Intramuscular Interferon Beta-1a and Evolving Treatment Options and Outcomes Measurement for MS: Considerations for Managed Care

Christopher J. Barnes, PhD; Christina Caon, RN, MSN, NP-C; John F. Foley, MD; Mark Friedman, MD; Joseph Menzin, PhD; Kavita V. Nair, PhD; Christine Nichols, BA; Eleanor L. Olvey, PharmD, PhD; Gary M. Owens, MD; Michael W. Pill, PharmD; Grant H. Skrepnek, PhD; Leigh Ann White, PhD; and Kristine Zerkowski, BA
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## DISCLOSURES

Biogen Idec Inc., the manufacturer of intramuscular interferon beta-1a (Avonex), natalizumab (Tysabri), and investigational drugs dimethyl fumarate (BG-12) and PEGylated interferon beta-1a, funded the development of this supplement. Literature search, medical writing, and editorial assistance were provided by Kristine Zerkowski, Jacqueline Cannon, and Christopher Barnes at Infusion Communications, Inc, and Christine Nichols at Boston Health Economics. Joseph Menzin and Mark Friedman are employed by Boston Health Economics. Their work was funded by Biogen Idec Inc. The other authors received no financial compensation from Biogen Idec Inc., Infusion Communications, or Boston Health Economics for their roles in developing this supplement. Biogen Idec Inc. reviewed and provided feedback on the supplement papers to the authors. The authors had full editorial control of the content of the supplement and provided their final approval of all content. The relevant financial and other relationships specific to each author are listed in the disclosure statements after each of the articles in this supplement.

**DISCLOSURE OF OFF-LABEL USE**

This supplement discusses several medications that have not been approved by the U.S. Food and Drug Administration for treatment and management of multiple sclerosis at the time of publication, including cladribine, teriflunomide, laquinimod, dimethyl fumarate (BG-12), alemtuzumab, PEGylated interferon beta-1a, daclizumab, and ocrelizumab.
**Intramuscular Interferon Beta-1a and Evolving Treatment Options and Outcomes Measurement for MS: Considerations for Managed Care**

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Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system that is thought to be autoimmune in nature. In addition to demyelination, axonal and neuronal damage occur in this disease. In recent years, MS has received significant focus from health plans and those who manage drug benefits. MS affects nearly 400,000 individuals in the United States, and the majority of those affected by the disease have relapsing-remitting MS (RRMS). RRMS is characterized by clearly defined attacks, or relapses, of worsening neurological function with periods of partial to complete recovery between each attack. This form of MS occurs more often in women than men, with disease onset typically occurring between the ages of 20 and 50 years. Ultimately, patients with RRMS experience an accumulation of central nervous system damage and associated cognitive and physical disability progression. With the widespread use of disease-modifying therapies (DMTs), health plans have observed improved clinical outcomes for MS together with increasing associated pharmacy-related expenses.

Prior to the 1993 launch of interferon beta-1b (IFNβ-1b), the first approved DMT for MS, there were only a few drugs available to treat the disease, with most emphasis on the treatment of exacerbations. Health plans were not overly concerned with managing the cost of care associated with this illness. However, over the past 2 decades, several additional DMTs have been developed to reduce relapse rates, improve short-term functionality, and modify the overall disease course. In 2010, prior to the launch of fingolimod, the first oral agent for the treatment of MS, there were 7 injectable DMTs on the market: once-weekly intramuscular IFNβ-1a (Avonex, Biogen Idec), 3-times weekly subcutaneous (SC) IFNβ-1a (Rebif, EMD Serono), alternating daily SC IFNβ-1b (Betaseron, Bayer Healthcare Pharmaceuticals; Extavia, Novartis), once-daily SC glatiramer acetate (GA; Copaxone, Teva Pharmaceutical Industries), once-monthly intravenous natalizumab (Tysabri, Biogen Idec and Elan Pharmaceuticals), and 4-times yearly mitoxantrone (Novantrone, Immunex). Among these therapies, IFNβ formulations and GA have generally been regarded as the mainstays of first-line treatment of MS.

Fingolimod represents only the first of many new agents for the treatment of MS. Over the next 5 years, additional MS treatments may be introduced, including laquinimod, teriflunomide, dimethyl fumarate (BG-12), alemtuzumab, PEGylated interferon beta-1a, daclizumab, and ocrelizumab. If approved by the U.S. Food and Drug Administration, these new agents will broaden the available MS treatment options, but they will also likely create management issues for health plans. MS agents often account for a significant portion of a health plan's specialty drug budget, and this expenditure is expected to increase as new agents come to market. Health plans must balance access to these new MS agents with the needs of patients, clinical outcomes, and the overall cost of care associated with those outcomes. Balancing the known effectiveness and safety of existing MS therapies with the relative unknowns of some of the new agents will challenge drug benefit managers. Additionally, the potential for combination therapy with existing agents and newer drugs will become a reality, and health plans must be equipped to evaluate not only new therapies, but also new therapeutic combinations. These challenges are further complicated by issues such as patient adherence, persistence, and side effects. With the evolving MS treatment options, there is increased need for better information on comparative clinical outcomes, long-term safety, drug tolerability, cost-effectiveness, newer imaging techniques, and adherence and persistence. This information will be critical as health plans evaluate MS risk-benefit considerations and develop cost-effectiveness information and clinical management strategies to improve adherence and patient outcomes. Selecting therapy for patients with MS will become more complex over the next few years with the introduction of new therapies, some of which have unique safety considerations.
Evidence for Long-Term Use of Intramuscular Interferon Beta-1a: An Overview of Relapse, Disability, and MRI Data from Selected Clinical Trials

John F. Foley, MD; Kristine Zerkowski, BA; and Kavita V. Nair, PhD

ABSTRACT

The treatment options for multiple sclerosis are rapidly changing. With the increasing number of products available to treat this disease, treatment decisions are becoming more complex. Over the years, diagnosis and assessment of treatment efficacy in multiple sclerosis have evolved, but the primary endpoints used to evaluate patients have remained relatively consistent. Relapse rates, magnetic resonance imaging parameters, and disability progression are all key considerations when assessing efficacy for multiple sclerosis treatments. As selection of therapy becomes increasingly complex for both patients and physicians, risk-benefit considerations that incorporate long-term efficacy and safety on an individualized basis will be of greater importance. The information provided in this article will help to elucidate these considerations.

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Summary Points Presented in this Article

- Multiple sclerosis (MS) is a chronic, immune-mediated neurologic disease that is associated with progressive disability and diminished quality of life by interfering with a person's ability to work, pursue leisure activities, and conduct typical life activities.
- Several approved disease-modifying therapies (DMTs) are available to treat MS. These DMTs have demonstrated efficacy in key traditional MS outcome measures, including relapses, disability progression, and magnetic resonance imaging (MRI) measures.
- This article provides an overview of the key traditional outcomes assessed in MS studies and critically evaluates phase 3 and long-term follow-up outcomes data for intramuscular interferon beta-1a (IM IFNβ-1a), one of the frequently prescribed treatments for patients with MS.
- IM IFNβ-1a administered once weekly has demonstrated efficacy in reducing relapse rates, disability progression, and disease activity visible on MRI in multiple MS studies.
- IM IFNβ-1a has been an effective first-line treatment option for patients with MS for more than 15 years. Its efficacy and safety profiles have been well established in the post-marketing setting, and no new safety considerations have emerged. The adverse reactions most commonly reported in patients associated with the use of IM IFNβ-1a are flu-like symptoms occurring within hours to days following an injection.

Several disease-modifying therapies (DMTs) are currently approved to treat multiple sclerosis (MS), with proven efficacy in reducing relapse rates, disability progression, and disease activity visible on magnetic resonance imaging (MRI).\(^1,2\) Positive outcomes for approved DMTs (subcutaneous [SC] interferon beta-1b [IFNβ-1b],\(^3,7\) intramuscular [IM] IFNβ-1a,\(^8-11\) glatiramer acetate,\(^12-16\) SC IFNβ-1a,\(^17-21\) natalizumab,\(^22,23\) fingolimod,\(^24,25\) and mitoxantrone\(^26\) have been demonstrated in patients with MS for many of these endpoints. Over the next few years, the introduction of new agents to treat MS will result in significant changes in treatment. Fingolimod is the most recently approved DMT for treatment of relapsing forms of MS, and several other drugs are currently in late-stage development. The pivotal studies for these latest therapies, which include laquinimod,\(^27,28\) teriflunomide,\(^29-31\) dimethyl fumarate (BG-12),\(^32,33\) alemtuzumab,\(^34\) and PEGylated interferon beta-1a,\(^35\) have primary endpoints (relapse rates, disability progression, MRI activity) similar to those used in the registration trials of currently approved DMTs.

Because traditional measures of efficacy in MS do not capture other important aspects of the disease, additional measures, including the Multiple Sclerosis Functional Composite (MSFC), cognition, and quality of life (QoL), as well as newer imaging techniques, such as brain atrophy and magnetization transfer, are often included as endpoints in more recent clinical trials.\(^24,27,35,36\) The objective of this article is to provide an overview of the key traditional outcomes assessed in MS studies and to summarize and critically evaluate the 2 published phase 3 studies and respective long-term follow-up outcomes data for IM IFNβ-1a, one of the more frequently prescribed treatments for patients with MS. This review provides an overview of traditional MS outcomes and is not a systematic review of all studies of the drug. The studies selected for this review examined patients who were naive to treatment with IFNβ. Evidence supporting the use of relapses, disability progression, and MRI activity in clinical trials will be summarized. A brief overview of the key clinical trials and a long-term follow-up study for IM IFNβ-1a are provided, and the primary and secondary efficacy outcomes from these studies are described. Finally, important considerations for clinical trials in MS are reviewed.

Traditional MS Outcome Measures

Expanded Disability Status Scale

Measures of disability have often been used to assess efficacy in the clinical trials of the treatments that have received approval of the U.S. Food and Drug Administration (FDA) for MS. Measuring disability is clinically relevant because it is an evaluation of the long-term progressive course of the disease. The Kurtzke Expanded Disability Status Scale (EDSS) is the most commonly used measure of neurologic impairment in MS clinical trials.\(^37-39\) The EDSS scale ranges from 0.0 (indicating no clinical effects) to 10.0 (indicating death due to MS) in 0.5-unit increments. EDSS scores are based on the sum of 8 functional systems, including pyramidal, cerebellar,brainstem, sensory, bowel and bladder, visual, and cerebral function.\(^37\) Functional system scores have a greater bearing on total scores of <4.5, whereas higher scores are influenced more by the patient’s ambulation status. The EDSS scale is nonlinear. A 1.0-point change in EDSS at the low end of the scale is often
associated with a lesser change in function compared with the midpoint of the scale, where a 1.0-point change represents a more substantial worsening of disability. A patient with an EDSS score of 7.0 must depend on a wheelchair for mobility but is self-moving, while a patient with a score of 8.0 is confined to a bed or a chair but still has the use of his or her arms. A score of 9.0 indicates that the patient is bedridden but can communicate and eat. In studies of MS, EDSS is assessed in multiple ways, including change over time, as well as time to sustained disability progression.

Relapses
Relapse rate is often the primary outcome measure in clinical trials evaluating therapies developed to treat relapsing-remitting MS (RRMS). In many MS studies, a relapse has been defined as the appearance of new or worsening neurological symptoms or the reappearance of old neurological symptoms preceded by a 30-day period of stability. However, a simplified definition of relapse, which does not include a 30-day period of stability, has also been used. Preventing relapses is critical to the patient's functional status, daily living activities, and QoL. Relapses are also important to quantify because they can be associated with significant residual deficits, and relapse rate in the early stages of the disease can be a key determinant of later accumulation of disability.

Relapse outcomes in most clinical trials are measured by (a) annualized relapse rate, (b) average number of relapses per patient, (c) proportion of patients who are relapse free, and (d) the cumulative probability of relapse. While annualized relapse rate, or the number of confirmed relapses per patient per year, is commonly used as the primary outcome measure in MS studies, it is difficult to compare annualized relapse rate with the relapse results of older trials of IM IFNβ-1a, SC IFNβ-1b, SC IFNβ-1a, and glatiramer acetate that used relapse counts per year as the primary outcome measure. Annualized relapse rate, calculated as the total number of relapses experienced by the patient cohort divided by the patient-years at risk, is currently the standard measure for assessing relapses. Because the measurement of annualized relapse rate is not consistent across studies, care should be taken when making cross-trial comparisons to ensure that a similar definition was utilized.

Early relapse activity that is evident while a patient is on treatment has been shown to be a contributing factor in predicting future disability. While it is generally understood that relapses in MS result in cumulative disability, the direct relationship between successive relapses and disability progression has been difficult to demonstrate in clinical trials. An observational study that examined the effect of relapses (defined as the appearance of a new neurological symptom or a worsening in a previous symptom) lasting more than 48 hours, without fever) on disability progression found that having 1 or more relapses during the first 2 years of IFNβ treatment was associated with earlier progression of disability. Progression of disability was defined by the following change in EDSS: 1.5-point increase for patients with a baseline EDSS score from 0.0 to 2.0, 1 point for scores from 2.5 to 4.0, and 0.5 points for scores equal to or higher than 4.5, confirmed 3 months later. Because of the observational nature of this study, a more simplified definition of relapse, which did not include neurologic stability for the previous 30 days, was employed. For patients who had 1 relapse in the past 2 years, the probability of disability progression was 3-fold greater than for patients who had no relapses (hazard ratio: 3.4; \( P = 0.005 \)). This increased to a 4-fold greater risk of disease progression in patients with 2 or more relapses during the first 2 years of treatment (hazard ratio: 4.3; \( P < 0.001 \)). There was no difference in probability of disability progression between patients who had 1 relapse in the past 2 years versus patients who had 2 relapses. However, there were also patients in the study who experienced no relapses and yet had a sustained increase in disability over the 2-year period. Results from a separate study showed that the occurrence of clinical relapses in patients treated with IFNβ had a low specificity in predicting accumulation of disability.

Magnetic Resonance Imaging Outcome Measures
MRI outcome measures play an important role in evaluating treatment efficacy in randomized controlled trials, as they provide objective, supportive evidence for clinical endpoints. Conventional MRI techniques, including T2-weighted and gadolinium-enhancing (Gd+) T1-weighted lesions, provide quantitative assessment of inflammatory activity and lesion load. A T2-weighted MRI scan shows the total number of hyperintense lesions, often referred to as the lesion load. A Gd+ MRI scan shows active lesions, signifying a breakdown of the blood-brain barrier and inflammation. Because T2-weighted and Gd+ T1-weighted lesions occur at a higher rate than relapses, these MRI measures are more sensitive indicators of disease activity. A meta-analysis demonstrated an association between lesion load measured early in the disease process and future relapse rate. However, lesion load was not a strong predictor of the development of cumulative impairment or disability. In addition, there is an apparent relationship between lesion load and the degree of accumulated disability over time. In a 15-year follow-up study assessing the predictive value of T2 lesions on the rate of progression of disability in MS, the number of T2 lesions had a small predictive value for progression of disability in RRMS but did not influence the rate of progression in progressive MS. MRI methods and endpoints have evolved to include such parameters as T1 hypointense lesions (so-called black holes) and brain atrophy. These newer methods allow for greater accuracy of lesion detection and the ability to detect unique lesion types, such as gray matter T2 lesions. Combining these newer techniques with conventional MRI-based measures may better predict clinical progression in MS. These MRI techniques and associated outcome measures will be reviewed in the following article of this supplement.

Evidence for Long-Term Use of Intramuscular Interferon Beta-1a: An Overview of Relapse, Disability, and MRI Data from Selected Clinical Trials
Development of CDMS

The development of clinically definite MS (CDMS) is also a common outcome in clinical trials of clinically isolated syndrome (CIS). CIS is defined as a first neurologic episode that lasts at least 24 hours and is caused by inflammation/demyelination in 1 or more sites in the central nervous system. Several studies have shown that approximately 60% to 80% of patients with CIS and demyelinating lesions will ultimately experience a second demyelinating event, thus confirming a diagnosis of MS (CDMS by Poser criteria, e.g., 2 relapses and clinical evidence of 2 separate lesions, or 2 relapses and clinical evidence of 1 lesion, and paraclinical evidence of another separate lesion).53,54,55 Future clinical trials will likely include patients who have been diagnosed earlier in their disease course by the use of the more sensitive McDonald criteria.53,56,57 McDonald criteria include the use of MRI findings for the diagnosis of MS in lieu of the presence of a second relapse, where Poser criteria do not. This allows for the diagnosis of MS in patients with a variety of presentations, including monosymptomatic disease; disease with a typical relapsing-remitting course; and disease with gradual progression, without clear attacks and remissions.58 Results from multiple studies have demonstrated an advantage in early initiation of treatment in order to slow the progression from a CIS to CDMS.59,60,61,62 Patients with CIS have a high risk of developing CDMS, and treatment with IFNβ has shown to be effective in the early stages of MS.63

IM IFNβ-1a in the Long-Term Treatment of Multiple Sclerosis

In 1996, IM IFNβ-1a was approved for use in the treatment of MS in the United States and in 1997 in Europe, and it is currently authorized for use in approximately 80 countries.64 As of April 2011, an estimated 402,250 patients with 1,492,407 years of cumulative exposure had been treated with IM IFNβ-1a (Biogen Idec Inc., unpublished data). IM IFNβ-1a is indicated for the treatment of patients with relapsing forms of MS to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations, including relapses.65 Patients with MS in whom efficacy has been demonstrated include those who have experienced a first relapse and have MRI features consistent with MS. The efficacy and safety of this DMT as a first-line treatment for MS is well established, and several clinical studies of IM IFNβ-1a have been published. Most patients who are treated with IM IFNβ-1a experience flu-like symptoms (fever, chills, sweating, muscle aches, and tiredness) early in the course of therapy, but for many patients, these symptoms decrease in frequency with continued treatment. The pivotal phase 3 trial for IM IFNβ-1a was published in 1996,66 followed by the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) in 2000;67 the 5-year CHAMPS extension study in 2006 (the Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurologic Surveillance [CHAMPIONS]);68 the Assessment of Drug Utilization, Early Treatment, and Clinical Outcomes (ASSURANCE) long-term follow-up study of the Multiple Sclerosis Collaborative Research Group (MSCRG) in 2010;69 and the 10-year CHAMPS extension study (CHAMPIONS) in 2011.70 A flow chart of the pivotal and follow-up studies of IM IFNβ-1a can be found in Figure 1. A brief overview of the designs of these studies can be found in Table 1, and a summary of study results for IM IFNβ-1a can be found in Table 2. With regard to the review of outcomes from clinical trials, it is important to consider the time frame in which the studies were conducted. The availability of therapies to treat MS has changed substantially over the past 15 years, thereby resulting in differences in the patient populations between earlier and later studies. There are now several DMTs approved to treat MS that were not commercially available at the time of the early studies in this disease, resulting in its being more difficult now to recruit patients who are naive to treatment.71 Additionally, MS is now being detected in patients earlier in the stage of the disease, resulting in clinical trial patient populations with lower overall EDSS scores. Therefore, disease activity in placebo groups will be much lower in more recent trials than in trials from more than 10 years ago.

Multiple Sclerosis Collaborative Research Group Study and Safety Extension Study

MSCRG, the pivotal study for IM IFNβ-1a in relapsing MS, was a phase 3, multicenter, double-blinded, placebo-controlled, randomized trial that examined whether systemically administered IFNβ-1a (30 micrograms [µg] IM once per week for up to 104 weeks; n = 158) compared with placebo (n = 143) could slow the progression of irreversible neurological disability associated with relapsing forms of MS.8 Patients were between the ages of 18 and 55 years and had a diagnosis of MS for at least 1 year, a baseline EDSS score between 1.0 and 3.5, at least 2 documented relapses in the prior 3 years, and no relapses for at least 2 months prior to study entry. The primary outcome measure was time to onset of sustained worsening in disability, defined as an increase in EDSS score of at least 1.0 that persisted for at least 6 months. MS relapses were also assessed and were defined as the appearance of new, or worsening of pre-existing neurological, symptoms lasting at least 48 hours in a patient who had been neurologically stable or improving for the previous 30 days, accompanied by objective change on neurological examination (worsening of EDSS score by at least 0.5 point or worsening by at least 1.0 point on the EDSS pyramidal, cerebellar, brainstem, or visual functional system scores). The number and volume of Gd+ lesions were assessed by MRI on a yearly basis. At the time this study was conducted, monitoring of Gd+ lesions was a new imaging modality being used in the clinical setting for the first time. The study was initiated in November 1990, and by early 1993, the reported patient drop-out rate (3%) was considerably lower than the anticipated drop-out rate of 10%.8 This low drop-out rate allowed investigators to end the study approximately 1 year earlier than originally planned without affecting the statistical robustness of the analyses. Fifty-seven percent of the 301 patients (87 placebo patients, 85 IM IFNβ-1a patients) were enrolled early enough to accumulate 2 years of follow-up data.
Results from the MSCRG study demonstrated that time to sustained disability progression was significantly greater in patients treated with IM IFNβ-1a than in those receiving placebo (P = 0.020). In addition, the proportion of patients with disability progression at 2 years was significantly lower in the IM IFNβ-1a group than in the placebo group (21.9% vs. 34.9%; P = 0.020) according to Kaplan-Meier estimates. There was also a significant difference between IM IFNβ-1a and placebo in the unsustained mean change in EDSS scores (0.25 for IM IFNβ-1a vs. 0.74 for placebo; P = 0.020) as well as in the mean sustained change in EDSS scores (0.02 for IM IFNβ-1a vs. 0.61 for placebo; P = 0.020).
Patients receiving IM IFNβ-1a experienced significantly fewer relapses (62%; n = 53/85) than those receiving placebo (74%; n = 64/87; P = 0.030). In this study, the definition of a relapse was based on that of a typical MS trial (the appearance of new neurological symptoms lasting at least 48 hours in a patient who had been neurologically stable or improving for the previous 30 days) but was more stringent in that patients also had to have had an objective change on neurological examination that lasted more than 48 hours. Additionally, patients receiving IM IFNβ-1a had a significantly lower mean number of Gd+ lesions at 1 year than placebo-treated patients (1.04, standard error [SE] = 0.28 vs. 1.59, SE = 0.31; P = 0.020). Similar results were seen for mean volume of Gd+ lesions in patients receiving IM IFNβ-1a (70.0 cubic millimeters [mm³], SE = 24.9) versus patients receiving placebo (96.5 mm³, SE = 21.2; P = 0.020). These differences between the groups were still evident at the end of the second year of the study.8
The majority of patients who enrolled early enough to accumulate 2 years of follow-up completed the MSCRG study (93%). One percent of patients (n = 2) in the placebo group who had CDMS reached an EDSS score ≥ 4.0; 6% of all patients and 10% of CDMS patients reached an EDSS score ≥ 6.0. At 10 years, 81% had EDSS scores < 3.0, 9% of all patients and 16% of patients who had CDMS reached an EDSS score ≥ 0.0, 6% of all patients and 10% of CDMS patients reached an EDSS score ≥ 2.0 to 2.5; 13% reached EDSS scores ≥ 3.0.

