of MS.
   a. True
   b. False

3. Which of the following is a common symptom of MS?
   a. Spasticity
   b. Fatigue
   c. Bladder dysfunction
   d. Cognitive dysfunction
   e. All of the above

4. Treatment with disease-modifying agents reduces the annual relapse rate in patients with MS by
   a. 20%
   b. 30%
   c. 50%
   d. 80%

5. An ideal platform therapy in MS would
   a. significantly slow the progression of sustained disability.
   b. reduce the annual relapse rate.
   c. reduce lesion activity apparent on MRI.
   d. reduce brain atrophy.
   e. All of the above

6. Over a 30-year period, what percentage of patients with a clinically isolated syndrome will develop definite MS?
   a. 90%
   b. 65%
   c. 50%
   d. 15%

7. Magnetic resonance imaging should be used in both the diagnosis and follow-up of patients with MS.
   a. True
   b. False

8. Rank (highest to lowest) the incidence of neutralizing antibodies (NAb) for the 3 interferons:
   a. IFNβ-1b > IFNβ-1a-Avonex > IFNβ-1a-Rebif
   b. IFNβ-1a-Rebif > IFNβ-1b > IFNβ-1a-Avonex
   c. IFNβ-1b > IFNβ-1a-Rebif > IFNβ-1a-Avonex
   d. IFNβ-1b = IFNβ-1a-Rebif = IFNβ-1a-Avonex

9. The presence of NAb is thought to decrease the efficacy of IFNβ products.
   a. True
   b. False

10. Which of the following factors affects immunogenicity of IFNβ products?
    a. Molecular structure
    b. Storage and manufacturing
    c. Route and frequency of administration
    d. All of the above
11. In patients in whom NAb develop, they often develop during the first year of treatment with IFNβ.
   a. True
   b. False

12. Which of the following agents is not used in combination therapy in MS patients with breakthrough disease?
   a. Methotrexate
   b. Alefacept
   c. Mycophenolate mofetil
   d. Azathioprine

13. The economic burden of multiple sclerosis per patient per year is approximately
   a. $16,000.
   b. $21,000.
   c. $34,000.
   d. $47,000.
   e. $62,000.

14. Which of the following agents is not being investigated as a treatment for MS?
   a. Simvastatin
   b. Natalizumab
   c. All-trans retinoic acid
   d. Ezetimibe
   e. Minocycline

15. A remittive therapy for psoriasis is defined as which of the following?
   a. Can be taken intermittently
   b. Provides time free of disease and its treatment
   c. Requires less drug use over time
   d. a and b
   e. All of the above

16. Select the list of psoriasis treatments that correctly ranks the products in order of duration of response after treatment, with the shortest first and the longest last.
   a. Cyclosporine < alefacept < etanercept
   b. Cyclosporine < etanercept < alefacept
   c. Alefacept < cyclosporine < etanercept
   d. Etanercept < alefacept < cyclosporine

17. In clinical trials, how many courses of alefacept therapy have patients received?
   a. 2 courses
   b. 5 courses
   c. 8 courses
   d. 12 courses

18. Biologic therapies for psoriasis are associated with what types of safety concerns?
   a. Risk of infection
   b. Major organ system toxicity
   c. Skin cancer
   d. All of the above

19. Key considerations for developing cost and drug utilization analyses for the biologic therapies in psoriasis include
   a. drug acquisition costs.
   b. side-effect/adverse-event frequencies.
   c. duration of therapy.
   d. All of the above

20. The most appropriate time frame to evaluate total costs of biologic therapies in psoriasis is
   a. over 3 months.
   b. over 6 months.
   c. over 12 months.
   d. over 24 months.
Meeting the Challenge of Incorporating Injectable Biologics Into Managed Care: Multiple Sclerosis and Psoriasis

Participant's name: ________________________________  Date: ______________

Your assistance in the evaluation process is greatly appreciated. Please return this form with the posttest answers.

Using the scale above for questions 1-7, please rate how well you will be able to accomplish the following objectives based upon successful completion of the program.

Objectives:
1. verbalize the importance and long-term potential of injectable biologic therapies for the treatment of multiple sclerosis (MS) and psoriasis;
2. describe strategies and considerations that optimize treatment success and ensure appropriate resource utilization for biologic therapies in MS and psoriasis;
3. recognize the complexity of treating MS and the importance of individualizing therapy and planning for long-term management of the disease;
4. employ (a) treatment protocols developed by neurologists for appropriate use of biologics in MS and (b) interventions for managing MS symptoms and treatment side effects;
5. describe an MS treatment algorithm developed by managed care professionals that provides guidelines for long-term disease management, including treatment initiation, recommended evaluations, and disease progression;
6. understand current clinical data concerning alefacept’s use in the treatment of patients with moderate-to-severe psoriasis, including long-term benefits and safety and tolerability considerations; and
7. identify key considerations for evaluating the cost implications and drug utilization for biologic therapies in psoriasis.

Using the scale above for questions 8 and 9, please indicate the number that best expresses your opinion.

8. What is your overall rating of this program?   __________
9. How would you rate the pertinence of this program material to your practice?  __________
10. To what degree was there promotional bias? (check one)  __________
    a. Not at all
    b. Somewhat
    c. A great deal

11. To what degree do you anticipate changes in patient care as a result of the material presented? (circle one)  __________
    1  2  3  4  5
    No change  Significant change

12. Please indicate the length of time it took to complete this program. (circle selection(s))  __________
    Hours: 1  2  3
    Minutes: 0  15  30  45

13. Please rate the difficulty factor for completing this CE program. (circle selection)  __________
    Easy  Moderate  Difficult

14. Please rate your willingness to recommend this program to colleagues. (circle selection)  __________
    Very willing  Willing  Not willing

15. Please indicate which venue you prefer for obtaining continuing education. (circle selection)  __________
    Written monograph  Slides  Videos  Internet-based
    Live sessions  Other: ________________________________

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