An open-label extension period of the MSCRG study was conducted to evaluate the safety and immunogenic properties of IM IFNβ-1a when administered to patients for over 6 years. The extension period was not restricted to patients who had participated in the main MSCRG study but was also open to new patients. All patients received once weekly IM IFNβ-1a (30 µg for 6 years (new patients) or up to 8 years (MSCRG new patients). All patients received once weekly IM IFNβ-1a as measured by EDSS score; 71% of patients had an EDSS score ≤ 1.5, 16% had EDSS scores from 2.0 to 2.5, 13% reached EDSS scores ≥ 3.0.

No differences between IT and DT groups in median number of new or enlarging T2 lesions were lower in the IT group versus the DT group (3.5 vs. 6.0; P = 0.050). Cumulative probability of developing CDMS was lower in the IT than the DT group (58% ± 10% vs. 69% ± 9%; unadjusted HR 0.64, 95% CI: 0.48-0.87, P = 0.004).
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review, only the study’s safety endpoints, the incidence of AEs and laboratory test results, will be presented.

Seventy-two percent (275/382) of patients completed the study.72 Of the 107 (28%) patients who discontinued, 38 (10%) voluntarily withdrew from treatment; 20 (5%) withdrew due to perceived worsening of MS, and 8 (2%) withdrew due to AEs. The incidence and types of AEs during the extension study were similar to those observed in the MSCRG study.6 The most frequently reported AEs were flu-like symptoms (74%), headache (58%), muscle aches (48%), cold symptoms (46%), and accidental injury (48%).72 A total of 120 patients (31%) experienced a serious AE, which included 36 (9%) patients with a relapse and 12 (3%) with accidental injury. Nine (2%) patients discontinued treatment due to AEs, and the most common of these types of events were flu-like symptoms (n = 3), asthenia (n = 2), fever (n = 2), and relapse (n = 2). Overall, the AEs that occurred in the extension study were similar to those that occurred in the MSCRG study.

Long-Term Follow-Up of MSCRG: The ASSURANCE Study

Patients who completed the 2-year MSCRG study were eligible to enter the ASSURANCE 15-year multicenter follow-up study.70 Data were captured using a mailed survey. The study objective was to evaluate the long-term tolerability of IM IFNβ-1a and effects on disability and QoL. Patient-reported EDSS scores, which have been shown to highly correlate with physician-derived scores,73 were recorded at 15 years.70 Of the 172 patients who were eligible for inclusion in ASSURANCE, the status of 136 (79%) was ascertained; 14 (8%) patients were reported as deceased. Of the 122 living patients, 56 were receiving IM IFNβ-1a, and 66 patients were receiving either another MS therapy or no therapy at the start of the ASSURANCE follow-up study. The primary study endpoints were change in EDSS score from baseline (start of MSCRG study) and percentage of patients with EDSS scores of ≥ 4.0, ≥ 6.0, and ≥ 7.0. Patients with a change in EDSS of < 1.0 were considered “progression free.”

Based on patients’ current treatment at the 15-year follow-up (on IM IFNβ-1a versus not on IM IFNβ-1a), significantly lower mean EDSS scores were seen in ASSURANCE patients who were receiving IM IFNβ-1a at MSCRG baseline (P = 0.034), 2 years (P = 0.031), 8 years (P = 0.0016), and 15 years (P = 0.011) compared with patients who were not.79 Patients who were on IM IFNβ-1a therapy also had a smaller mean change from baseline in EDSS score than patients not currently taking IM IFNβ-1a (2.3 vs. 3.3; P = 0.011). Fewer patients who were on IM IFNβ-1a had progressed to EDSS scores ≥ 4.0 (P = 0.062), ≥ 6.0 (P = 0.007), and ≥ 7.0 (P = 0.008). There was no statistically significant difference in the percentage of patients receiving IM IFNβ-1a who were “progression free” from the time of enrollment in the MSCRG study versus patients not currently on IM IFNβ-1a (26.8% vs. 16.7%; P = 0.326).

The overall results indicated that long-term treatment with IM IFNβ-1a was well tolerated, and no new safety concerns arose over the course of treatment.70 For the 14 deceased patients, the mean time to death since MSCRG enrollment was 9.4 years. Of the 6 patients originally randomized to receive IM IFNβ-1a, the mean time to death since MSCRG enrollment was 11.5 years (median, 12.4; range, 8.0-13.0), and for the 8 deceased patients randomized to placebo, the mean time to death was 7.8 years (median, 6.9; range, 2.6-16.6). There was no significant difference in time to death for the 2 groups (P = 0.058). With regard to the evaluation of the results from this study, it is, however, important to note the relatively small patient population. Additionally, 18 of the 56 patients in the ASSURANCE IM IFNβ-1a treatment group had originally received placebo in the MSCRG study.

Early Initiation of Therapy: Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study

CHAMPS was a randomized, placebo-controlled, double-blind trial of 383 patients who had a first CIS, defined as a first acute clinical demyelinating event, and evidence of prior subclinical demyelination on MRI of the brain.11 Patients were randomly assigned to receive weekly injections of IM IFNβ-1a 30 µg (n = 193) or placebo (n = 190). Patients were eligible for the study if they were between the ages of 18 and 50 years and were considered at a high risk for developing CDMS. Patients had a CIS involving the optic nerve, spinal cord, brain stem, or cerebellum that was confirmed on ophthalmologic or neurologic examination. Additionally, patients had to have had at least 2 asymptomatic brain lesions that were at least 3 mm in diameter, and at least 1 lesion had to be periventricular, or ovoid, in shape. The primary study endpoint was the development of CDMS, as defined by Posner criteria.91 Patients were also assessed using MRI for the number of new or enlarging T2 lesions, the volume of T2-weighted lesions, and the number of T1-weighted Gd+ lesions.

MRI outcomes showed significant differences in the median change in volume of T2 lesions between IM IFNβ-1a- and placebo-treated patients at 6 months (IM IFNβ-1a, -123 mm3; placebo, 40 mm3; P < 0.001), 12 months (IM IFNβ-1a, 102 mm3; placebo, 214 mm3; P = 0.004), and 18 months (IM IFNβ-1a, 28 mm3; placebo, 313 mm3; P < 0.001).11 At 18 months, the median increase in lesion volume was 1% in the IM IFNβ-1a group versus 16% in the placebo group (P < 0.001). At 6, 12, and 18 months, patients treated with IM IFNβ-1a had fewer new or enlarging T2 lesions (P = 0.001, P < 0.001, P < 0.001, respectively) and fewer T1 Gd+ lesions (P = 0.030, P = 0.020, P = 0.001, respectively) than those treated with placebo. Patients treated with IM IFNβ-1a had 42% fewer Gd+ lesions at 6 months (mean ± standard deviation (SD) IM IFNβ-1a, 0.9 ± 2.3; placebo, 1.5 ± 3.1; P = 0.030), 55% fewer lesions at 12 months (IM IFNβ-1a, 0.7 ± 2.0; placebo, 1.6 ± 3.8; P = 0.020), and 67% fewer lesions at 18 months (IM IFNβ-1a, 0.4 ± 1.5; placebo, 1.4 ± 3.6; P < 0.001).

Immediate treatment initiation of IM IFNβ-1a after a CIS significantly reduced the development of CDMS in high-risk patients.11 The cumulative probability of the development of CDMS was significantly lower in the IM IFNβ-1a treatment group compared with the placebo group at 3 years (rate ratio = 0.56, 95% confidence interval [CI] = 0.38-0.81,
5- and 10-Year Extension Studies of CHAMPS: Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurologic Surveillance

The CHAMPIONS study was an ongoing open-label extension study of CHAMPS. The CHAMPIONS study was designed to determine if the benefits of IM IFNβ-1a observed in CHAMPS were sustained over the long term. For the purposes of this article, the 5- and 10-year results were reviewed. Patients were eligible to continue in the 10-year extension if they had participated in CHAMPS and their study site elected to participate in CHAMPIONS. Patients were required to meet the following enrollment criteria: (a) completion of the 1-month follow-up visit in CHAMPS, (b) signed informed consent, (c) willingness to enroll in CHAMPIONS less than 5 years after CHAMPS enrollment, (d) no evidence of systemic disease with significant organ dysfunction or potential mortality within 3 years of CHAMPS enrollment, (e) no alternative neurologic diagnosis other than MS following enrollment in CHAMPS, and (f) no participation in another clinical trial of an investigational drug or device. At the end of the enrollment visit, the patient was provided with IM IFNβ-1a and instructions for use, if necessary.

CHAMPIONS specifically examined whether immediate initiation of IM IFNβ-1a was more effective than delayed initiation of treatment. Treatment groups were determined based on the original randomization in CHAMPS; patients who received IM IFNβ-1a in CHAMPS were considered the immediate-treatment (IT) group, while patients receiving placebo were considered the delayed-treatment (DT) group. Patients in the CHAMPS study were given the opportunity to remain on or switch to IM IFNβ-1a 30 µg at the end of the study. Those who had originally received placebo could be treated with IM IFNβ-1a when they developed CDMS or at the completion of the study, whichever occurred first. Because placebo patients could start on IM IFNβ-1a at the onset of CMD or at the end of the study, whichever came first, there was a range of time during which patients were without treatment. The median time to initiation of IM IFNβ-1a or the first DMT in the DT group was 29 months. Over the course of CHAMPIONS, patients could be on IM IFNβ-1a, on another treatment, or no treatment, according to the discretion of their treating physicians. The primary outcome measure was the rate of development of CDMS. Additional outcomes included annualized relapse rate, EDSS score at 5 years, and MRI assessments at 5 years. Significance was predefined at P < 0.01 to take into account multiple assessments.

In the CHAMPIONS 5-year study, 64% (32/50) of the CHAMPS study sites participated; 53% (203/383) of patients from CHAMPS were enrolled. An equal distribution of patients from the original CHAMPS IM IFNβ-1a group (n = 100) and the placebo group (n = 103) enrolled in the CHAMPIONS 5-year study. Not all of the CHAMPIONS study sites participated in CHAMPIONS, which is the main reason for patients not continuing in CHAMPIONS. Patient demographics and disease characteristics in the CHAMPIONS 5-year study were similar to those in the CHAMPS study. Ninety-six percent (195/203) of patients completed their 5-year visits, and 98% (198/203) completed the 5-year or subsequent yearly visits per protocol. (Three patients missed the 5-year visit; therefore, therapy at 5 years was reported retrospectively at a subsequent visit.)

Patients who participated in the CHAMPIONS 5-year study were eligible to continue in the 10-year extension if they had no alternative neurologic diagnosis other than MS following enrollment in CHAMPS, if they provided informed consent, and if the study site at which they were enrolled was willing to participate in the 10-year extension. A total of 155 patients enrolled in the 10-year extension. There was a slightly higher number of patients from the IT group (n = 81, 81% of the CHAMPIONS 5-year group) who enrolled in the 10-year study versus the DT group (n = 74, 72% of the CHAMPIONS 5-year group). Reasons given for not participating in the 10-year extension included the following: the patient was lost to follow-up (n = 13), had refused to participate (n = 5), was deceased (n = 1), was participating in another study (n = 1), or there was no reason given (n = 4). The patients who did not participate in the 10-year extension study were predominantly from the original CHAMPIONS DT group (68% [19 of 28]) and had a higher rate of conversion to CDMS at 5 years (57% [16 of 28]) than the 155 patients who did participate (45% [70 of 155]). In the DT group, the median time to initiation of IM IFNβ-1a was 30 months, similar to that seen at the at the start of the 5-year follow-up period.

In the CHAMPIONS 5-year study, very few patients developed significant neurologic disability, as measured by EDSS score. The majority (71%) of patients had an EDSS score ≤ 1.5; 16% had an EDSS score of 2.0 to 2.5; and 13% had an EDSS score ≥ 3.0. At 10 years, the majority of patients (81%, n = 103) had EDSS scores < 3.0, as seen in Table 3. Nine percent of all patients and 16% of patients with CDMS reached an EDSS score ≥ 4.0; 6% of all patients and 10% of CDMS patients reached an EDSS score ≥ 6.0. There was no significant difference between the IT and DT groups in the distribution of EDSS scores at both 5 and 10 years.

In the CHAMPIONS 5-year study, the annualized relapse rate for different treatment epochs was evaluated to determine if the reduction in relapses during CHAMPS was sustained once patients originally randomized to placebo were switched to IM IFNβ-1a. Mean (SD) annualized relapse rate between years 0 and 2 for the IT and DT populations was 0.15 (0.31) and 0.31 (0.45), respectively (P = 0.004). At 5 years, mean (SD) annualized relapse rates were 0.17 (0.24) and 0.32 (0.51), respectively.
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respectively (P=0.020). Between years 3-5, the annualized relapse rate (SD) was lower in the IT group (0.18 [0.36]) than in the DT group (0.32 [0.71]), although the difference was not statistically significant (P=0.280). However, between years 5 and 10, the annualized relapse rate in the DT group was more than double that in the IT group (0.31 vs. 0.14; P=0.03) despite IM IFNβ-1a use being comparable between groups during that time.62

In the 5-year study, the median number of new or enlarging T2 lesions was lower in the IT group compared with the DT group (3.5 vs. 6.0; P=0.050) at 5 years.63 There was no significant difference between the IT and DT groups in the change in T2 lesion volume from CHAMPS baseline to CHAMPIONS at 5 years. No statistically significant difference was observed in the percentage of patients with Gd+ lesions between the IT (≥1, 29%; ≥2, 11%) and DT (≥1, 30%; ≥2, 13%) treatment groups. Additionally, at 10 years, there were no significant differences between the IT (n=55) and DT (n=55) groups in median number of new or enlarging T2 lesions (5.0 vs. 7.0, P=0.500), number of Gd+ lesions (0 lesions: 81 vs. 80; 1 lesion: 11 vs. 15; ≥2 lesions: 4 vs. 3; P=0.870), median T2 lesion volume (1,906 mm3 vs. 2,089 mm3, P=0.79), or median change in T2 lesion volume from baseline to 10 years (+2,600 mm3 vs. +2,516 mm3, P=0.640). A summary of MRI outcomes at 10 years is presented in Table 3.43

At 5 years, the cumulative probability of developing CDMS was significantly lower in the IT group compared with the DT group (5-year mean [SD] incidence: 36 [9%] vs. 49 [10%]; P=0.030). Similarly, at year 10, the cumulative probability of developing CDMS was significantly lower in the IT group than in the DT group (58% ± 10% vs. 69% ± 9%; unadjusted hazard ratio [HR] 0.64, 95% CI = 0.48-0.87, P=0.0044; Figure 2).2 The treatment effect was comparable when adjusting for age, CHAMPS qualifying event, CHAMPS baseline brain MRI T2 lesions number, and baseline number of Gd+ lesions (adjusted HR = 0.61, 95% CI = 0.45-0.82, P = 0.001).

During the entire follow-up period (both 5- and 10-year extensions) of CHAMPIONS, 34 serious AEs occurred in 25 patients, including 2 deaths (metastatic breast cancer and an automobile accident).64,65 Unblinded investigators determined that all serious AEs were unlikely to be related or were unrelated to treatment.65 No new safety concerns arose with IM IFNβ-1a during either study.

### Important Considerations for Clinical Trials in MS

With increasing numbers of approved MS drugs available, important considerations have emerged with regard to the design of newer MS trials.74,75 Considerable difficulty exists for initiating placebo-controlled trials for relapsing forms of MS, with patient populations limited to those who have failed therapy or perhaps those who refuse approved therapies because of their expense or mode of administration.74 Some MS trials are incorporating an active comparator, since placebo-controlled trials do not provide information on the comparative efficacy among available agents. As mentioned previously, MS trials are also evolving to include patient populations that are earlier in their disease course and have more advanced MRI methods. These and other shifts in MS trial design must be considered when making comparisons between older and newer studies of MS therapies.

There are several important limitations to consider when interpreting the results of the studies discussed in this article. It is important to note that while patients in the CHAMPS study had a diagnosis of CIS and were naïve to therapy, patients in the MSCRG study had been diagnosed with CDMS for at least 1 year and may have received prior treatment for MS. Also, patients in the CHAMPS study had a significantly lower rate of CDMS during CHAMPS than in CHAMPIONS. Both the ASSURANCE and CHAMPIONS extension studies enrolled patient populations that were relatively small, based on select criteria for disease activity, potentially introducing selection bias in the continuing patients. As with all studies, caution should be taken when making cross-trial comparisons.

### TABLE 3 Disability and MRI Outcomes at 10 Years in CHAMPIONS

<table>
<thead>
<tr>
<th>MRI outcome</th>
<th>Immediate-Treatment Group</th>
<th>Delayed-Treatment Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of new or enlarging T2 lesions</td>
<td>5 (1, 12)</td>
<td>7 (3, 17)</td>
<td>0.5062</td>
</tr>
<tr>
<td>Number of Gd+ lesions, n (%)</td>
<td>44 (81)</td>
<td>43 (80)</td>
<td>0.8762</td>
</tr>
<tr>
<td>T2 lesion volume at 10 years, mm3, median (quartiles)</td>
<td>4,741 (1,906, 11,902)</td>
<td>4,946 (2,089, 11,611)</td>
<td>0.7964</td>
</tr>
<tr>
<td>Change in T2 volume, mm3, from baseline to 10 years, median (quartiles)</td>
<td>+2,600 (+398, +5,862)</td>
<td>+2,516 (+721, +6,682)</td>
<td>0.6464</td>
</tr>
</tbody>
</table>


Limited to 127 of 155 patients who completed the 10-year visit. Results were similar using last observation carried forward for the 28 subjects who did not complete the 10-year visit (data not shown).

Fisher exact test. Because of multiple comparisons, P values ≥0.01 were considered not significant in the secondary analyses.

Missing for 2 MRI scans.

Wilcoxon rank-sum test.

n=108 with T2 volume available at both baseline and 10 years.

CHAMPIONS = Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study; CHAMPS = Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study; EDSS = Expanded Disability Status Scale; Gd+ = gadolinium enhancing; mm3 = cubic millimeter; MRI = magnetic resonance imaging.
new safety considerations have emerged. As selecting therapy for patients will become more complicated over the next few years with the introduction of new therapies, some of which have unique safety considerations, the information presented here should be useful when evaluating risk-benefit considerations.

Conclusions

Disability (as determined by EDSS), annualized relapse rate, and standard MRI measures continue to be the mainstays of efficacy assessment in MS clinical trials. Although newer endpoints, such as MSFC, brain atrophy, and QoL, are becoming more common in MS studies, the traditional outcome measures should continue to be evaluated when considering any new treatment for MS. Both conventional and newly evolving outcome measures should be considered together when evaluating efficacy. For more than 15 years, IM IFNβ-1a has been an effective first-line treatment option and among the most commonly prescribed therapies for patients with MS. With approximately 402,250 patients having been treated with IM IFNβ-1a at the time of this publication, the efficacy and safety profile of IM IFNβ-1a has been well established in the post-marketing setting, and no


Immediate Treatment

Delayed treatment group: patients who received IM IFNβ-1a at the original randomization of the CHAMPS.

Immediate treatment group: patients who received placebo at the original randomization of CHAMPS.

CHAMPS = Controlled High-Risk Avonex Multiple Sclerosis Prevention Study; CI = confidence interval; IM = intramuscular; IFNβ = interferon beta.

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Foley and Nair contributed to the concept and design, data collection, data interpretation, writing, and revision of the manuscript. Zerkowski primarily performed the literature search and data collection, wrote the initial manuscript, and provided revisions. The authors acknowledge editorial assistance provided by Jacqueline Cannon from Infusion Communications, Inc.

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Evidence for Long-Term Use of Intramuscular Interferon Beta-1a: An Overview of Relapse, Disability, and MRI Data from Selected Clinical Trials


Emerging Methods for Evaluating the Effectiveness of Intramuscular Interferon Beta-1a for Relapsing-Remitting Multiple Sclerosis

John F. Foley, MD; Christopher J. Barnes, PhD; and Kavita V. Nair, PhD

ABSTRACT

Newer outcome-based assessment methods have been developed that complement and improve upon the ability of historical clinical and magnetic resonance imaging (MRI) outcome measures to measure multiple sclerosis (MS) disease activity, patient functionality, treatment efficacy, and the risk of MS disease progression. These newer MS outcome assessments include instruments to evaluate cognitive function and patient quality of life; enhanced measures of disability, such as the Multiple Sclerosis Functional Composite instrument; and newer MRI measures of MS disease activity and neuronal changes, such as permanent T2 hypointensities and central nervous system atrophy. When utilized in conjunction with standard MS outcome measures, these newer MS outcomes provide a more comprehensive picture of disease status and course and hold promise as tools for use in the development and testing of future MS therapies. The well-established first-line MS therapy intramuscular interferon beta-1a, which has been evaluated using a broad range of assessment methods, was used as a reference MS disease-modifying therapy to provide specific examples of studies utilizing newer evaluation methods. Utilization of evolving disease and assessment measures for patients with MS should improve MS patient diagnosis, treatment decisions, and monitoring of therapy.

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Summary Points Presented in this Article

• Multiple sclerosis (MS) is a chronic, immune-mediated neurologic disease that is associated with progressive patient disability and diminished quality of life (QoL).
• Historical clinical outcomes, such as MS relapses, physical disability measures, and magnetic resonance imaging (MRI) endpoints, do not capture important elements of MS, such as the impact of MS and MS therapies on a patient’s QoL.
• This article provides an overview of several key newer MS patient outcomes, including instruments used to assess MS patient cognition, QoL, composite disability measures, and emerging MRI clinical endpoints.
• Newer MS patient outcomes have the potential to improve MS patient care and the development and testing of future therapeutics for the treatment of MS.

First-line disease-modifying therapies (DMTs) for relapsing-remitting multiple sclerosis (RRMS) have consistently demonstrated positive effects on historical clinical outcomes such as MS relapses; magnetic resonance imaging (MRI) outcomes such as the number, location, and volume of brain and lesions; and in some studies, disability progression, as measured by the Expanded Disability Status Scale (EDSS). However, older measures do not capture the entire impact of the disease (e.g., cognition, upper limb function, etc.) on patient function and well-being.

Newer outcome measures are being developed with the purpose of capturing additional aspects of the disease and facilitating a more comprehensive assessment of MS disability, progression, and therapeutic efficacy. The primary purpose of this article is to provide the managed care audience with an overview of the most prominent newer MS measures. The potential benefits of these newer outcomes are illustrated using published clinical data on intramuscular interferon beta-1a (IM IFNβ-1a) as an extensively evaluated, representative first-line MS therapy.

Measures of Disability: Cognition and the MS Functional Composite

Cognitive Dysfunction: A Key Component of Disability

Maintenance of cognitive function is an important long-term consideration in MS and has been evaluated in a number of MS clinical trials as a secondary study endpoint. Given the substantial impact of cognitive deficits in MS, it is noteworthy that these deficits are not incorporated into the EDSS, which has been widely used for measuring disability in MS.1 Cognitive measures and their relationships with MS disease outcomes have been gaining increasing prominence in MS clinical research. Since complete clinical cognitive assessment is expensive and requires expert staff and specialized equipment, brief cognitive assessment instruments have been developed to assess cognition in the clinical setting with minimal impact on patients, staff, and resources. This section reviews the instruments that are currently used to assess cognitive function in patients with MS. For representative illustration, published IM IFNβ-1a clinical data are presented to show the impact of MS therapy on these outcomes.

Cognitive impairment occurs in roughly 50% of patients with MS,2 and cognitive deficits are frequently observed even in patients with early disease3 or mild physical disability,4 with reported incidences of 26% and 20% of MS patients, respectively. These cognitive deficits can negatively impact many aspects of a patient’s life, including employment, social and family relationships, and self-care.3,5

Based on a reported meta-analysis of 57 studies that enrolled a total of 3,891 participants,6 patients with RRMS are more likely than healthy control subjects to be impaired in general cognitive function (intellectual ability, verbal-intellectual
Although methods for cognitive assessment in MS continue to evolve, first-line DMTs for MS such as IFNβ are generally reported to slow cognitive change in relapsing MS. Using data on the DMT IM IFNβ-1a as an example, a prospective analysis of the placebo-controlled phase 3 Multiple Sclerosis Collaborative Research Group (MSCRG) study also demonstrated the beneficial effects of IM IFNβ-1a on cognitive function in patients with clinically definite RRMS. In these analyses, IM IFNβ-1a (n = 83) performed significantly better than placebo (n = 83) at 2 years on both a composite endpoint of information processing and learning/recent memory measures (P = 0.036) and a composite measure of visual-spatial abilities and executive functions (P = 0.005). However, the latter result was nonsignificant following adjustment for baseline group differences (P = 0.085). Longitudinal analyses showed that IM IFNβ-1a also significantly lengthened the time to sustained deterioration in patient PASAT scores (Figure 1), with fewer IM IFNβ-1a patients (19.5%) than placebo patients (36.6%) meeting criteria for sustained PASAT deterioration by the end of the treatment phase.

Several instruments are currently used to assess cognitive function in patients with MS. These instruments include the Functional Independence Measure (FIM) scale, a 30-minute assessment of physical and cognitive disability that focuses on the level of patient disability as an indicator of the burden of care; the Symbol Digit Modalities Test (SDMT), a 5-minute assessment that screens the participant for any kind of cerebral dysfunction using a simple substitution task; and the Paced Auditory Serial Addition Test (PASAT), a validated, 15-minute tool that evaluates a patient’s sustained attention, working memory, and speed of information processing. In addition, the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) was recently developed by an international committee as a brief cognitive assessment for MS that is optimized for small centers. A validation protocol has been prepared for regional language groups, and validation studies for BICAMS are underway.

Although methods for cognitive assessment in MS continue to evolve, first-line DMTs for MS such as IFNβ are generally reported to slow cognitive change in relapsing MS. Using data on the DMT IM IFNβ-1a as an example, a prospective analysis of the placebo-controlled phase 3 Multiple Sclerosis Collaborative Research Group (MSCRG) study also demonstrated the beneficial effects of IM IFNβ-1a on cognitive function in patients with clinically definite RRMS. In these analyses, IM IFNβ-1a (n = 83) performed significantly better than placebo (n = 83) at 2 years on both a composite endpoint of information processing and learning/recent memory measures (P = 0.036) and a composite measure of visual-spatial abilities and executive functions (P = 0.005). However, the latter result was nonsignificant following adjustment for baseline group differences (P = 0.085). Longitudinal analyses showed that IM IFNβ-1a also significantly lengthened the time to sustained deterioration in patient PASAT scores (Figure 1), with fewer IM IFNβ-1a patients (19.5%) than placebo patients (36.6%) meeting criteria for sustained PASAT deterioration by the end of the treatment phase.

A separate study that assessed the effect of IM IFNβ-1a on long-term cognitive function is CHAMPIONS, a 10-year, open-label, long-term observational extension study of the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS), which examined the benefits...
of IM IFNβ-1a therapy in patients with clinically isolated syndrome (CIS). Analysis of PASAT scores obtained during study years 5-10 showed that more than 95% of the patients followed in CHAMPIONS 10 and treated with IM IFNβ-1a remained cognitively stable over this span. However, data from serial cognitive assessments must be interpreted with caution because of the potential for practice effects resulting from test repetition to influence results.

### TABLE 1: Overview of Studies Investigating the Effect of Intramuscular IFNβ-1a on Quality of Life in Patients with Relapsing-Remitting Multiple Sclerosis

<table>
<thead>
<tr>
<th>Study (Year Published) Country</th>
<th>Design</th>
<th>N</th>
<th>QoL Measures</th>
<th>Comparator</th>
<th>Results</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnoldus (2000) Netherlands</td>
<td>6-month prospective, observational, single-center study</td>
<td>51</td>
<td>SF-36 questionnaire</td>
<td>Baseline</td>
<td>During treatment there was a significant linear trend indicating improvement in the role-physical functioning scale of the SF-36 (P = 0.032).</td>
<td>No control group; no adjustment for multiple evaluations; no follow-up longer than 6 months.</td>
</tr>
<tr>
<td>Vernersch (2002) France</td>
<td>1-year prospective, observational, single-center study</td>
<td>121</td>
<td>SF-36 questionnaire</td>
<td>Baseline</td>
<td>QoL scores remained stable, except for physical function, where a slight but significant decrease was seen (P = 0.03).</td>
<td>Methodology did not enable the correlation between patient QoL and treatment-related adverse events.</td>
</tr>
<tr>
<td>Zivadinov (2003) Italy</td>
<td>1-year prospective, open-label, single-center follow-up study</td>
<td>27</td>
<td>FAMS, FIM, MMSE, HDRS, HARS, FSS</td>
<td>Baseline</td>
<td>QoL remained stable over the follow-up period.</td>
<td>No quantification of side effects during the first 6 months of therapy; small cohort with follow-up.</td>
</tr>
<tr>
<td>Putzki (2009) Germany</td>
<td>1-year prospective, observational, open-label, multicenter study</td>
<td>1,157</td>
<td>EQ-5D questionnaire</td>
<td>Baseline</td>
<td>The mean utility component increased from 0.75 at baseline to 0.77 with IFNβ-1a (P = 0.005). Similarly, the VAS component improved from a mean value of 64.8 to 70.1 (P &lt; 0.001).</td>
<td>Use of different QoL measures and different patient clinical characteristics limits comparison with other studies.</td>
</tr>
<tr>
<td>Bermel (2010) USA</td>
<td>15-year open-label follow-up of patients who completed 2 years in the MSCRG study (ASSURANCE)</td>
<td>136</td>
<td>SF-36 questionnaire and a VAS for independence with self-care</td>
<td>Patients no longer using IM IFNβ-1a</td>
<td>After 15 years, patients currently on IM IFNβ-1a had better mean scores on the physical component summary (39.3 vs. 31.0, P &lt; 0.001) and the subscales of physical functioning (P &lt; 0.001), role-physical (P &lt; 0.05), and general health (P &lt; 0.05) on the SF-36. Patients using IM IFNβ-1a also had better scores on the social functioning scale compared with nonusers (P &lt; 0.05) and had lower median VAS scores (3.0 vs. 9.0, P = 0.002), indicating greater independence in self-care.</td>
<td>Incomplete ascertainment, lack of randomization beyond the core clinical trial.</td>
</tr>
<tr>
<td>Jongen (2010) Netherlands, Belgium, Luxemburg</td>
<td>2-year prospective, multicenter, observational phase 4 study</td>
<td>284</td>
<td>MSQoL-54 questionnaire</td>
<td>Baseline</td>
<td>Mean values for MSQoL-54 increased from 56.6 to 61.0 for physical domains (P &lt; 0.05) and from 57.2 to 61.1 for mental domains (P = 0.07). The effect was particularly noticeable in younger patients with low disability.</td>
<td>Observational study, lack of comparator.</td>
</tr>
<tr>
<td>Miller (2011) USA</td>
<td>Retrospective analysis of a 2-year randomized, placebo-controlled, multicenter study (MSCRG)</td>
<td>158</td>
<td>SIP</td>
<td>Placebo</td>
<td>Overall, QoL remained stable. In patients with low SIP scores, indicating moderate or severe disability at baseline, treatment with IM IFNβ-1a significantly improved physical SIP subscores versus placebo.</td>
<td>Retrospective, post hoc design; patients with SIP scores &lt; 10 were not included in the analyses.</td>
</tr>
</tbody>
</table>

ASSURANCE = ASsessment of Drug Utilization, EarRly TreAtmeNt, and Clinical OutcomEs; EQ-5D = EuroQol health questionnaire; FAMS = Functional Assessment in MS; FIM = Functional Independence Measure; FSS = Fatigue Severity Scale; HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale; IFNβ = interferon beta; IM = intramuscular; MMSE = Mini-Mental State Examination; MSCRG = Multiple Sclerosis Collaborative Research Group; MSQoL-54 = Multiple Sclerosis Quality of Life-54; QoL = quality of life; SF-36 = Short-Form Health Survey-36; SIP = Sickness Impact Profile; VAS = Visual Analog Scale.
The MSFC: An Enhanced Measure of Disability Progression Incorporating Cognitive Function

Among the alternate assessments of disability that have been developed to overcome the limitations of EDSS, the MS Functional Composite (MSFC) has been the most widely studied. The MSFC is a 20- to 30-minute quantitative instrument consisting of 3 timed tests of neurologic function, which are combined into a single score that is expressed along a continuous scale. The 3 parts of MSFC measure arm, leg, and cognitive function with the 9-Hole Peg Test (arm/hand dexterity), the Timed 25-Foot Walk (leg function), and the PASAT 3-second version (PASAT3; cognition), respectively. This instrument is reported to have excellent test-retest reliability and provides a focused and sensitive evaluation of disability in patients with MS. But, the MSFC also has certain limitations. Indeed, the PASAT in MSFC may lack sufficient sensitivity to detect mild cognitive changes in MS, and the SDMT, which is reported to show greater sensitivity to cognitive changes than PASAT, has been suggested as a replacement. However, MSFC also has the beneficial qualities of providing information on patient upper limb and ambulatory function and good sensitivity and reliability with minimal patient inconvenience.

The ability of MSFC to predict future disability during treatment for RRMS was demonstrated in a reported 8-year follow-up of a phase 3 study of IM IFNβ-1a. In this study, the change in patient MSFC scores from baseline to year 2 correlated with the EDSS score and the severity of whole brain atrophy at follow-up. Significant correlations were also identified between MSFC scores during the clinical trial and patient-reported quality of life (QoL) at follow-up. This relationship between MSFC and disability has also been confirmed elsewhere.

Looking Beyond Disability: QoL as an Outcome Measure in the Treatment of Patients with MS

Patient QoL has received increasing recognition as a critical consideration in MS management. Patient Qol measures in MS and data on the impact of IM IFNβ-1a on patient QoL are reviewed below.

Patients with MS rank their QoL an average of 30% lower than individuals who do not have MS and score lower on QoL assessments than patients affected by other chronic diseases such as inflammatory bowel disease and rheumatoid arthritis. For example, patients with MS also score lower on the Short Form 36 Health Survey-36 (SF-36) physical functioning subscale (21 of a possible 100) than patients with Parkinson’s disease (32). However, another study found no difference between these 2 populations.

A number of studies in RRMS have demonstrated that measures of patient QoL negatively correlate with disability as assessed by EDSS or MSFC, although other studies have not found a correlation. QoL has been shown to correlate separately with relapses, brain lesions, brain atrophy, and changes in cognitive function (as assessed by PASAT), vision, and ambulation. In addition, QoL has been shown to correlate with employment status in MS. Continuing the use of IM IFNβ-1a as a widely evaluated, representative DMT, Table 1 provides an overview of studies that have investigated the effects of IM IFNβ-1a on QoL in RRMS. The majority of studies show a consistent trend of improved QoL with IFNβ-1a therapy, particularly in the physical domains of QoL ratings. Even in the studies that did not show an improvement with therapy, patient QoL was stable and did not worsen over time.

The ASSURANCE (ASSeessment of Drug Utilization, EaRly TreAtmeNt, and Clinical OutcomEs) study is particularly worth highlighting, given its long-term findings. ASSURANCE was a 15-year, single time point follow-up of patients who originally participated in the randomized, placebo-controlled phase 3 trial of IM IFNβ-1a in RRMS. The purpose of ASSURANCE was to evaluate the long-term tolerability of IM IFNβ-1a and effects on disability and QoL. After 15 years, patients on IM IFNβ-1a therapy versus those no longer taking IM IFNβ-1a had a better QoL based on SF-36 physical component summary (PCS) scores (39.3 vs. 31.0, P < 0.001) and were more likely to be living independently (P = 0.002) based on a visual analog scale (VAS) for independence with self-care. A subanalysis of data from ASSURANCE revealed that patients who demonstrate IFNβ-1a clinical efficacy early in their treatment course, as measured by disability progression or relapse status at 2 years after starting treatment, had significantly better QoL outcomes than those who continued to have MS disease activity at 2 years. Thus, in addition to the established clinical benefits of early initiation of therapy in MS, early evidence of clinical efficacy may help guide treatment decisions and enable patients to maximize their longer-term QoL outcomes as well.

Evolving MRI Methods for Improved Imaging in MS

Conventional MRI measures have proven useful for detecting subclinical lesion activity in patients with MS. Common measures evaluated in patients with MS include changes in T2-weighted lesions, which appear as bright spots on MRI, and gadolinium-enhancing (Gd+) lesions, which are detected using Gd contrast enhancement of brain MRI scans. Relapses are clearly an important measure, since they have an immediate impact on patients’ functional mobility and QoL and can be associated with significant residual deficits. However, changes on MRI can provide evidence of disease activity that may be of great benefit in patient monitoring, since inflammatory events occur more often than clinical events. For example, in a study of 222 patients with RRMS who were treated with IM IFNβ-1a, the combined presence of new active lesions on MRI and presence of relapses (odds ratio [OR] 4.4; 95% confidence interval [CI] 1.6-12.5), disability progression (OR 7.1; 95% CI = 1.6-33.9), or both factors (OR 6.5; 95% CI = 1.9-23.4) after 1 year were shown to have predictive value in identifying patients...
who went on to experience clinical disease activity in the sec-
ond and third year of therapy. Composite MRI scores have
also been shown to correlate more strongly with EDSS than
do individual MRI measures and may prove to be important
prognostic indicators in MS.

Improvements in MRI methodology and broader availability
of instruments with more powerful 3-tesla magnets are increas-
ing the accuracy of lesion detection and the ability to detect
certain lesion types such as gray matter T2 lesions. One
study used an optimized MRI protocol incorporating 3-tesla
MRI endpoints and monthly brain imaging to document MRI
lesion evolution and to compare the efficacy of IFNβ-1b and
glatiramer acetate (GA) for treatment of relapsing MS. Results
indicated that greater than 40% of enhancing lesions detected
using the trial MRI protocol represented persistent enhance-
ment. New contrast-enhancing brain lesions were rare, with
only 77 out of 1,161 monthly scans (6.6%) showing new T2
lesions from baseline through month 24. Another study using
ultra-high-field 7-tesla MRI imaging to evaluate MRI-detected
white matter lesions in MS diagnosis found that perivenous
white matter lesion appearance was more predictive of MS
(OR 14, P<0.001) than subcortical or periventricular lesion
location (OR 4.5, P<0.001, and OR 2.4, P<0.009). With tra-
ditional standard MRI enhancement protocols that incorporate
monthly MRI, the majority of lesions enhance for approxi-
ately 1 month. However, newer high-sensitivity contrast
enhancement techniques can extend lesion enhancement to
several months. To this end, in a direct comparison, 3-tesla
imaging detected a higher lesion load than 1.5-tesla imaging.
Comparison of older 1-tesla and 1.5-tesla images with newer,
higher-resolution MRI images to gain insight into MS lesion
evolution over time may prove challenging.

Despite the value of conventional MRI in characterizing
discrete lesions in MS, it does not detect diffuse abnormalities
in normal-appearing tissue. Also, mainstream MRI approaches
capture both reversible and irreversible components of MS
neuronal pathology. Researchers have investigated new imaging
measures that are thought to be more closely related to the
most disabling pathological features of MS, such as irreversible
demyelination and neuroaxonal injury. Promising but less fre-
frequently used MRI tools to assess neuronal and axonal damage
in MS include central nervous system (CNS) atrophy and T1
hypointensities (“black holes”). A summary of these measures
is provided below, together with an overview of relevant stud-
ies conducted to date with IM IFNβ-1a as examples of DMT
impact on these measures.

CNS Atrophy

Unlike more conventional MRI endpoints such as T2 hyper-
tense and Gd+ lesions, CNS atrophy reflects the net impact
of severe and potentially irreversible processes such as demy-
elination and axonal loss in both white matter (WM) and gray
matter (GM). Brain atrophy is present even at the earliest
stages of MS, and longitudinal structural imaging studies
have provided robust evidence of progressive brain atrophy in
patients with MS, especially in the frontotemporal cortices.
Unsurprisingly, then, CNS atrophy has been shown to be
linked to clinical aspects of MS, including patient disability
progression and cognitive decline. Indeed, several studies have
demonstrated that CNS atrophy is a stronger predictor of dis-
bility progression than conventional MRI endpoints.

Early studies assessing the impact of DMTs on whole-brain
atrophy in MS used a measurement termed the brain parenchym-
al fraction (BPF), which is defined as the ratio of the brain
parenchymal volume to the total brain volume. Computation of
the BPF involves selection of the intensity threshold that best
separates the brain parenchyma from the cerebrospinal fluid
(CSF) surrounding the brain and in the ventricles and applica-
tion of that threshold to pixel intensity maps of brain images.

A post hoc analysis of BPF using MRI scans from the 2-year,
phase 3 placebo-controlled MSCRG trial found that while the
percentage change in BPF during the first year was similar in
the IM IFNβ-1a and placebo groups, brain atrophy during the
second year was significantly reduced (55% decrease) in the
IM IFNβ-1a group compared with the placebo group. Over
another 2 years of follow-up, the percentage change in BPF was
18% lower in the IFNβ-1a group than in the placebo group.
Long-term follow-up of this MSCRG trial of IM IFNβ-1a found
that BPF at entry into the trial, and its change over 2 years, was
correlated with disability change over 8 years.

Subsequent studies of 2 or 3 years’ duration incorporating
various study designs assessing the effects of IM IFNβ-1a
alone or in combination have all demonstrated the ability of
this DMT to reduce the progression of whole-brain atrophy
or cortical-brain atrophy versus placebo or no treatment.
In addition, a recent study of patients with RRMS evaluating
the effects of daily GA, weekly IM IFNβ-1a, or subcutaneous
IFNβ (IFNβ-1a or IFNβ-1b) use on brain volume loss over 5
years found that all DMTs significantly reduce the loss of
brain volume in MS compared with no treatment. While it has
been argued that early changes in brain volume, so-called
pseudoatrophy, observed during the first year of treatment
with anti-inflammatory treatments such as IFNβ, may be due
to resolution of edema related to MS-associated inflammation;
data on microglial activation in MS suggest that treatment-
related inactivation and shrinkage of microglia may underlie
the volume changes associated with pseudoatrophy.

Whole-brain, GM, and WM atrophy have all been associated
with MS disability progression, but GM atrophy has emerged
as the type of atrophy that is potentially most closely linked
to functional decline in MS. GM involvement is detect-
able at the earliest stages of MS and may occur earlier than
WM atrophy. Several studies have suggested that GM atrophy
is more strongly correlated with disability than whole-brain or WM atrophy, particularly in early MS. In the AvonexSteroid-Azathioprine (ASA) study, changes in GM volume over 5 years were significantly correlated with disability progression as assessed with EDSS. A separate 3-year, open-label, controlled, single-blind, post-marketing observational study in 54 patients with MS reported that IM IFNβ-1a therapy significantly slowed the progression of whole-brain atrophy compared with no therapy, predominantly through inhibition of the progression of GM atrophy. Similar findings with IFNβ-1a were seen in a recent study presented by Fisher et al. However, a recent report on GM atrophy in 105 patients presenting with CIS and 42 normal controls studied over 4 years found that except for cerebellar cortical volume, there were no differences in brain volume change between CIS and controls. When a subgroup analysis compared results for the 59 patients with CIS who converted to MS during the follow-up with results from the control group, statistically significant atrophy was identified in the precentral gyrus, superior frontal gyrus, thalamus, and putamen. Additional support for a relationship between GM atrophy, MS diagnosis, and MS disability progression may come from ongoing clinical trials and observational studies in MS.

T1 Hypointensities (“Black Holes”) 
T1 hypointense lesions (“black holes”) are focal areas of severe CNS tissue damage detected by MRI in patients with MS. Persistent T1 hypointensities are thought to represent tissue loss, including axonal damage, and appear to be better predictors of disability progression than are T2 or Gd+ lesions. For example, post hoc analysis of MRI data from the MSCRG study of IM IFNβ-1a for MS revealed that treatment with the DMT IM IFNβ-1a reduced T1 hypointensity formation by 68% versus placebo. In this analysis, the median change from baseline over a 2-year interval in brain MRI T1 lesion load was 40.0 cubic millimeters (mm³); range, -2,424 to 4,042 for patients treated with IFNβ-1a (P=0.164) and 124.5 mm³ for placebo (P<0.001). Although the cohort treated with IM IFNβ-1a showed reduced accumulation of T1 hypointense lesions over 2 years, this difference was not statistically significant (P=0.065). Due to the challenges of measuring the conversion of T1 lesions to persistent “black holes” using repeated MRI, limited data are currently available demonstrating the relationship between baseline T1 hypointensities and disability progression. In a randomized controlled trial of patients with RRMS receiving IM IFNβ-1a, T1 hypointensities were found to be a strong predictor of disability progression (OR 6.8; P<0.001). Another small study of T1 cortical hypointense lesions using 3-tesla MRI found that patients with lesions performed more poorly (P=0.020) than patients without lesions on the delayed recall component of the California Verbal Learning Test, demonstrat-

Other Emerging Imaging Measures 
Other imaging techniques have been investigated, including functional MRI (fMRI), an MRI procedure that measures brain activity by detecting associated changes in blood flow; MRI diffusion tensor imaging, which measures random motion of water molecules in tissue; MRI magnetization transfer imaging, which uses pulsed radio frequencies to improve image contrast; and optical coherence tomography, a non-MRI assessment that uses high resolution and cross-sectional images of the eye to measure the thickness of the retinal nerve fiber layer, which frequently atrophies in MS. However, further data from well-designed, prospective clinical trials are needed to confirm the validity of these techniques.

Conclusions 
Conventional clinical and MRI outcome measures are moderately predictive of a patient’s risk of MS disease progression. Other outcome assessments have been introduced to overcome these limitations, such as tools to evaluate cognitive function, enhanced measures of disability such as the MSFC, and expanded imaging parameters such as T1 hypointense lesions and CNS atrophy. When utilized in conjunction with the standard assessment tools discussed in this article, these measures permit a much broader yet also more precise assessment of MS disease status and progression. Standardization, validation, and adoption of newer measures may provide a more comprehensive view of a patient’s disease than historical measures alone and can also help guide individual therapy choices to potentially reduce disease progression and future disability. It will be important to critically evaluate the implications of new disease measures relative to the clinical effectiveness and personal and economic costs associated with different DMTs as well as the costs of untreated disease.

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REFERENCES

Emerging Methods for Evaluating the Effectiveness of Intramuscular Interferon Beta-1a for Relapsing-Remitting Multiple Sclerosis


Narrative Review of the Literature on Adherence to Disease-Modifying Therapies Among Patients with Multiple Sclerosis

Joseph Menzin, PhD; Christina Caon, RN, MSN, NP-C; Christine Nichols, BA; Leigh Ann White, PhD; Mark Friedman, MD; and Michael W. Pill, PharmD

ABSTRACT
While no curative treatment exists for multiple sclerosis (MS), several disease-modifying therapies (DMTs) have been developed to reduce relapse rates, slow disability progression, and modify the overall disease course. However, because of the chronic nature of the disease, long-term therapy adherence can be challenging for some patients with MS. Low adherence to DMTs has been shown to be associated with higher rates of disease relapses and progression as well as with an increase in medical resource utilization. As new MS treatments are developed, a comprehensive understanding of current adherence rates and the impact of adherence on clinical and economic outcomes is of particular interest. Our objective was to conduct a review of the published literature to evaluate rates of adherence to DMTs in MS and the impact of adherence on both clinical and economic outcomes from the patient and payer perspectives.

Systematic literature searches were conducted using MEDLINE, EMBASE, and the Cochrane Central Register for Controlled Trials. Studies were limited to those completed on human subjects, written in the English language, and published between May 1, 2001, and May 1, 2011. Additional inclusion criteria required that studies involve a population of patients with MS, utilize the administration of DMTs, and report a measurement of adherence. Studies reporting persistence measures (e.g., treatment discontinuation rates) or rates of switching between DMTs (with no other measure of adherence reported) were excluded if they did not also assess adherence.

Among the 24 studies meeting inclusion criteria, adherence to DMTs ranged from 41% to 88%. Weighted mean adherence rates were higher for intramuscular (IM) interferon beta-1a (IFNβ-1a) administered once a week (69.4%), and subcutaneous (SC) IFNβ-1a administered every other day (63.8%) than for SC IFNβ-1b administered 3 times a week (58.4%) and glatiramer acetate administered daily (56.8%). There was a numerically greater risk of MS relapse or disease progression among patients nonadherent to therapy versus adherent patients, with findings statistically significant in 2 of 4 studies. Additionally, 2 studies showed statistically significant reductions in inpatient or emergency room utilization and total MS-related medical costs among patients adherent to therapy compared with nonadherent patients. Higher patient out-of-pocket copayments and coinsurance were significantly associated with lower adherence to DMTs, while the use of interventional or disease therapy management programs were associated with improved adherence.

Lack of medication adherence remains a problem among patients with MS. Improvements in adherence have the potential to improve patient and payer burden in terms of improved clinical outcomes and lower nonpharmacy medical resource utilization.

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Summary Points Presented in this Article
• Because of the chronic nature of multiple sclerosis (MS), long-term adherence to disease-modifying therapies (DMTs) can be challenging.
• Common barriers to adherence include forgetting to inject; a patient-perceived lack of efficacy; anxiety over injections or self-injecting; and adverse effects, including injection site reactions, flu-like symptoms, and fatigue.
• Recent reviews have cited that 60% to 76% of patients are adherent to either interferon beta-1a (IFNβ-1a) or glatiramer acetate (GA) therapies. This review identified 24 studies of adherence to injectable DMTs (including once-weekly intramuscular [IM] and 3 times a week subcutaneous [SC] IFNβ-1a, every other day SC IFNβ-1b, and daily GA), with adherence rates ranging between 41% and 88%.
• Adherence was generally higher in studies with prospective rather than retrospective study designs. Weighted mean adherence rates were higher for IM IFNβ-1a (69.4%) and SC IFNβ-1a (63.8%) than for SC IFNβ-1b (58.4%) and GA (56.8%).
• Selected studies showed that patients who were more adherent to therapy had a lower risk of MS relapse. One study showed patients adherent to therapy had a lower risk of MS-related hospitalizations and lower total MS-related costs (excluding pharmacy costs).

Multiple sclerosis (MS) is a chronic, recurrent inflammatory disease of the white and grey matter of the central nervous system (CNS), affecting approximately 400,000 persons in the United States and 2.5 million people worldwide.1 MS is characterized by inflammatory attacks on CNS myelin, thought to be autoimmune in nature, which result in a variety of symptoms such as blurred vision, walking and coordination problems, bladder or bowel dysfunction, numbness, and cognitive impairment. Relapsing-remitting MS (RRMS) is characterized by clearly defined attacks, or relapses, of worsening neurological function with periods of partial to complete recovery between each attack.2 This form of the disease comprises approximately 85% of presenting MS diagnoses.1

While no curative treatment exists for RRMS, several disease-modifying therapies (DMTs) have been developed to reduce relapse rates, slow disability progression, and modify the overall disease course.3 The U.S. Food and Drug Administration (FDA) has approved several DMTs (Table 1),4-12 including once-weekly intramuscular (IM) interferon beta-1a (IFNβ-1a; Avonex), 3 times a week subcutaneous (SC) IFNβ-1a (Rebif), alternating daily IFNβ-1b (Betaseron, Extavia), once-daily SC glatiramer acetate (GA; Copaxone), once-monthly intravenous (IV) natalizumab (Tysabri), and 4 times yearly IV
| Drug and Date of 
FDA Approval | Dosing and Administration | FDA-Approved Indications |
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta-1b SC (Betaseron)¹⁴ July 1993</td>
<td>“Recommended dose is 0.25 mg injected SC every other day. Generally, start at 0.0625 mg (0.25 mL) SC every other day, and increase over a 6-week period to 0.25 mg (1 mL) every other day.”</td>
<td>“Treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations. Patients with MS in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with MS.”</td>
</tr>
<tr>
<td>Interferon beta-1a IM (Avonex)³ May 1996</td>
<td>“The recommended dosage is 30 mcg injected IM once a week. To reduce the incidence and severity of flu-like symptoms that may occur when initiating Interferon beta-1a IM therapy at a dose of 30 mcg, Interferon beta-1a IM may be started at a dose of 7.5 mcg and the dose may be increased by 7.5 mcg each week for the next three weeks until the recommended dose of 30 mcg is achieved. All Interferon beta-1a IM dosage forms are single-use (injection of reconstituted solution, prefilled syringe, and prefilled autoinjector).”</td>
<td>“Treatment of patients with relapsing forms of MS to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Patients with MS in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with MS.”</td>
</tr>
<tr>
<td>Glatiramer acetate SC (Copaxone)⁶ December 1996</td>
<td>“For SC injection only, recommended dose is 20 mg/day.”</td>
<td>“Reduction of the frequency of relapses in patients with Relapsing-Remitting MS, including patients who have experienced a first clinical episode and have MRI features consistent with MS.”</td>
</tr>
<tr>
<td>Interferon beta-1a SC (Rebif)⁷ March 2002</td>
<td>“Dosages shown to be safe and effective are 22 mcg and 44 mcg injected SC 3 times per week (tw). IFN beta-1a SC should be administered, if possible, at the same time (preferably in the late afternoon or evening) on the same 3 days (e.g., Monday, Wednesday, and Friday) at least 48 hours apart each week. Generally, patients should be started at 20% of the prescribed dose tw and increased over a 4-week period to the targeted dose, either 22 mcg or 44 mcg tw.”</td>
<td>“Treatment of patients with relapsing forms of MS to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability. Efficacy in chronic progressive MS has not been established.”</td>
</tr>
<tr>
<td>Natalizumab (Tysabri)¹⁸ November 2004, reintroduced July 2006</td>
<td>“300 mg infused intravenously over approximately 1 hour, every 4 weeks. Do not give as an intravenous push or bolus. Natalizumab solution must be administered within 8 hours of preparation. Natalizumab is available only through a special restricted distribution program called the TOUCH Prescribing Program and must be administered only to patients enrolled in this program.”</td>
<td>“As monotherapy for the treatment of patients with relapsing forms of MS to reduce the frequency of clinical exacerbations. Natalizumab is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy.”</td>
</tr>
<tr>
<td>Interferon beta-1b SC (Extavia)⁹ August 2009</td>
<td>“The recommended dose is 0.25 mg injected SC every other day. Generally, patients should be started at 0.0625 mg (0.25 mL) SC every other day, and increased over a 6-week period to 0.25 mg (1 mL) every other day.”</td>
<td>“Treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations. Patients with MS in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with MS.”</td>
</tr>
<tr>
<td>Dalfampridine (Ampyra)¹⁰ January 2010</td>
<td>“Maximum recommended dose is 10 mg twice daily (approximately 12 hours apart) with or without food.”</td>
<td>“Indicated to improve walking in patients with MS. This was demonstrated by an increase in walking speed.”</td>
</tr>
<tr>
<td>Fingolimod (Gilenya)¹¹ September 2010</td>
<td>“The recommended dose is 0.5 mg orally once daily, with or without food.”</td>
<td>“Treatment of patients with relapsing forms of MS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.”</td>
</tr>
<tr>
<td>Mitoxantrone (Novantrone)¹² January 2000</td>
<td>“The recommended dosage of NOVANTRONE is 12 mg/m² given as a short (approximately 5 to 15 minutes) intravenous infusion every 3 months.”</td>
<td>“Reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (i.e., patients whose neurologic status is significantly abnormal between relapses). NOVANTRONE is not indicated in the treatment of patients with primary progressive multiple sclerosis.”</td>
</tr>
</tbody>
</table>

¹⁾Information for column 2 comes from the prescribing information for each drug, which is referenced in column 1.
FDA = U.S. Food and Drug Administration; IFN = interferon; IM = intramuscular; m² = meters squared; mcg = microgram; mg = milligram; mL = milliliter; MRI = magnetic resonance imaging; MS = multiple sclerosis; SC = subcutaneous; TOUCH = Tysabri Outreach: Unified Commitment to Health.

mitoxantrone (Novantrone).¹³ All injectable DMTs have been approved to reduce the frequency of clinical relapses, with IM IFNβ-1a, SC IFNβ-1a, and natalizumab also indicated by the FDA to slow disability progression; IM IFNβ-1a, SC IFNβ-1b, and GA are also indicated in patients who have experienced a first clinical episode and have magnetic resonance imaging (MRI) features consistent with MS (Table 1).³ In 2010, oral fingolimod (Gilenya) was approved by the FDA to reduce the frequency of clinical relapses and delay the accumulation of physical disability in patients with RRMS.³
Medication persistence is commonly reported in the MS literature as the percentage of patients discontinuing therapy or with a significant gap in therapy (e.g., at least more than a 30-day gap). We chose to focus on adherence rates in this review, as this not only encompasses treatment discontinuations, but also the actual patient experience while on treatment in terms of the number of doses taken as prescribed. This gives a fuller picture of the proportion of patients who not only are able to actively remain on therapy, but who also are able to follow a complex and often burdensome treatment regimen.

As new treatments are developed for MS, a comprehensive understanding of current adherence rates and the impact of adherence on clinical and economic outcomes will be beneficial in clinical decision making and overall disease management. In addition to the traditional factors of clinical efficacy, safety, and costs, differences in patient adherence to therapies in MS may be important in formulary decision making. Our objective was to conduct a thorough review of the literature to evaluate various definitions and rates of adherence to MS DMTs, the impact of adherence on clinical outcomes and resource use and costs, and the implications of adherence to DMTs for both patients and payers.

Because of the chronic nature of the disease, long-term therapy adherence can be challenging for some patients with MS. Common barriers to adherence with injectable DMTs include forgetting to inject; patient-perceived lack of efficacy; injection anxiety; and adverse effects, including injection-site reactions, flu-like symptoms, and fatigue. Nonadherence to DMTs has been shown to have a negative impact on clinical outcomes, including higher rates of relapse and disease progression, as well as an increase in hospital resource utilization. However, according to the the European Multiple Sclerosis Therapy Consensus Group (MSTCG) guidelines, patients may discontinue treatment with DMTs after 3 years, if there is no evidence of relapse and/or progression.

This review focuses on patient adherence to therapy, a distinct concept from persistence to therapy. As defined by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Special Interest Group, adherence is the percentage of doses taken as prescribed, over a set time period for analysis (either from the first to last medication dispensing date or for a fixed follow-up time frame). Persistence is defined as the total number of days taking medication over a set time period. Medication persistence is commonly reported in the MS literature as the percentage of patients discontinuing therapy or with a significant gap in therapy (e.g., at least more than a 30-day gap). We chose to focus on adherence rates in this review, as this not only encompasses treatment discontinuations, but also the actual patient experience while on treatment in terms of the number of doses taken as prescribed. This gives a fuller picture of the proportion of patients who not only are able to actively remain on therapy, but who also are able to follow a complex and often burdensome treatment regimen.

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Narrative Review of the Literature on Adherence to Disease-Modifying Therapies Among Patients with Multiple Sclerosis

Methods

Literature search strategies and data extraction were followed as outlined in the Cochrane Collaboration Handbook of Systematic Reviews for Interventions. This included pre-specifying a search strategy and search terms; use of MEDLINE, EMBASE, and the Cochrane library; and use of 2 reviewers. Two reviewers created search terms; 1 reviewer scanned preliminary titles returned in the search results; 1 reviewer performed supplementary searches using author names and conference abstracts; and 2 reviewers evaluated the full list of potentially relevant abstracts to select studies relevant for full-text review.

Systematic literature searches were conducted using MEDLINE (PubMed), EMBASE, and the Cochrane Central Register for Controlled Trials, using the same search terms in all databases, as summarized in Appendix A. In order to cross-check findings from these searches, reference lists of all relevant review articles retrieved were examined to identify any additional publications not returned in the database searches. Additionally, targeted searches of neurological and MS-specific conferences were conducted to identify relevant abstracts that may have resulted in full-text publications not already identified through the database searches described above. Conferences included the American Academy of Neurology (AAN), the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), and the European Federation of Neurological Societies (EFNS). PubMed and the Internet were used to identify any full-text publications resulting from relevant abstracts.

Studies were limited to those completed on human subjects, written in the English language, and published between May 1, 2001, and May 1, 2011. Additional inclusion criteria required that studies involve a population of patients with MS, utilize the administration of DMTs, and report a measurement of adherence. Studies reporting persistence measures (e.g., treatment discontinuation rates) or rates of switching between DMTs (with no other measure of adherence reported) were excluded if they did not also cover adherence. These persistence-only articles were not evaluated in this review, since we were interested in assessing the full patient experience while on therapy (i.e., dosing taken as prescribed).

A total of 257 unique titles was initially identified through the search methodology previously outlined, of which 101 abstracts were reviewed in more detail; 33 full texts were pulled; and 24 full texts summarized. Main exclusionary criteria included studies with no measures of medication adherence reported (i.e., persistence only, adherence to guidelines) and general opinion or discussion pieces with no adherence rates reported. Figure 1 provides a complete flowchart of the study selection methodology. For each study meeting our selection criteria, the following data were abstracted: study type and objective, DMT type(s) evaluated, patient population, study period/duration of follow-up, definition of adherence, reported adherence rates, study limitations, and implications.

Results

Of the 24 studies included in this review, 16 were prospective observational studies, and 8 were retrospective database or cohort studies. In the following sections, we provide a brief description of the studies included, specific definitions of treatment adherence used, adherence rates by DMT agent and study design, and the relationship between therapy nonadherence and clinical and economic outcomes. Appendix B provides a full description of each study, including the author, year of publication, and study sponsor; treatments and the specific patient population evaluated; mean time since MS diagnosis and mean duration on MS therapy; length of follow-up over which adherence was measured; definition of adherence; and adherence rates reported.

Studies included in this review varied in terms of the patient population, with 11 studies examining patients with RRMS only,16,23,25-33 12 studies examining patients with any form of MS,17,18,34-43 and only 1 study examining the progressive form of the disease exclusively.44 Among studies reporting time since MS diagnosis, mean time since diagnosis ranged between 2 and 12 years. All prospective studies included patients who were already on some form of DMT prior to assessing adherence (mean years on therapy ranged from 2 to 6 years across studies).25,30,44 Three retrospective studies evaluated adherence specifically among those initiating a DMT,17,40,42 while the remaining 5 either did not specify prior treatment or included patients who had already received treatment with a DMT.16,18,41,43

There were 6 different measures used in the literature to measure patient adherence, including 2 variations of the medication possession ratio (MPR; used among 11 studies), the missed dose ratio (MDR; 3 studies), total number of missed doses (2 studies), percentage of days not covered by therapy (2 studies), and no missed doses over a pre-specified time period (7 studies). The MPR was most commonly used to quantify patient adherence and was calculated using either a fixed-interval or variable-interval approach. The fixed-interval approach divided the total number of days supply of a DMT dispensed by a fixed-time interval (e.g., 365 days), while the variable-interval approach divided the total number of days supply by the time (in days) between the first and last dispensing date. The third ratio used was the MDR, which accounted for variability in dosing frequencies across DMTs. The following MDR methodology was used by Siegel et al. (2008): a single missed dose of once-weekly IM IFNβ-1a was equated to a weight of 7.5 (i.e., 7.5 × 4 doses per month totals 30 days), while a missed dose of once-daily GA was given a weight of 1 (i.e., 1 × 30 doses per month totals 30 days).37 However, other studies simply reported a total number of missed doses or the percentage with no missed doses over a specific time period, regardless of differing dosing regimens. The most advanced
measurement of adherence assessed the percentage of days not covered with a DMT using an electronic Medication Event Monitoring System (MEMS). This system used an electronic monitoring cap to record the date and time of a DMT needle disposal by a patient in order to measure the number of individual days in which a medication was not taken (adjusted for variable dosing frequencies).29

When looking across all studies identified in this review, adherence to DMTs ranged between 41% and 88%, regardless of adherence definition used, type of DMT agent, or study design. Adherence rates were higher for IM IFNβ-1a (69.4%) and SC IFNβ-1a (63.8%) than for SC IFNβ-1b (58.4%) and GA (56.8%; Table 2 and Figure 2). Of the 6 studies that reported statistical differences in adherence rates by DMT agent, 3 showed that patients treated with IM IFNβ-1a had statistically better adherence compared with those treated with SC GA, SC IFNβ-1a, or SC IFNβ-1b (in terms of MPR, percentage with at least 1 missed dose in the past month, or mean number of missed doses in the past 28 days).22,34,40 An additional study showed IM IFNβ-1a to have significantly better adherence than SC IFNβ-1a and SC GA at baseline; however, no significant difference was observed in a survey administered at 2 years of follow-up.25 In another study that did not report a specific adherence threshold rate (i.e., did not report a cut-off MPR value to specify adherence), patients treated with IM IFNβ-1a had statistically higher MPRs than patients treated with the 3 other DMTs.42

When stratifying adherence by study type, adherence was greater among studies with a prospective study design (weighted by study sample size, mean adherence of 72.8%) compared with those with a retrospective study design (53.1%). Of the studies reporting adherence by DMT agent in Table 2, only Halpern et al. (2011) used a retrospective study design.40 Among prospective studies only, the weighted mean adherence by DMT agent is IM IFNβ-1a (83.9%) > SC IFNβ-1a (72.0%) > SC IFNβ-1b (64.7%) > SC GA (60.4%; Figure 2).

Of particular importance, improved patient adherence to DMTs may lead to better clinical outcomes, including risk of relapse or MS disease progression. In a large retrospective database study using claims data from 2,446 privately insured patients initiating a DMT, patients who were adherent

### TABLE 2 Rates of Adherence by DMT Agent

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study</th>
<th>Reference</th>
<th>Adherence Rate (%)</th>
<th>N</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM IFNβ-1a</td>
<td>Arroyo 2011a</td>
<td>25</td>
<td>87.5</td>
<td>56</td>
<td>Prospective</td>
</tr>
<tr>
<td></td>
<td>Devonshire 2011b</td>
<td>26</td>
<td>85.0</td>
<td>764</td>
<td>Prospective</td>
</tr>
<tr>
<td></td>
<td>Wicks 2011c</td>
<td>34</td>
<td>84.0</td>
<td>87</td>
<td>Prospective</td>
</tr>
<tr>
<td></td>
<td>Treadaway 2009d</td>
<td>31</td>
<td>79.0</td>
<td>223</td>
<td>Prospective</td>
</tr>
<tr>
<td></td>
<td>Halpern 2011e</td>
<td>40</td>
<td>62.3</td>
<td>2,305</td>
<td>Prospective</td>
</tr>
<tr>
<td></td>
<td>Weighted Mean</td>
<td></td>
<td>69.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC IFNβ-1a</td>
<td>Arroyo 2011a</td>
<td>25</td>
<td>77.6</td>
<td>54</td>
<td>Prospective</td>
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<tr>
<td></td>
<td>Devonshire 2011b</td>
<td>26</td>
<td>73.0</td>
<td>511</td>
<td>Prospective</td>
</tr>
<tr>
<td></td>
<td>Wicks 2011c</td>
<td>34</td>
<td>69.0</td>
<td>81</td>
<td>Prospective</td>
</tr>
<tr>
<td></td>
<td>Treadaway 2009d</td>
<td>31</td>
<td>68.0</td>
<td>149</td>
<td>Prospective</td>
</tr>
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<td></td>
<td>Halpern 2011e</td>
<td>40</td>
<td>58.5</td>
<td>1,211</td>
<td>Prospective</td>
</tr>
<tr>
<td></td>
<td>Weighted Mean</td>
<td></td>
<td>63.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC IFNβ-1b</td>
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<td>25</td>
<td>85.2</td>
<td>49</td>
<td>Prospective</td>
</tr>
<tr>
<td></td>
<td>Devonshire 2011b</td>
<td>26</td>
<td>70.0</td>
<td>571</td>
<td>Prospective</td>
</tr>
<tr>
<td></td>
<td>Wicks 2011c</td>
<td>34</td>
<td>51.0</td>
<td>63</td>
<td>Prospective</td>
</tr>
<tr>
<td></td>
<td>Halpern 2011e</td>
<td>40</td>
<td>52.2</td>
<td>894</td>
<td>Prospective</td>
</tr>
<tr>
<td></td>
<td>Treadaway 2009d</td>
<td>31</td>
<td>49.0</td>
<td>203</td>
<td>Prospective</td>
</tr>
<tr>
<td></td>
<td>Weighted Mean</td>
<td></td>
<td>58.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC GA</td>
<td>Arroyo 2011a</td>
<td>25</td>
<td>80.0</td>
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<td>66.0</td>
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<td>Halpern 2011e</td>
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<td>2,270</td>
<td>Prospective</td>
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<tr>
<td></td>
<td>Treadaway 2009d</td>
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<td>49.0</td>
<td>223</td>
<td>Prospective</td>
</tr>
<tr>
<td></td>
<td>Wicks 2011c</td>
<td>34</td>
<td>49.0</td>
<td>101</td>
<td>Prospective</td>
</tr>
<tr>
<td></td>
<td>Weighted Mean</td>
<td></td>
<td>56.8%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

:aAdherence defined as no missed injection in past 4 weeks (as measured at last follow-up visit).
bAdherence defined as no missed injection in past 4 weeks. For SC IFNβ-1a used values reported for 44 mcg dosing.
cAdherence defined as missing at least 1 dose in past 28 days.
dAdherence defined as no missed injection in past 4 weeks.
eAdherence defined with MPR (variable interval), with adherent patients having an MPR ≥ 80%.
fWeighted by study sample sizes.

DMT = disease-modifying therapy; GA = glatiramer acetate; IM = intramuscular; IFNβ = interferon beta; mcg = microgram; MPR = medication possession ratio; SC = subcutaneous.
to therapy (defined as an MPR ≥ 80%) were significantly less likely to experience a relapse in 1 year of follow-up compared with patients who were nonadherent to therapy (odds ratio [OR] = 0.71; 95% confidence interval [CI] 0.59-0.85), controlling for baseline demographics, health plan type, geographic region, Charlson score (a measure of patient comorbidity burden), specific comorbid conditions, and baseline health care utilization.17 In another retrospective database study by Steinberg et al. (2010), it was shown that patients who were adherent to therapy (defined as an MPR ≥ 85% in the base year of 2005) had a significantly lower risk of relapse in the first year of follow-up (relative risk [RR] = 0.89; 95% CI = 0.81-0.97; P < 0.05); however, this did not hold true in years 2 or 3 of follow-up.16 When stratifying based on varying adherence thresholds (MPRs of < 70%, < 65%, and < 60%), lower levels of adherence were significantly associated with a higher risk of relapse any time over the 3-year study period (P < 0.05).16

In addition to improved clinical outcomes, patients more adherent to a DMT may have lower medical resource utilization and costs. A retrospective study by Tan et al. (2011) found that patients who were adherent to therapy were significantly less likely to experience an MS-related inpatient hospitalization than those who were nonadherent (OR = 0.63; 95% CI = 0.47-0.83; P = 0.001) and had significantly lower annual MS-related medical costs (excluding pharmacy; adjusted mean $3,380 [95% CI: $3,046-$3,750] vs. $4,348 [95% CI: $3,828-$4,940; P = 0.003]).17 There was no significant association between adherence and MS-related emergency room (ER) visits. In a separate retrospective study by Steinberg et al. that evaluated all-cause inpatient and ER visits, no significant difference was shown in resource use between adherent and nonadherent patients.16

In addition to patient-centered reasons for nonadherence, such as forgetting to inject, self-injection fears and problems, adverse effects, and either real or perceived lack of efficacy, among others, literature also suggests a link between the magnitude of out-of-pocket DMT treatment costs and patient adherence. In a study of 224 patients enrolled in a large multispecialty practice, patients with greater copayments (each $5 increase in copayment amount) had significantly lower adherence compared with those with lower copayments (OR = 0.72; 95% CI = 0.57-0.92; for each $5 increase).23 However, this association only held for the MPR definition using a fixed denominator (730-day observation period, mean MPR of 68.0%) versus the variable-interval MPR definition (mean 580-day observation period, mean MPR of 83.8%).23 Another
retrospective study of 1,974 commercially insured patients on DMTs found a significant association between coinsurance levels and adherence. A 10% increase in cost sharing in the first 6 months following initiation of a DMT was associated with an 8.6% decline in adherence in the following 12 months (adjusting for demographic variables, Charlson score, and other baseline comorbid diagnoses).

There is some literature pointing to a positive impact of interventional programs on patient adherence to therapy. Stockl et al. (2010) evaluated the effect of a disease therapy management program on patient adherence to MS therapies compared with those receiving prescriptions through a specialty pharmacy with no disease therapy management program implemented and also with patients receiving prescriptions from a regular retail pharmacy. The disease therapy management program consisted of telephone consultations, a care plan developed by the physician and sent to both the patient and pharmacist, and educational mailings. Results showed that adherence was significantly better in the disease therapy management group (mean [SD] MPR = 0.92 [0.13]) compared with the retail pharmacy group (mean [SD] MPR = 0.86 [0.18], \( P < 0.001 \)), but not when compared with the specialty pharmacy-alone group (mean [SD] MPR = 0.90 [0.16], \( P = 0.23 \)). In a study evaluating the impact of a specialty care management program (consisting of mailed medications and educational materials and nurse assessment phone calls), the mean [SD] MPR of patients participating in the program was significantly higher (0.86 [0.20]) compared with nonparticipants (0.64 [0.33], \( P < 0.001 \)). Additionally, participants in the program were significantly less likely to experience an MS-related hospitalization in 1 year of follow-up compared with those not participating in the care management program (adjusted OR = 0.51, 95% CI = 0.39–0.67). Total MS-related medical costs (excluding pharmacy) decreased by $264 in 1 year of follow-up among program participants while costs increased by $1,536 among nonparticipants.

**Discussion**

This review of adherence to DMTs found that adherence rates ranged from 41% to 88%, with lower estimates reported for retrospective (weighted mean adherence 53.1%) versus prospective study designs (weighted mean adherence 72.8%). Among studies reporting adherence by DMT agent, IM IFN-\( \beta \) was generally associated with the highest rate of adherence (weighted mean adherence 69.4%). In some studies, patients who were adherent were found to have a lower risk of relapse as well as lower risk of inpatient or ER visits and lower total MS-related costs (excluding pharmacy costs).30,37,32

Many other chronic conditions have assessed adherence primarily to oral (not injectable) therapies, making direct comparisons of adherence rates difficult. However, in a recent systematic review of medication adherence among patients with rheumatic conditions, 1 study included in the review assessed adherence to the self-injectable medication etanercept among patients with rheumatoid arthritis (RA). Adherence in this study was assessed through retrospective review of pharmacy records and was defined as an MPR ≥ 80%.43 Adherence over the 1 year following treatment initiation was measured at 68%, which is similar to rates (52%-68%) reported in 3 database studies of MS therapies that used a similar definition of adherence (MPR ≥ 80%).17,23,40

This review assessed adherence only (evaluating the extent to which patients followed a prescribed dosing schedule over a specified time period) and not persistence (percentage remaining on treatment, i.e., treatment discontinuations). We chose to examine only adherence measures in this review as it provides a fuller evaluation of the patient experience while on treatment. However, future reviews could be focused on the rates of treatment discontinuation among different DMTs. One review by Costello et al. (2008) evaluated this set of literature, citing that approximately 60% to 76% of patients remain on IFN-\( \beta \) or GA for 2 to 5 years.15 However, several studies, including an analysis of persistence, have been published since the Costello et al. review, such as the retrospective database analyses by Kleinman et al. (2010), Reynolds et al. (2010), and Wong et al. (2011). Future research is warranted to evaluate persistence to therapy over variable follow-up time periods, specific to each DMT.15,22,42,46

There are various pros and cons associated with each of the adherence definitions used in the MS literature. Fixed-interval MPR allows for more consistent comparison of MPRs across studies (providing the same length of time is used for the denominator). However, this approach does not account for any discontinuations in therapy, which may lead to an inaccurate MPR estimate. In comparison, variable-interval MPR does account for patient discontinuations in therapy but may not be as useful for comparison across studies due to highly variable denominators. Studies that did not account for variability in DMT dosing regimens may have over-reported or under-reported actual adherence rates dependent upon the specific mix of therapies the patient populations were prescribed. The strictest measure of adherence used in the literature defined patients as adherent only if there were no missed doses within a specified time period. This dichotomous measure does not fully capture the degree of patient adherence, as some patients may have missed only 1 dose while others may have missed several. Not surprisingly, this measure gave the lowest adherence estimates. Finally, one of the retrospective studies identified in this review examined adherence and its association with MS relapse or progression rates over the same follow-up time period. This study design may lead to confounding results, since patients could potentially have exhibited lower adherence due to a relapse, rather than low adherence subsequently causing a relapse.17 Future studies should have well-defined baseline periods for assessing adherence and then nonoverlapping follow-up time periods to look for evidence of disease relapse.
The measures of adherence reported in this review are focused on MPRs and other similar health-economic measures. It should be noted that other definitions of adherence exist that are more patient focused. Adherence in the MS community can alternatively be defined as a patient's continuous, voluntary, and collaborative participation in a mutually accepted behavior, resulting in a specific therapeutic outcome. This emphasis on patient-provider collaboration is not identified through traditional measurements of adherence (i.e., MPRs), which primarily focuses on a patient's commitment to prescribed dosing intervals.

Generally, prospective studies have relied on patient self-report for adherence estimates while retrospective studies used prescription claims data. Patient self-report may be inaccurate due to the cognitive decline associated with progressing MS and the inability to accurately recall missed doses over the entire observation period (often the prior month). Retrospective claims data are limited in that these analyses assume that all doses filled were properly taken by the patient. In real-world practice, just because a medication was dispensed does not ensure proper administration. Only 1 study in this review utilized an advanced MEMS system that used an electronic monitoring cap to record the date and time of a DMT needle disposal by a patient, thus addressing the issue of actual medication dosing as opposed to simply filling a prescription. Additionally, there are limitations with the accuracy of coding in retrospective claims data used in retrospective studies. Since DMTs can be covered under both pharmacy and medical benefits, studies based on pharmacy claims alone for evaluation of DMTs prescribed could miss patients whose MS drug coverage was wholly or partially under a medical benefit. For example, 1 study of managed care organizations showed that almost half (49%) covered self-injectable MS drugs under the pharmacy benefit; 38% covered them under both the pharmacy and medical benefit; and 13% covered them under the medical benefit only.

In an analysis of Medicaid claims data versus written medical records, injection frequencies of palivizumab (a humanized monoclonal antibody used to prevent serious respiratory syncytial virus in children) matched for only 46% of patients. While this drug is administered in the office setting, unlike the vast majority of MS therapies, it still highlights the lack of accuracy of coding for injectable medications. Finally, a retrospective study identified in this review found that DMT adherence (≥ 80% adherent based on using the medication possession ratio) significantly reduced the mean MS relapse rate compared with the rate for patients that were <80% adherent over a 12-month follow-up period (27.3% vs. 34.7%, P < 0.001). However, the observation database study was limited by not having data on patient MS type or disability level, although the study groups had similar baseline MS-related symptoms.

This literature review highlights the importance of improved adherence to therapy. Two studies showed a significant association between greater treatment adherence and a lower risk of MS relapse while one showed a significant association between nonadherence and greater MS-related inpatient utilization and total MS-related medical costs. Another study, which was published after this literature search was conducted, found that adherence to DMTs was associated with a lower rate of severe relapse and lower direct and indirect costs. These findings are of importance to payers as improved patient adherence may be associated with better patient outcomes and thus lower MS-related medical resource utilization and costs. In order to achieve such savings, there are several opportunities to improve patient adherence. Several studies have pointed to specific patient populations that are at high risk of nonadherence, including patients with high injection anxiety, mental illness, lower perceptions of injection self-efficacy (i.e., the ability to self-inject), or the misconception that the drug is not working for them because they do not see immediate or daily benefits from injections. The implementation of targeted disease therapy management programs may help to improve adherence among these patients. We identified 2 studies in the recent literature that concluded that use of disease therapy management or interventional programs among broader (nontargeted) cohorts of patients with MS have improved patient adherence to DMTs. If these programs were implemented among the targeted high-risk populations mentioned above, it may be possible to achieve greater adherence, although results would need to be confirmed with a randomized controlled trial.

Two studies have shown a link between higher patient copays or coinsurance and diminished adherence to DMTs suggesting that reducing patient out-of-pocket (OOP) pharmacy burden may be an opportunity to improve adherence, either through lower copayments or coinsurance levels. However, as these were the only 2 studies identified linking patient financial burden to adherence, further study is needed to confirm these findings. If improvements in adherence were marked enough, there could be opportunities for cost savings in terms of reduced medical resource use. However, there is a need for further study evaluating the direct impact of reduced patient OOP burden on MS relapse rates and associated MS-related medical resource use and costs, as well as costs to payers.

To our knowledge, there is no support in the literature for a direct link between patient adherence to DMTs and health-related quality of life (HRQoL). A recent systematic review that evaluated the effect of DMTs on HRQoL in patients with MS concluded that there is evidence from randomized controlled trials (RCTs) and nonrandomized prospective studies that IM and SC IFNβ-1a or SC IFNβ-1b improves HRQoL in patients with secondary progressive MS. However, evidence among patients with RRMS is less conclusive as studies used varying instruments that are not directly comparable. It may be indirectly inferred from available literature that since
diminished adherence can lead to greater risk of relapse\textsuperscript{16,17} and progression in disability has been suggested in 1 small prospective study to lower QoL.\textsuperscript{52} Adherence may have an impact on a patient’s overall HRQoL. Nonetheless, further empirical research is needed to directly quantify the effects of patient adherence to therapy and its effect on QoL.

With the advent of oral therapies, there will likely be concern over the high costs of these novel drugs to patients in addition to payers. If the ease of oral administration significantly improves patient adherence in comparison with standard injectable therapies, there is potential for some cost offsets in the form of lower MS-related medical resource use and costs. In addition, oral therapy has the potential to impact patient QoL by eliminating the need for frequent injections. It will be important to study the effect of oral administration on patient adherence, as well as on the difference in adherence rates between injection and oral administration, in real-world practice.

**Conclusions**

Current published literature has shown that lack of medication adherence remains a significant problem among patients with MS. There is a need for further study in this area, such as using reliable and valid adherence measures, conducting studies based on a large nationally representative cohort of patients with MS, understanding the impact of mode of administration or injection frequency on adherence, and evaluating the direct impact of patient OOP burden on DMT adherence and associated MS-related resource use and costs. Large databases contain medical and pharmacy claims data that could be used to examine many of these adherence-related research questions in a retrospective fashion. It is notable, however, that only 6 of the 21 studies identified in this review used retrospective claims data.\textsuperscript{16-18,40-42} Large claims databases also have been used in recent studies to examine MS-related costs.\textsuperscript{53-57} With the rich amount of claims information available to individual health plans, further studies in specific populations to quantify the impact of DMT adherence on clinical and economic outcomes for patients with MS would be of great interest.

**DISCLOSURES**

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**REFERENCES**


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Narrative Review of the Literature on Adherence to Disease-Modifying Therapies Among Patients with Multiple Sclerosis


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**APPENDIX A Literature Search Terms**

- (“Multiple Sclerosis” [MeSH] AND “Medication Adherence” [MeSH])
- (“Multiple Sclerosis” [MeSH]) and (Anti-rheumatic Agents [MeSH] OR “Medication Adherence” [MeSH])
- (“Multiple Sclerosis” [MeSH] or “Multiple sclerosis” [All Fields]) AND (((“interferon beta 1a” [Supplementary Concept]) OR “interferon beta-1b” [Supplementary Concept]) OR “copolymer 1” [Supplementary Concept]) OR “fingolimod” [Supplementary Concept]) OR “Mitoxantrone” [MeSH]) OR “natalizumab” [Supplementary Concept]) AND Adherence [All Fields]
- (“Multiple Sclerosis/drug therapy” [MeSH] OR “Multiple Sclerosis/therapy” [MeSH]) AND (adherence [All Fields] OR persistence [All Fields])
- (“Multiple Sclerosis” [MeSH]) AND “Patient Compliance” [MeSH])

All search terms used in MEDLINE (PubMed) searching.

*Used in PubMed, EMBASE, and Cochrane Register of randomized controlled trials (RCTs).

*Used in PubMed and Cochrane Register of RCTs.*
# APPENDIX B Description of Studies Included in Literature Review

## PROSPECTIVE STUDIES

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<tr>
<td>1</td>
<td>Arroyo 2011 (Biogen Idec)</td>
<td>SC IFNβ-1a (22 mcg, n = 43) SC IFNβ-1a (44 mcg, n = 54) SC IFNβ-1b (n = 49) IM IFNβ-1a (n = 56) SC GA (n = 52)</td>
<td>Spanish patients with RRMS; &gt; 18 years old; on monotherapy with current DMT for &gt; 6 months prior to study enrollment (Spanish subset of Devonshire 2011 study population) Excluded if progressive MS, patient involved in drug studies within 6 months of enrollment, undergone treatment with immunosuppressive drugs or IVIG in last 12 months</td>
<td>6 years (range 0-37)</td>
<td>28 months (range 0-124)</td>
<td>2 years</td>
<td>Not missing a single DMT injection in past 4 weeks (by self-report and by neurologist report)</td>
<td>As last follow-up visit: • 82.4% adherence rate • Adherence not significantly different across DMTs</td>
</tr>
<tr>
<td>2</td>
<td>Devonshire 2011 (Biogen Idec)</td>
<td>SC IFNβ-1a (22 mcg) (n = 245) SC IFNβ-1a (44 mcg) (n = 511) SC IFNβ-1b (n = 571) IM IFNβ-1a (n = 764) SC GA (n = 475)</td>
<td>Patients with RRMS; &gt; 18 years old; on monotherapy with current DMT for &gt; 6 months prior to study enrollment Excluded if progressive MS, patient involved in drug studies within 6 months of enrollment, undergone treatment with immunosuppressive drugs or IVIG in last 12 months Patients enrolled from 22 countries</td>
<td>6 years (range 0-56)</td>
<td>31 months (range 0-192)</td>
<td>4 weeks</td>
<td>Not missing a single DMT injection in past 4 weeks (patients filled out retrospective questionnaire)</td>
<td>Overall: 73% IM IFNβ-1a: 85% SC IFNβ-1a (22 mcg): 78% SC IFNβ-1a (44 mcg): 73% SC IFNβ-1b: 70% SC GA: 66% Adherence significantly higher for IM IFNβ-1a than all other DMTs (P &lt; 0.01)</td>
</tr>
<tr>
<td>3</td>
<td>Hancock 2011 (National MS Society)</td>
<td>SC GA (n = 59) IM IFNβ-1a (n = 7) SC IFNβ-1b (n = 9) *Adherence not stratified by treatment type</td>
<td>Same population as the Bruce 2010 (National MS Society) study: &quot;RRMS patients with no alcohol/drug abuse, no other nervous system disorder, no relapse and/or corticosteroid use within 4 weeks, an absence of severe physical impairment, and the use of an injected DMT for at least 2 months&quot;</td>
<td>117.38 months (SD = 90.27)</td>
<td>N/A</td>
<td>8 weeks</td>
<td>Percentage of days not covered by DMT was monitored using MEMS (specific to the prescribed dosage of DMT; e.g., missing a 1x weekly dosing equals 7 days not covered) Additionally, patient adherence diaries and self-report were used</td>
<td>Adherence rates not reported, only relational data: Patients with higher annualized relapse rates prior to start of study had significantly lower percentage of missed doses using the MEMS, adherence diary, and self-reported methodology for tracking adherence: • MEMS (r = 0.327, P &lt; 0.01) • Diary (r = 0.312, P &lt; 0.01) • Self-report (r = 0.383, P &lt; 0.01)</td>
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## APPENDIX B

### Description of Studies Included in Literature Review (continued)

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| 4  | Wicks 2011 (Novartis Pharmaceuticals Corp./PatientsLikeMe, Inc.) | SC GA (n = 101) | Patients self-reporting a MS diagnosis recruited from an online community (PatientsLikeMe) to participate in online survey (MS-TAQ) | 11 years [SD = 9] | 22 months | N/A | MDR = (no. of doses missed)/ (no. of prescribed doses in 28 days) | Overall 16%-51% of patients reported missing ≥1 dose of their DMT in the past 28 days:
SC GA: 51% missed ≥1 dose; MDR 0.08
IM IFNβ-1a: 16%; MDR 0.07
SC IFNβ-1a: 31%; MDR 0.09
SC IFNβ-1b: 49%; MDR 0.14 |
| 5  | Zwibel 2011 (Teva Pharmaceuticals) | SC GA (N = 234) | Patients > 18 years old with RRMS receiving GA therapy for the first time. Excluded if illness other than MS, hypersensitivity to GA, or pregnant/breastfeeding. Patients were either: Treatment-naïve (TN): no prior IMT experience (n = 146) Treatment-experienced (TE): had used IFNβ-1a therapy previously (n = 88); IM IFNβ-1a was most common prior therapy | Adherent: 4.2 years [SD = 6.0] Nonadherent: 1.9 years [SD = 3.9] | N/A | 12 weeks | Adherence based on response to the following:
"Has the patient used the study therapy continuously for the past month or 2 months? If the patient stopped therapy, is the patient willing to restart?"
*If patient stopped therapy, but was willing to restart at office visit, patient was considered adherent |
| 6  | Bruce 2010 (National MS Society) | SC GA (n = 53) | RRMS patients with no alcohol/drug abuse, no other nervous system disorder, no relapse and/or corticosteroid use within 4 weeks, an absence of severe physical impairment, and the use of an injected DMT for at least 2 months | 10.04 years [SD = 7.75] | 3.91 years [SD = 3.69] | 8 weeks | Percentage of DMT doses missed:
Poor adherence: 20% Variable adherence: 10%-19.99%
Adequate adherence: 1%-9.99%
Excellent adherence: 0-0.99% Measured using MEMS - percentage of days not covered by DMT. Additionally, patient adherence diaries and self-report were used for percentage of doses missed |

### Narrative Review of the Literature on Adherence to Disease-Modifying Therapies Among Patients with Multiple Sclerosis
# APPENDIX B

## Description of Studies Included in Literature Review (continued)

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<tr>
<td>7</td>
<td>Bruce 2010 (National MS Society)</td>
<td>SC GA (n = 45) IM IFNβ-1a (n = 3) SC IFNβ-1b (n = 7) <em>Adherence not stratified by treatment type</em></td>
<td>RRMS patients with no alcohol/drug abuse, no other nervous system disorder, no relapse and/or corticosteroid use within 4 weeks, an absence of severe physical impairment, and the use of an injected DMT for at least 2 months, no assistance taking DMT, no history of learning disability, less than 61 years of age</td>
<td>8.51 years [SD = 3.99]</td>
<td>5.72 years [SD = 3.49]</td>
<td>8 weeks</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>8</td>
<td>Stockl 2010 (No outside funding)</td>
<td>IM IFNβ-1a (n = 137) SC IFNβ-1b (n = 92) SC GA (n = 149) SC IFNβ-1a (n = 90) Total N = 468</td>
<td>Claims data population (disease therapy management group): Completed DMT program AND had filled prescription for an injectable MS medication at the PBM’s specialty pharmacy Specialty pharmacy group: Claim for injectable MS medication in PBM’s specialty pharmacy but did not complete the therapy management program Retail group: Injectable MS medication claim from location other than PBM’s specialty pharmacy</td>
<td>N/A</td>
<td>N/A</td>
<td>8 months</td>
<td>MPR - level for adherence not specified; MPRs compared between populations</td>
<td>MPR: Therapy management group: 0.92 [SD = 0.13] Specialty pharmacy group: 0.90 [SD = 0.16] Retail pharmacy group: 0.86 [SD = 0.18] Adherence significantly better in the therapy management group compared with retail pharmacy group (P &lt; 0.001)</td>
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<tr>
<td>9</td>
<td>Treadaway 2009 (Biogen Idec)</td>
<td>SC GA (n = 223) SC IFNβ-1b (n = 203) IM IFNβ-1a (n = 223) SC IFNβ-1a (n = 149)</td>
<td>Relapsing form of MS; 18 years or older; maintained therapy with 1 DMT for at least 6 months</td>
<td>7.3 years [SD = 6.28]</td>
<td>All participants at least 6 months; majority &gt; 2 years</td>
<td>2 months</td>
<td>Missing any injection in prior 4 weeks</td>
<td>Treatment specific nonadherence rates: • SC GA: 51% • SC IFNβ-1b: 51% • IM IFNβ-1a: 21% • SC IFNβ-1a: 32%</td>
</tr>
<tr>
<td>10</td>
<td>Turner 2009 (Dept. of VA Rehabilitation Research)</td>
<td>SC IFNβ-1a (n = 8) SC IFNβ-1b (n = 19) IM IFNβ-1a (n = 20) SC GA (n = 42)</td>
<td>Patients with diagnosis of MS and currently self-administering a DMT, visiting an outpatient MS clinic at a VA medical center (N=89). Patients had been on therapy for a mean of 3.4 years Excluded if injections primarily from an injection clinic nurse or caregiver</td>
<td>11.79 [SD = 7.93]</td>
<td>3.43 years [SD = 3.29]</td>
<td>6 months</td>
<td>See definition below in Turner 2007 [26 (#13)]</td>
<td>Rates primarily assessed in Bruce 2010 [29] In multivariate analysis controlling for demographics, MS disability, DMT type, and time on DMT, higher baseline injection anxiety significantly predicted lower adherence at 4 months (OR = 0.44; 95% CI = 0.20-0.96) and 6 months (OR = 0.53; 95% CI = 0.28-0.99)</td>
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### APPENDIX B  Description of Studies Included in Literature Review (continued)

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<tr>
<td>11</td>
<td>Siegel 2008 (Dept. of VA Rehabilitation Research)</td>
<td>SC IFNβ-1a (n = 13) SC IFNβ-1b (n = 12) IM IFNβ-1a (n = 7) SC GA (n = 22)</td>
<td>Patients visiting a VA medical center with a diagnosis of MS, current use of a DMT, active participation in medication administration, and identified a primary caregiver in their lives</td>
<td>12.96 years [SD = 7.82]</td>
<td>3.50 years [SD = 2.94]</td>
<td>6 months</td>
<td>≥ 80% or more of prescribed doses (total no. of doses taken = total no. prescribed) based on single, self-report question: “How many times have you missed taking your DMT in the past month?” A weighted metric was used specific to each drug’s prescribed dosage - missing a 1 x weekly dosing equals 7.5 missed doses (i.e., 7.5 x 4 = 30)</td>
<td>• Adherent: 85.1%; CI = 75.6%-94.8% • Nonadherent: 15%; CI = 5.2%-24.4%</td>
</tr>
<tr>
<td>12</td>
<td>Tremlett 2008 (Multiple Sclerosis International Federation)</td>
<td>SC IFNβ-1b (n = 67) SC high-dose IFNβ-1a (n = 15) SC GA (n = 15)</td>
<td>MS confirmed by MRI, able to walk without assistance or support, 2 relapses in last 2 years, had RRMS, on therapy for at least 1 month, and taking IMT at first F/U</td>
<td>10.79 years [SD = 8.41]</td>
<td>27.8 months [SD = 19.53]</td>
<td>Mean of 2.4 years</td>
<td>“Fully adherent” = missed 0 doses • “Missed few doses” = missed 1-5 • “Missed multiple doses” = missed &gt; 5 “History of missed doses” ≥ 1 missed dose in month prior to baseline</td>
<td>26.8% fully adherent 50.5% missed few doses 22.7% missed multiple doses 88% adhered to at least 80% of intended (prescribed) doses at each F/U</td>
</tr>
<tr>
<td>13</td>
<td>Turner 2007 (Dept. of VA Rehabilitation Research)</td>
<td>SC IFNβ-1a (n = 8) SC IFNβ-1b (n = 19) IM IFNβ-1a (n = 20) SC GA (n = 42)</td>
<td>Patients from a VA medical center with a diagnosis of MS, current use of 1 DMT, and active participation in medication administration Excluded if injection received by nurse or caregiver</td>
<td>11.79 years [SD = 7.93]</td>
<td>3.41 years [SD = 3.29]</td>
<td>6 months</td>
<td>MPR = (no. of doses taken) / (no. of doses prescribed in 1 month) Adherent: MPR ≥ 80%</td>
<td>Adherence rates by F/U: • 2 months: 88.1% (n = 59) • 4 months: 86.3% (n = 60) • 6 months: 87.1% (n = 74)</td>
</tr>
<tr>
<td>14</td>
<td>Fraser 2004 (Teva Neuroscience)</td>
<td>SC GA (N = 104)</td>
<td>Patients diagnosed with MS (either RRMS or progressive MS) initiating GA therapy, ≥ 18 years old</td>
<td>Adherent: 3.9 years [SD = 1.2] Nonadherent: 6.3 years [SD = 1.5]</td>
<td>Initiating therapy (&lt;21 days)</td>
<td>6 months</td>
<td>Continuous therapy with SC GA from therapy initiation to 6-month F/U</td>
<td>79% (n = 82) adherent 21% (n = 22) nonadherent</td>
</tr>
<tr>
<td>15</td>
<td>Fraser 2003 (Teva Neuroscience)</td>
<td>SC GA (N = 199)</td>
<td>Patients identified from the CMSC/NARCOMS Patient Registry database and the Shared Solutions MS patient support database with self-reported progressive forms of MS and had taken or discontinued therapy with SC GA Excluded if RRMS (sample analyzed in Fraser 2001)</td>
<td>Adherent: 11 years Nonadherent: 10 years</td>
<td>Adherent: 22 months Nonadherent: 8 months</td>
<td>1 year</td>
<td>Adherence defined as continuous therapy with SC GA for at least 1 year</td>
<td>54% (n = 107) adherent 46% (n = 92) nonadherent</td>
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<td>16</td>
<td>Fraser 2001 (Teva Neuroscience)</td>
<td>SC GA (N = 341)</td>
<td>Patients identified from the CMSC/NARCOMS Patient Registry database and the Shared Solutions MS patient support database who had RRMS and had taken or discontinued therapy with SC GA Excluded if had progressive types of MS or taking multiple DMTs</td>
<td>Adherent: 7.36 years [SD = 6.35]  Nonadherent: 7.59 years [SD = 7.39]</td>
<td>Adherent: 21.99 months [SD = 10.46]  Nonadherent: 5.52 months [SD = 5.28]</td>
<td>1 year</td>
<td>Adherence defined as continuous therapy with SC GA for at least 1 year</td>
<td>66% (n = 223) adherent 34% (n = 116) nonadherent</td>
</tr>
<tr>
<td>17</td>
<td>Halpern 2011 (Biogen Idec)</td>
<td>IM IFNβ-1a (n = 2,305) SC IFNβ-1a (n = 1,211) SC IFNβ-1b (n = 894) SC GA (n = 2,270)</td>
<td>Patients with ≥ 1 claim with diagnosis of MS and ≥ 1 claim for a DMT; commercially insured population Excluded if taking Extavia or had index claim with HCPCS code J1825 and no subsequent claims that identified IM/SC INFβ-1b were adherent N/A patients initiating treatment</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>12 months</td>
<td>MPR = (total days supply dispensed) ÷ (total no. of days from index Rx to switch or end of F/U) Adherent: MPR ≥ 80% IM IFNβ-1a: 62% SC IFNβ-1a: 59% (OR vs. IM IFNβ-1a = 0.829; CI = 0.719-0.957) SC IFNβ-1b: 52% (OR = 0.656; CI = 0.561-0.768) SC GA: 55% (OR = 0.749; CI = 0.665-0.844) Overall comparison, P &lt; 0.001</td>
</tr>
<tr>
<td>18</td>
<td>Tan 2011 (Biogen Idec)</td>
<td>IM IFNβ-1a (n = 734) SC IFNβ-1a (n = 543) SC IFNβ-1b (n = 303) SC GA (n = 866)</td>
<td>Patients with ≥ 1 claim with diagnosis of MS and ≥ 1 claim for a DMT; treatment naive for 6-month baseline; commercially insured population using HealthCore Integrated Research Database Patients aged &gt; 65 years excluded</td>
<td>N/A</td>
<td>N/A patients initiating treatment</td>
<td>12 months</td>
<td>MPR = (total days supply dispensed) ÷ (total no. of days in F/U) Adherent: MPR ≥ 80% Overall: 59.6% were adherent in 1-year F/U</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Dor 2010 (Not reported)</td>
<td>IM IFNβ-1a SC IFNβ-1a SC IFNβ-1b GA (Overall N = 1,974)</td>
<td>Patients with ≥ 1 diagnosis of MS and ≥ 1 prescription claim or procedure code for a DMT; commercially insured population using MedStat Marketscan Database Excluded if had negative total copayments, both copayments and coinsurance in post-period, or total nonpositive number of days supplied</td>
<td>N/A</td>
<td>Not reported</td>
<td>13 years</td>
<td>MPR = (total no. of days supply prescribed) ÷ 365 Copayment cohort: Mean MPR = 0.72 ± 0.26 Coinsurance cohort: Mean MPR = 0.66 ± 0.30 Overall: Mean MPR = 0.69 ± 0.28</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Kleinman 2010 (Biogen Idec)</td>
<td>IM IFNβ-1a (n = 179) SC IFNβ-1a (n = 20) SC IFNβ-1b (n = 63) SC GA (n = 96)</td>
<td>Patients with diagnosis of MS and a claim for a DMT, or ≥ 2 claims for a DMT; commercially insured population using Human Capital Management Services Research Reference Database. Excluded patients with &gt; 1 DMT agent in 1-year F/U (i.e., patients who switched)</td>
<td>N/A</td>
<td>N/A patients initiating treatment</td>
<td>12 months</td>
<td>MPR = (total days supply dispensed) ÷ 365 IM IFNβ-1a: 0.76 ± 0.021 SC IFNβ-1a: 0.761 ± 0.049 SC IFNβ-1b: 0.705 ± 0.036 SC GA: 0.698 ± 0.028</td>
<td></td>
</tr>
</tbody>
</table>
## APPENDIX B

### Description of Studies Included in Literature Review (continued)

<table>
<thead>
<tr>
<th>#</th>
<th>Author Year Published (Sponsor)</th>
<th>Treatments and Sample Sizes</th>
<th>Population Inclusion/Exclusion Criteria</th>
<th>Mean Time Since MS Diagnosis</th>
<th>Mean Duration on MS Therapy</th>
<th>Duration F/U for Adherence Measurement</th>
<th>Definition of Adherence</th>
<th>Adherence Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>Steinberg 2010 (Merck-Serono)</td>
<td>IFN-β1b or IFN-β1a (Overall N = 1,606)</td>
<td>RRMS patients with ≥2 claims for an INF treatment in 2005 (with no requirements for a claim in F/U); commercially insured population; Patients excluded if taking Extavia as the study period preceded U.S. approval (August 2009)</td>
<td>N/A</td>
<td>Not reported</td>
<td>N/A</td>
<td>MPR=(total days supply dispensed 360 days following index Rx) ÷ 360 days</td>
<td>Adherent: MPR≥85%</td>
</tr>
<tr>
<td>22</td>
<td>Tan 2010 (WellPoint Inc.)</td>
<td>IM IFN-β1a (n = 1,489)</td>
<td>Patients with ≥2 claims with diagnosis of MS and ≥1 claim for a DMT; commercially insured population using HealthCore Integrated Research Database</td>
<td>N/A</td>
<td>Program participant: 16.8 months [SD = 10.1]</td>
<td>Nonparticipant: 14.6 months [SD = 9.8]</td>
<td>12 months</td>
<td>MPR=(total days supply dispensed) ÷ (total no. of days in F/U)</td>
</tr>
<tr>
<td>23</td>
<td>Wundes 2010 (NIAID, United Spinal Association, National MS Society, NIDRR)</td>
<td>Mitoxantrone-intended treatment regimen: IV 12 mg/m² every 3 months for a total lifetime infusion of 140 mg/m² (N = 96)</td>
<td>Patients with worsening MS treated at the University of Washington, with &gt;1 mitoxantrone infusion; 81 initiated treatment due to disease progression, intolerance of first-line treatment (n = 16), or nonadherence to first-line treatment (n = 9)</td>
<td>9.7 years (range 0.3-37.4)</td>
<td>Not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Lafata 2008 (Teva Neuroscience)</td>
<td>IM IFN-β1a</td>
<td>Patients with ≥1 IP or ≥2 OP claims with diagnosis of MS, with diagnosis of MS (including type) verified by chart review; cohort of patients receiving care from large multispecialty practice in Michigan</td>
<td>N/A</td>
<td>N/A</td>
<td>2 years</td>
<td>Definition 1: MPR=(total days supply dispensed) ÷ (total no. of days between first and last dispensing date)</td>
<td>Adherent: MPR≥80%</td>
</tr>
</tbody>
</table>

**Legend:**
- CI = confidence interval
- CMSC = Consortium of Multiple Sclerosis Centers
- DMT = disease-modifying therapy
- F/U = follow-up
- GA = glatiramer acetate
- HCPCS = Healthcare Procedure Coding System
- IFN = intramuscular interferon beta 1-a
- IM = intramuscular
- IP = inpatient
- IV = intravenous
- IVIG = intravenous immunoglobulin
- mcg = microgram
- MDR = missed dose ratio
- MERS = Medication Event Monitoring System
- mg = milligram
- m² = meters squared
- MPR = medication possession ratio
- MS-TAQ = Multiple Sclerosis Treatment Adherence Questionnaire
- NA = not available (and/or not applicable)
- NARCOMS = North American Research Committee on Multiple Sclerosis
- NIAID = National Institute of Allergy and Infectious Diseases
- NIDRR = National Institute on Disability and Rehabilitation Research
- OP = outpatient
- OR = odds ratio
- PBM = pharmacy benefit manager
- RRMS = relapsing-remitting multiple sclerosis
- SD = standard deviation
- TE = treatment experienced
- TN = treatment naïve
- VA = Veterans Affairs
- β = beta
- γ = gamma
Perspectives for Managed Care Organizations on the Burden of Multiple Sclerosis and the Cost-Benefits of Disease-Modifying Therapies

Gary M. Owens, MD; Eleanor L. Olvey, PharmD, PhD; Grant H. Skrepnek, PhD; and Michael W. Pill, PharmD

ABSTRACT

Disease-modifying therapies (DMTs) are a core component of multiple sclerosis (MS) management. Given current constraints on health care expenditures, the relative cost-effectiveness of these therapies needs to be considered when making treatment decisions. The objective of this article is to review the burden of illness of MS, discuss the cost-effectiveness data for DMTs, and summarize the implications for payers.

For the burden of illness in MS, a retrospective analysis of managed care administrative data from the IMS LifeLink Health Plan Claims Database was performed. Data from claims submitted for patients with confirmed MS (ICD-9-CM code 340) over a period of 1 year (2009) were analyzed. A literature review was conducted to put these data into perspective.

The retrospective analysis determined that the mean annual cost of treating MS in the United States in 2009 was $23,434, which varied according to the presence of comorbidities/complexities. Overall, DMTs accounted for 69% of the total costs of managing the disease. According to the literature review, the typical first-line DMTs (interferon beta [IFNβ] formulations and glatiramer acetate [GA]) are generally associated with incremental cost-utility or cost-effectiveness ratios in excess of $100,000 per quality of life year gained. Natalizumab may have cost benefits over other agents in patients with more aggressive disease. According to the available data, studies indicate that DMT cost-effectiveness (specifically cost per quality-adjusted life years) appears to improve with treatment initiation during the early stages of the disease.

In relapsing-remitting MS, there is currently little evidence to differentiate between the DMTs that are typically used first-line (interferon betas and glatiramer acetate) based on cost-effectiveness or cost-utility studies. Presently, optimal therapy decisions for DMT-naïve patients are likely to be made individually based on cost-effectiveness or cost-utility studies.

Optimal therapy decisions for DMT-naïve patients are likely to be made individually based on disease presentation, patient and provider preference, adherence, and medication risk-benefit profiles.

Summary Points Presented in this Article (continued)

• According to the retrospective analysis, DMTs account for 69% of the total cost to treat MS in the United States and are associated with high incremental cost-effectiveness ratios ranging from $20,000 to more than $1 million per quality of life year gained. In line with efficacy findings, cost-effectiveness is improved by initiating treatment in early disease stages.
• In relapsing-remitting MS, there is currently little evidence to differentiate between the DMTs that are typically used first-line (interferon betas and glatiramer acetate) based on cost-effectiveness or cost-utility studies.
• Optimal therapy decisions for DMT-naïve patients are likely to be made individually based on disease presentation, patient and provider preference, adherence, and medication risk-benefit profiles.

Multiple sclerosis (MS) is a progressive inflammatory and degenerative autoimmune disease of the central nervous system (CNS) that is thought to be autoimmune in nature. Most individuals diagnosed with MS experience their first clinical symptoms between 20-40 years of age. Initial signs of illness may include weakness, sensory symptoms, ataxia, visual symptoms, diplopia, and vertigo. These symptoms intensify and abate with relapses or exacerbations separated by periods of stability. Over time, these symptoms accumulate and persist, and other negative effects arise such as bowel and bladder dysfunction, fatigue, muscle spasms, speech disorders, memory loss, and other neuropsychiatric signs. Ultimately, these effects become increasingly permanent, resulting in sustained disability; reductions in quality of life; a decline in work productivity; and considerable costs to the individual, family, and society. Given the typical early age of MS onset, a profound burden of this disease is borne by patients and their families over many years.

Managing MS requires both pharmacologic and nonpharmacologic (e.g., physical therapy, occupational therapy, medical devices, and counseling) interventions to control symptoms and delay disease progression and accumulation of disability. Disease-modifying therapies (DMTs) are a core component in the pharmacologic management of MS. Of the DMTs, interferon beta (IFNβ) formulations and glatiramer acetate (GA) have generally been regarded as the mainstay of first-line treatment in patients experiencing a first neurologic episode (known as clinically isolated syndrome [CIS]) and in those with relapsing-remitting MS (RRMS). These immunomodulatory first-line DMTs delay conversion to clinically definite MS (CDMS) in
patients with CIS.8,12 Although head-to-head clinical trials are lacking in this patient population, the adjusted reductions in the risk of CDMS were generally similar with GA, IFNβ-1a, and IFNβ-1b (ranging from 35% with subcutaneous [SC] IFNβ-1a to 55% with intramuscular [IM] IFNβ-1a over 2 to 3 years).8,12 However, SC IFNβ-1a has not yet demonstrated efficacy to the standard required from the U.S. Food and Drug Administration (FDA) for an approved indication for use after CIS.10 Data for patients with CIS are not currently available for the other FDA-approved DMTs: natalizumab (a monoclonal antibody that targets the α4 subunit of α4β1 and α4β7 integrins), mitoxantrone (a cytotoxic agent with immunosuppressive and immunomodulatory properties), or fingolimod (a recently introduced sphingosine 1-phosphate receptor modulator).

All approved DMTs (IFNβs, GA, natalizumab, fingolimod, and mitoxantrone) have demonstrated efficacy in patients diagnosed with RRMS. In pivotal studies in patients with RRMS, use of these agents significantly decreased annualized relapse rates, with most also reducing disability progression rates versus placebo.13-19 In general, the available data on the efficacy of these agents is restricted to second-line therapy.22

With respect to the other agents, fingolimod, natalizumab, and mitoxantrone currently require close patient monitoring. In clinical trials, fingolimod 0.5 milligram (mg) has been associated with bradycardia (1%-2%), atrioventricular block (0.5%), leukopenia (3%), lymphopenia (3.5%), increased risk for certain infections (e.g., 10% incidence of lower respiratory tract infections in one trial), macular edema (0-0.5%), and hepatic effects (6%-16% incidence of raised liver enzyme levels).13,22 All patients initiated on fingolimod must be observed for signs and symptoms of bradycardia for at least 6 hours after their first dose. Patients at higher risk because of a coexisting medical condition or certain concomitant medications should be observed overnight with continuous electrocardiogram (ECG) monitoring.

Natalizumab use is associated with a risk for developing progressive multifocal leukoencephalopathy (PML), a rare, opportunistic brain infection caused by the John Cunningham virus (JCV),21 that can result in severe disability or death. As of February 29, 2012, PML incidence among patients on natalizumab ranged from approximately 0.09/1,000 (95% confidence interval [CI] 0 to 0.48) to 11/1,000 (95% CI = 8.3-14.5), depending on an individual's anti-JCV antibody positive status, prior immunosuppressant use, and duration of natalizumab exposure.22 A commercial assay that detects anti-JCV antibodies in human serum and plasma has recently become available.21 This assay, together with the assessment of other recognized risk factors, enables clinicians to stratify patients who may be at higher and lower risk of developing PML.23 The reported incidence of PML in patients who tested negative for anti-JCV antibodies prior to PML onset is 0.11/1,000, or greater than 20-fold lower than the PML incidence in patients who are positive for anti-JCV antibodies.24 As a consequence of the risk of PML, the FDA indication currently recommends natalizumab as monotherapy for the treatment of relapsing forms of MS to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations in patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy, although its recommended use is not restricted to second-line therapy.22

Mitoxantrone therapy for MS is restricted by the FDA to patients with secondary progressive MS, progressive-relapsing MS, and worsening RRMS. This approval was based on the results from a pivotal trial of mitoxantrone for MS conducted in patients with more advanced disease27 and on a lifetime dose restriction for mitoxantrone due to the drug's toxicity, which has been associated with blood cancers, clinically significant myelosuppression, increased risk of infections, and potentially fatal cardiotoxicity.25

Given the current availability of several DMTs for MS and the demands that continuous therapy places on health care expenditure, the relative cost-effectiveness of these options must be regularly evaluated, and the results of these evaluations can become a guide to treatment decisions.

The main objectives of this article are to summarize the burden of illness associated with MS, to discuss the per-patient costs associated with individual DMTs that are approved by the FDA for treating MS, to provide an overview of cost-utility and cost-effectiveness data for these therapies, and to discuss the impact of MS on work productivity and absenteeism. We will also describe the gaps in our current knowledge on these topics and their potential implications for payers.

**Methods**

This article presents the results of a descriptive, retrospective report of patient-level medical and pharmacy claims data in the United States, supplemented by a literature review.

**Total Resource Utilization Benchmarks Analysis**

**Source Data.** Patient-level administrative claims data were obtained from the IMS LifeLink Health Plan Claims Database, a large data warehouse of administrative claims that has been used for previous analyses of data on patients with MS.26-28 At the time these analyses were conducted, the database...
Flow Chart of Article Selection for Locating Articles on the Cost and Cost-Effectiveness of Disease-Modifying Therapies for the Management of Multiple Sclerosis

1,357 records identified through PubMed searches

- 549 excluded (using automated PubMed tools) that were not English articles with abstracts, were published before January 1996, or were editorials or letters
- 226 excluded (manually) that were review articles or practice guidelines (excluding systematic reviews), or were focused on pre-clinical research
- 516 excluded that were not related to FDA-approved DMTs for MS AND treatment cost, cost-effectiveness, productivity decline, or absenteeism according to the information in the abstract
- 13 excluded that focused on adherence, which is the topic of another article within this supplement

582 abstracts assessed for suitability

808 PubMed records after application of automated limitations

53 articles included in the qualitative synthesis

DMT = disease-modifying therapies; FDA = U.S. Food and Drug Administration; MS = multiple sclerosis.

Literature Search Strategy.

To locate articles on cost and cost-effectiveness, the following targeted (nonsystematic) literature review was performed using PubMed on September 15, 2011: (Health Care Economics and Organizations [MeSH Major Topic] OR costs OR cost OR cost-effectiveness OR employ OR employment OR employee OR absenteeism OR absentee) AND multiple sclerosis OR “multiple sclerosis/economics” [MeSH Terms]. Overall, 1,357 articles were selected using this search strategy (Figure 1). The search was limited to English language articles with abstracts published since IFNβ-1a became available for the treatment of MS, from January 1996 to the present. Editorials and letters were excluded. After applying these limitations using the automated limit function in PubMed, and then manually excluding review articles (aside from systematic reviews) and articles focused on pre-clinical research, the search yielded a total of 582 articles. Following an evaluation of abstracts, 53 final articles were incorporated that contained information on FDA-approved DMTs and treatment cost, cost-effectiveness, productivity decline, or absenteeism. A further 43 references were included to supplement the introduction, methods, and “gaps in knowledge” sections of the article based on awareness of the literature and additional searching where appropriate.

Results

Overall Cost of Illness

Total Resource Utilization Benchmarks Analysis. The baseline characteristics for the 31,401 patients included in the MS Benchmarks analysis are summarized in Table 1. In line with MS in the U.S. population, the majority of patients (77%) were women, and nearly one-half (44%) were between 26 and 39 years of age.

Patients were selected for study inclusion if they had 12 months of continuous eligibility for 2009, valid data for age and gender, and evidence of treatment for MS. For selection, patients were identified by the presence of an ETG-defined episode of care and specific International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding using the ETG codes ETG 149 (inflammation of the CNS, with surgery) and ETG 150 (inflammation of the CNS, without surgery). Only patients with these ETG-based episodes and a diagnosis code for MS (ICD-9-CM code 340.xx) were included.

Once selected, ETG data were stratified using the Total Resource Utilization (TRU) Benchmarks process (Gemini Healthcare, Westbrook, CT, www.diseasebenchmarks.com). The dataset captures information across the continuum of patient care and organizes it into consistently formatted, episode-based benchmarks for comparison. TRU Benchmarks reports episode-based metrics of costs, units of use, and services utilized. Example benchmarks used previously for TRU Benchmarks studies in MS and other diseases include the drug therapy used, patient demographics, the presence and number of complications and comorbidities, episode costs, and resource utilization across all health care service categories.
According to the findings from this analysis, in 2009, the average annual total for MS-related health care costs in the United States was $23,434 (Table 2). This amount is higher than a previous report and is most likely due to differences in prior DMT use between the 2 populations analyzed and how the ETG software captures claims. Cost varied by the type of comorbidities/complications, with patients experiencing ataxia ($31,483), abnormality of gait ($28,353) incurring the largest costs.

The annual costs per patient for managing MS in the MS Benchmark analysis came from pharmacy costs (73%; $17,013) and outpatient visits (21%; $5,030), inpatient services (5%; $1,082), and emergency room visits (1%; $310; Table 2). The types of pharmacotherapies used overall by patients in the analysis included DMTs (51%), migraine agents (46%), anti-inflammatory drugs (NSAIDS; 22%), and benzodiazepines (22%). Despite the widespread use of other drugs, DMTs accounted for 95% ($16,104) of the total annual pharmacy costs per patient and 69% of the total costs for managing MS. Of the remaining pharmacotherapies, no single drug class accounted for more than 1.5% of the total pharmacy costs.

**TABLE 1** Baseline Characteristics of Patients Included in the Total Resource Utilization Benchmarks Analysis

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>n</th>
<th>Overall %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-25</td>
<td>667</td>
<td>2</td>
</tr>
<tr>
<td>26-39</td>
<td>13,880</td>
<td>44</td>
</tr>
<tr>
<td>40-64</td>
<td>13,762</td>
<td>44</td>
</tr>
<tr>
<td>≥ 65</td>
<td>3,092</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>31,401</td>
<td>100</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24,053</td>
<td>77</td>
</tr>
<tr>
<td>Male</td>
<td>7,348</td>
<td>23</td>
</tr>
<tr>
<td><strong>Comorbidities and conditions (≥ 10% overall)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>9,690</td>
<td>31</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9,603</td>
<td>31</td>
</tr>
<tr>
<td>Asthenia</td>
<td>7,944</td>
<td>25</td>
</tr>
<tr>
<td>Depression</td>
<td>6,672</td>
<td>21</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5,310</td>
<td>17</td>
</tr>
<tr>
<td>Burning, numbness, tingling</td>
<td>5,221</td>
<td>17</td>
</tr>
<tr>
<td>Thyroid disorder</td>
<td>4,826</td>
<td>15</td>
</tr>
<tr>
<td>Low back pain</td>
<td>4,537</td>
<td>14</td>
</tr>
<tr>
<td>Headache</td>
<td>3,809</td>
<td>12</td>
</tr>
<tr>
<td>Abnormality of gut</td>
<td>3,417</td>
<td>11</td>
</tr>
<tr>
<td>Malignancy</td>
<td>3,398</td>
<td>11</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3,221</td>
<td>10</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3,078</td>
<td>10</td>
</tr>
</tbody>
</table>
the MS Benchmarks analysis did not include indirect societal costs such as reduced productivity, absenteeism, early retirement, and additional types of earning losses, which have been accounted for in other studies.³⁴⁵ Kohlet et al. (2006) found that 37% of total costs were due to production losses or informal care.³⁷ Therefore, the Total Resource Utilization Benchmarks analysis may underestimate the total economic burden of MS ($23,434 in 2009 values) when compared with other U.S.-based studies that have included societal costs ($45,284 to $52,830 in 2008 values).³⁷,⁴⁰ This difference also likely explains why studies such as the one by Kobelt et al.³⁷ suggest that DMTs account for a lower proportion of the total MS costs relative to the MS Benchmarks analysis (34% vs. 69%, respectively) and to another U.S. study that only included direct costs³⁸ (34% vs. 71%-76% [depending on the DMT], respectively). Nevertheless, whichever study is considered, DMTs make up a large portion of the total costs of MS. It is therefore important to consider which DMTs are most likely to deliver optimal cost-effectiveness.

**Costs for Patients with MS by DMT**

**Total Resource Utilization Benchmarks Analysis.** According to the MS Benchmark analysis, patient groups using each of the main first-line DMTs (GA and IFNβ formulations) had similar average annual costs specific to the treatment of MS. There was no practical difference among the 4 studied DMTs in average annual medical costs. Average costs ranged narrowly from $36,006 for patients on intramuscular (IM) IFNβ-1a to $36,775 for patients on subcutaneous IFNβ-1b (Table 3). Comparisons across DMT treatment groups showed that IM IFNβ-1a had the lowest inpatient, outpatient, and emergency room costs and the lowest cost of concomitant pharmacy treatments (Table 3; statistical testing not performed).

**Literature Search.** Previously, studies have evaluated the “real-world” costs of DMTs in the past 5 years in the United States.⁵,²⁷,³⁴-⁴²,⁴⁶ As seen in the MS Benchmarks analysis, several reports stated that there were no substantial differences between the costs of the studied DMTs.³⁷,⁴⁷,⁴⁸ Bell et al. (2007) estimated that the total costs per patient over a lifetime were $352,760, $364,267, $377,996, and $358,509 for GA, IM IFNβ-1a, SC IFNβ-1a, and SC IFNβ-1b, respectively.³⁷ Conversely, several other studies concluded that the costs may be different among the DMTs.²⁷,⁴²-⁴⁶,⁴⁹ Prescott et al. (2007) found that the annual costs of GA ($16,928) were lower than those of IM IFNβ-1a, SC IFNβ-1a, and SC IFNβ-1b, respectively.³⁷ Data for this study were reported in 2004; therefore, drug cost comparisons may no longer be accurate. However, similar findings showing lower total costs with GA were reported elsewhere.⁵,⁴⁴

Regarding natalizumab, which was not evaluated in the current MS Benchmarks analysis, a study indicated that the annual costs of this DMT (in 2008 U.S. dollars) are higher than for typical first-line agents (IFNβs and GA).⁴⁶ However, data from a new decision analytic model developed to estimate the incremental cost per relapse avoided with natalizumab and fingolimod from a U.S. managed care payer perspective showed that estimated 2-year treatment costs in the United States are lower for natalizumab than the recently introduced DMT fingolimod ($86,461 vs. $98,748, respectively).⁴⁹

While evaluating the total costs to treat patients with various DMTs is useful, it is more important to evaluate these costs as they relate to effectiveness. In this regard, the numerous published analyses of the cost-effectiveness and cost-utility of DMTs for MS are summarized below.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Average Annual Costs (U.S. Dollars) Associated with the Use of Disease-Modifying Therapies: Findings from the Total Resource Utilization Benchmarks Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inpatient</strong></td>
<td><strong>Mean [SD]</strong></td>
</tr>
<tr>
<td>IM IFNβ-1a (n = 4,485)</td>
<td>809 [10,503]</td>
</tr>
<tr>
<td>SC IFNβ-1a (n = 3,130)</td>
<td>793 [5,778]</td>
</tr>
<tr>
<td>IFNβ-1b (n = 2,059)</td>
<td>1,285 [10,747]</td>
</tr>
<tr>
<td>GA (n = 6,969)</td>
<td>1,285 [10,747]</td>
</tr>
<tr>
<td><strong>Outpatient</strong></td>
<td><strong>Mean [SD]</strong></td>
</tr>
<tr>
<td>IM IFNβ-1a (n = 4,485)</td>
<td>4,205 [7,653]</td>
</tr>
<tr>
<td>SC IFNβ-1a (n = 3,130)</td>
<td>3,36 [2,085]</td>
</tr>
<tr>
<td>IFNβ-1b (n = 2,059)</td>
<td>383 [2,412]</td>
</tr>
<tr>
<td>GA (n = 6,969)</td>
<td>338 [1,996]</td>
</tr>
<tr>
<td><strong>Emergency room</strong></td>
<td><strong>Mean [SD]</strong></td>
</tr>
<tr>
<td>IM IFNβ-1a (n = 4,485)</td>
<td>28,895 [16,132]</td>
</tr>
<tr>
<td>SC IFNβ-1a (n = 3,130)</td>
<td>28,814 [17,037]</td>
</tr>
<tr>
<td>IFNβ-1b (n = 2,059)</td>
<td>28,814 [17,037]</td>
</tr>
<tr>
<td>GA (n = 6,969)</td>
<td>28,814 [17,037]</td>
</tr>
<tr>
<td><strong>Pharmacy</strong></td>
<td><strong>Mean [SD]</strong></td>
</tr>
<tr>
<td>IM IFNβ-1a (n = 4,485)</td>
<td>29,720 [16,132]</td>
</tr>
<tr>
<td>SC IFNβ-1a (n = 3,130)</td>
<td>29,180 [16,132]</td>
</tr>
<tr>
<td>IFNβ-1b (n = 2,059)</td>
<td>29,180 [16,132]</td>
</tr>
<tr>
<td>GA (n = 6,969)</td>
<td>29,180 [16,132]</td>
</tr>
<tr>
<td><strong>Product specific</strong></td>
<td><strong>Mean [SD]</strong></td>
</tr>
<tr>
<td>IM IFNβ-1a (n = 4,485)</td>
<td>30,793 [26,974]</td>
</tr>
<tr>
<td>SC IFNβ-1a (n = 3,130)</td>
<td>30,651 [19,953]</td>
</tr>
<tr>
<td>IFNβ-1b (n = 2,059)</td>
<td>30,651 [19,953]</td>
</tr>
<tr>
<td>GA (n = 6,969)</td>
<td>30,651 [19,953]</td>
</tr>
<tr>
<td><strong>All other pharmacy</strong></td>
<td><strong>Mean [SD]</strong></td>
</tr>
<tr>
<td>IM IFNβ-1a (n = 4,485)</td>
<td>30,671 [16,132]</td>
</tr>
<tr>
<td>SC IFNβ-1a (n = 3,130)</td>
<td>30,033 [14,954]</td>
</tr>
<tr>
<td>IFNβ-1b (n = 2,059)</td>
<td>29,534 [17,037]</td>
</tr>
<tr>
<td>GA (n = 6,969)</td>
<td>29,534 [17,037]</td>
</tr>
<tr>
<td><strong>Total annual costs</strong></td>
<td><strong>Mean [SD]</strong></td>
</tr>
<tr>
<td>IM IFNβ-1a (n = 4,485)</td>
<td>36,006 [21,002]</td>
</tr>
<tr>
<td>SC IFNβ-1a (n = 3,130)</td>
<td>36,775 [22,480]</td>
</tr>
<tr>
<td>IFNβ-1b (n = 2,059)</td>
<td>36,775 [22,480]</td>
</tr>
<tr>
<td>GA (n = 6,969)</td>
<td>36,775 [22,480]</td>
</tr>
</tbody>
</table>

References:
- IFNβ = interferon beta; IM = intramuscular; min/max = minimum/maximum; GA = glatiramer acetate; SC = subcutaneous; SD = standard deviation.
- Supplement to Journal of Managed Care Pharmacy    S45

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Cost-Utility and Cost-Effectiveness Analyses of DMTs

Costs Per Quality-Adjusted Life Year. Certain institutions, such as the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom, use quality-adjusted life years (QALYs) to compare different drugs and measure their clinical effectiveness and use cost per QALY as a measure of cost-effectiveness.\(^\text{30}\) In the United States, a cost per QALY value of $50,000 is sometimes used as a threshold for cost-effectiveness.\(^\text{45,48}\) Numerous studies have assessed the cost per QALY of the approved DMTs for MS, aside from fingolimod (Table 4).\(^\text{45,47,48,51-66}\) These studies arrived at widely different estimates, with costs per QALY varying from around $20,000 to over $1 million.

It is difficult to make comparisons across these studies because of differences in study time horizons, data inputs, geographical locations, utility values, and associated assumptions, all of which can have a large influence on model results.\(^\text{39}\) The trend was for the studies to show high cost per QALY estimates, indicating that by this measure DMTs may not be cost-effective. However, consideration of only direct medical costs has a number of limitations, most notably not always considering social values such as absenteeism, productivity, and impact on family and caregivers.\(^\text{50}\) The impact of DMTs on employment and absenteeism in patients with MS is addressed below.\(^\text{50}\)

Multiple analyses comparing IFN\(\beta\) formulations and GA have been published (Table 4) using cost per QALY, but conflicting results between the studies make it difficult to conclusively determine whether or not there are any differences in cost-effectiveness among these drugs.\(^\text{30,45,47,56}\) Regarding natalizumab, in 2 analyses comparing different treatments, this DMT appeared to have an improved cost per QALY relative to the IFN\(\beta\)s and GA.\(^\text{55,56}\) This was mostly due to the efficacy benefits observed with natalizumab in clinical trials of patients with highly active RRMS and SPMS. Another economic model reporting increased patient benefits with natalizumab or GA compared with symptom management (increased years in Expanded Disability Status Scale [EDSS] 0.0-5.5, years relapse-free, and QALYs) also suggested a similar or slightly improved lifetime cost per QALY for GA versus natalizumab in patients with RRMS when the impact of discontinuation and antimatilizumab antibodies was also considered.\(^\text{58}\) However, the study was limited by the assumptions made for cost estimates and utility weights associated with EDSS progression because of a lack of data on change in clinical efficacy and discontinuation over time for patients receiving natalizumab. Similarly, another analysis showed an improvement in the cost-effectiveness of mitoxantrone versus IFN\(\beta\)-1b when used to treat patients with SPMS or progressive-relapsing MS.\(^\text{52}\)

Several studies summarized in Table 4 suggest DMT cost-utility estimates improve when DMTs are given earlier in the disease course.\(^\text{47,63,64}\) Lazzaro et al. (2009) found that treatment with IFN\(\beta\)-1b after CIS is highly cost-effective compared with delaying treatment until a patient has CDMS (incremental cost per QALY: £2,574.94).\(^\text{64}\) In patients with CDMS, Tappenden et al. (2009) found that the cost of IFN\(\beta\)-1b per QALY gained was considerably better for treating RRMS versus treating both RRMS and SPMS ($91,515 to $168,793 vs. $122,202 to $312,344).\(^\text{65}\) Finally, Noyes et al. (2011) showed that for all evaluated agents, early treatment initiation with DMTs (EDSS score 2.0-2.5) improved the cost of DMT therapy per QALY gained compared with waiting to start a DMT until after patients had reached a higher rate of disability (EDSS score 3.0-4.0).\(^\text{67}\)

Costs Per Relapse Avoided. DMT costs may be partially offset by preventing relapses.\(^\text{4}\) Treating the symptoms associated with relapses costs, at 2002 price levels, between $243 for the mildest cases and $12,870 for severe relapses that required hospitalization.\(^\text{67}\) Consequently, a number of studies have investigated the cost of DMTs per each relapse avoided.\(^\text{46,47,60,66,68-71}\) Here, the focus is on comparative studies that examined differences in cost per relapse avoided among the various DMTs.

A study that included patients with both RRMS and SPMS found that the costs per relapse-free year were similar among the SC IFN\(\beta\) formulations and GA ($188,973 to $216,426) and higher with IM IFN\(\beta\)-1a ($303,339).\(^\text{47}\) In patients with RRMS, a German model indicated that SC IFN\(\beta\)-1a ($1,250) is more cost-effective than IM IFN\(\beta\)-1a ($133,770), GA ($71,416), or IFN\(\beta\)-1b ($54,475) in terms of cost per relapse avoided.\(^\text{71}\) In contrast, a Markov model using long-term clinical RRMS data determined that the incremental cost per relapse-free year was comparable for IM IFN\(\beta\)-1a, IFN\(\beta\)-1b, and GA ($17,599 to $24,327), but slightly higher with SC IFN\(\beta\)-1a ($32,207).\(^\text{45}\) Finally, in another analysis of these 4 agents, which included data from patients with RRMS who had received treatment for at least 2 years, the estimated costs per relapse avoided were similar among IM IFN\(\beta\)-1a ($77,980), SC IFN\(\beta\)-1a ($80,121), IFN\(\beta\)-1b ($86,572), and GA ($87,767).\(^\text{69}\)

With regard to natalizumab, a model that included data from patients on this DMT, 1 of the IFN formulations, or GA found that the 2-year cost of therapy was highest for natalizumab. However, the cost per relapse avoided was lower for natalizumab ($56,594) relative to the IFN\(\beta\)s and GA ($87,791 to $103,665), which was attributed to its association with fewer relapses.\(^\text{56}\) The cost-effectiveness of natalizumab for preventing relapses relative to these DMTs is supported by another analysis.\(^\text{70}\) More recently, O’Day et al. (2011) examined the cost per relapse avoided for natalizumab versus fingolimod.\(^\text{49}\) Natalizumab was found to be more cost-effective than fingolimod for relapse prevention as a result of its lower costs and apparent greater efficacy in reducing relapses, although head-to-head studies are lacking.

Costs for Prevention of Disability

The ultimate goal for MS treatment should be to prevent the progression of disability for the benefit of patients and society. In terms of burden on society, a systematic review...
### Table 4: Summary of Results from Economic Evaluation Studies Investigating Cost Per QALY Associated with Disease-Modifying Therapies

<table>
<thead>
<tr>
<th>Study (Year Published)</th>
<th>Country [Sponsor]</th>
<th>Population (Time Horizon); Perspective</th>
<th>Treatments</th>
<th>Comparators</th>
<th>Results[^a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell et al. (2007); United States [Teva Neuroscience][^5]</td>
<td>RRMS (lifetime); societal</td>
<td>Symptom management combined with SC GA, SC IFNβ-1a, IM IFNβ-1a</td>
<td>Symptom management alone</td>
<td>Cost per QALY (compared with symptom management alone): SC GA $US258,465, SC IFNβ-1a $US416,301, IM IFNβ-1a $US303,968</td>
<td></td>
</tr>
<tr>
<td>Earnshaw et al. (2009); United States [Teva Neuroscience][^8]</td>
<td>RRMS (lifetime); health care and societal</td>
<td>SC GA, Natalizumab</td>
<td>Symptom management</td>
<td>SC GA $US496,222, Natalizumab $US606,228</td>
<td></td>
</tr>
<tr>
<td>Noyes et al. (2011); United States [National MS Society, University of Rochester, and NIH][^7]</td>
<td>RRMS or SPMS (10 years); societal</td>
<td>SC GA, SC IFNβ-1a, SC IFNβ-1b, IM IFNβ-1a</td>
<td>Supportive care</td>
<td>SC GA $US763,036, SC IFNβ-1a $US1,255,088, SC IFNβ-1b $US958,738, IM IFNβ-1a $US988,169</td>
<td></td>
</tr>
<tr>
<td>Prosser et al. (2004); United States [National MS Society, Harvard Program on the Economic Evaluation of Medical Technology, Harvard Center for Risk Analysis, and the Thomas O. Pyle Fellowship][^6]</td>
<td>Newly diagnosed with nonprimary progressive MS (10 years), societal</td>
<td>IM IFNβ-1a, SC IFNβ-1b, SC GA</td>
<td>No treatment</td>
<td>No treatment dominated both SC IFNβ-1b and SC GA. IM IFNβ-1a (compared with no treatment): cost per QALY $US2.2 million for women and $US1.8 million for men</td>
<td></td>
</tr>
<tr>
<td>Touchette et al. (2003); United States [Immunex Corporation][^62]</td>
<td>SPMS or progressive relapsing MS (20 years); health care and societal</td>
<td>Mitoxantrone SC, IFNβ-1b</td>
<td>Standard supportive care</td>
<td>Mitoxantrone hydrochloride: cost per QALY $US34,317, SC IFNβ-1b: cost per QALY $US228,934</td>
<td></td>
</tr>
<tr>
<td>Bose et al. (2001); United Kingdom [None stated][^56]</td>
<td>RRMS (8 years); health care</td>
<td>SC GA</td>
<td>Supportive care</td>
<td>Cost per QALY £20,929</td>
<td></td>
</tr>
<tr>
<td>Chikcott et al. (2003); United Kingdom [National Institute for Clinical Excellence][^50]</td>
<td>RRMS (all drugs) or SPMS (only IFNβ-1b) (20 years); health care</td>
<td>IM IFNβ-1a 6 MIU/ wk, SC IFNβ-1a 22 μg/ wk, SC IFNβ-1a 44 μg/ wk, SC IFNβ-1b 8 MIU/ wk, SC GA 20 mg/wk</td>
<td>No treatment</td>
<td>Cost per QALY: IM IFNβ-1a 6 MIU/ wk £73,137, SC IFNβ-1a 22 μg/ wk £105,718, SC IFNβ-1a 44 μg/ wk £124,034, SC IFNβ-1b 8 MIU/ wk £86,127, SC GA 20 mg/ wk £168,539, SC IFNβ-1b 8 MIU/ wk (RRMS and SPMS) £78,722</td>
<td></td>
</tr>
<tr>
<td>Forbes et al. (1999); United Kingdom [None stated][^57]</td>
<td>SPMS (2.5 years); health care</td>
<td>SC IFNβ-1b</td>
<td>Best practice without IFNβ</td>
<td>Cost per QALY £1,024,667</td>
<td></td>
</tr>
<tr>
<td>Gani et al. (2008); United Kingdom [Biogen Idec][^58]</td>
<td>Highly active RRMS (30 years); societal</td>
<td>Natalizumab</td>
<td>Best supportive care IFNβ SC GA</td>
<td>Cost per QALY of natalizumab compared with Best supportive care £8,200, IFNβ £2,300, SC GA £2,000</td>
<td></td>
</tr>
<tr>
<td>Nuijten and Hutton (2002); United Kingdom [None stated][^59]</td>
<td>RRMS (lifetime); health care and societal</td>
<td>SC IFNβ-1b</td>
<td>Usual care</td>
<td>Health care: cost per QALY £51,582, Societal: cost per QALY £49,641</td>
<td></td>
</tr>
<tr>
<td>Parkin et al. (2000); United Kingdom [NHS Health Technology Assessment program][^60]</td>
<td>RRMS (5 years and 10 years); health care</td>
<td>SC IFNβ-1b</td>
<td>No treatment</td>
<td>5 years: cost per QALY £328,300, 10 years: cost per QALY £228,300</td>
<td></td>
</tr>
</tbody>
</table>
demonstrated that the total costs of MS rose significantly with increases in disease severity as measured by EDSS scores. These cost increases were driven by relapses and productivity costs more so than the direct costs of DMTs. Interventions aimed at delaying disease progression may reduce total societal costs by decreasing the need for additional care such as rehabilitation, nursing care, and other caregivers.

Two studies have investigated the costs of DMTs for each year of disability avoided. Brown et al. (2000) found that use of IFNβ-1b for MS prevented 2 years of disability over a 40-year time horizon versus health care without a DMT, with an estimated cost per year of disability avoided of $181,395. However, the study did not consider work absenteeism, lost productivity, and patient dependency on care, or the long-term costs of care. Another model analyzing costs for patients with RRMS that considered long-term savings found that treatment with SC IFNβ-1a was cost-effective; treatment with IFNβ-1a in the United Kingdom was estimated to cost $453 per month over 10 years and £222 per month of disability prevented over 20 years. Data were not reported for other DMTs.

**Impact of DMTs on Work Productivity and Absenteeism**

MS is associated with high unemployment rates, with only 20%-60% of people with MS remaining employed in longitudinal studies. This observation is of consequence given that MS affects an estimated 400,000 people in the United States. The North American Research Committee on Multiple Sclerosis (NARCOMS) database, a global registry for MS research, treatment, and patient education, is a probability sampling that contains detailed data submitted confidentially by MS patients. An analysis reported in September 2011 in a congress abstract that evaluated the impact of treatment on employment status found that unadjusted mean 10-year patient employment rates were higher with once-weekly IM IFNβ-1b (55%) than with GA (48%; difference not significant), SC IFNβ-1a (55%); IM IFNβ-1a (55%); SC IFNβ-1b (55%); SC GA (55%); Natalizumab is dominant (costs are €3,830 lower and increase of 0.34 QALYs).

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**TABLE 4** Summary of Results from Economic Evaluation Studies Investigating Cost Per QALY Associated with Disease-Modifying Therapies (continued)

<table>
<thead>
<tr>
<th>Study (Year Published)</th>
<th>Country [Sponsor]</th>
<th>Population (Time Horizon); Perspective</th>
<th>Treatments</th>
<th>Comparators</th>
<th>Resultsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phillips et al. (2001); United Kingdom [None stated]</td>
<td>RRMS (10/20 years); societal</td>
<td>SC IFNβ-1b</td>
<td>Usual care</td>
<td>10 years: cost per QALY £14,600 20 years: cost per QALY £3,000</td>
<td></td>
</tr>
<tr>
<td>Kobelt et al. (2000); Sweden [Schering AG]</td>
<td>SPMS (10 years); societal</td>
<td>SC IFNβ-1b</td>
<td>Usual care</td>
<td>Cost per QALY $US39,250</td>
<td></td>
</tr>
<tr>
<td>Kobelt et al. (2002); Sweden [Schering AG]</td>
<td>SPMS (10 years); societal</td>
<td>SC IFNβ-1b</td>
<td>Usual care</td>
<td>Cost per QALY $US25,700</td>
<td></td>
</tr>
<tr>
<td>Kobelt et al. (2003); Sweden [None stated]</td>
<td>RRMS or SPMS (10 years); societal</td>
<td>SC IFNβ-1b</td>
<td>Usual care</td>
<td>Cost per QALY €38,700</td>
<td></td>
</tr>
<tr>
<td>Kobelt et al. (2008); Sweden [Biogen Idec and Elan Corp.]</td>
<td>RRMS or SPMS (20 years); societal</td>
<td>Natalizumab</td>
<td>SC IFNβ-1a IM IFNβ-1a SC IFNβ-1b SC GA</td>
<td>Natalizumab is dominant (costs are €3,830 lower and increase of 0.34 QALYs)</td>
<td></td>
</tr>
<tr>
<td>Lazzaro et al. (2009); Italy [Bayer Schering Pharma]</td>
<td>CIS/CDMS (25 years); health care and societal</td>
<td>SC IFNβ-1b since CIS diagnosis</td>
<td>SC IFNβ-1b since CDMS diagnosis</td>
<td>Cost per QALY €2,574</td>
<td></td>
</tr>
<tr>
<td>Iskedjian et al. (2005); Canada [Biogen Idec]</td>
<td>CIS (12/15 years); health care and societal</td>
<td>IM IFNβ-1a</td>
<td>Usual care</td>
<td>12 years (health care): cost of 1 year without progressing to MS $Can53,110 15 years (societal): cost of quality-adjusted monosymptomatic life-year $Can189,286</td>
<td></td>
</tr>
</tbody>
</table>


**a**All studies are models.

CDMS = clinically definite multiple sclerosis; CIS = clinically isolated syndrome; GA = glatiramer acetate; IFNβ = interferon beta; IM = intramuscular; mg = milligram; MIU/mw = million international units per week; MS = multiple sclerosis; NHS = National Health Service; NIH = National Institutes of Health; QALY = quality-adjusted life year; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary progressive multiple sclerosis; μg = micrograms.

Currency: $Can = Canadian dollars; € = euros; £= pounds; $US = U.S. dollars.

### Notes

- The North American Research Committee on Multiple Sclerosis (NARCOMS) database, a global registry for MS research, treatment, and patient education, is a probability sampling that contains detailed data submitted confidentially by MS patients.
- An analysis reported in September 2011 in a congress abstract that evaluated the impact of treatment on employment status found that unadjusted mean 10-year patient employment rates were higher with once-weekly IM IFNβ-1b (55%) than with GA (48%; difference not significant).
- SC IFNβ-1a (55%); IM IFNβ-1a (55%); SC IFNβ-1b (55%); SC GA (55%); Natalizumab is dominant (costs are €3,830 lower and increase of 0.34 QALYs).
- Patients receiving DMTs were more likely to be employed after 10 years than untreated patients.
- Absenteeism is high for patients who maintain employment. In 1 study, annual absenteeism rates for employees with MS ranged from 2.98 to 8.13 days; total sick time ranged from 7.33 to 20.67 days; and sick-leave costs ranged from $523 to $1,431. While the proportion of patients with MS in any given workforce will be low, those companies that do have employees with this illness may be affected by loss from reduced output while an employee is at work and from absenteeism as well as from extra staffing costs incurred to cover sick leave.
- DMTs may allow employees to continue working and thus help reduce absenteeism. Several analyses have examined the impact of DMTs on costs and absences due to sick leave. However, these analyses were generally limited by their retrospective designs, small samples sizes, and conflicting results.
Only 1 prospective study has assessed the impact of DMTs on absenteeism.64 Collectively, these studies generally found benefits of DMTs on reducing the costs associated with absenteeism.7,16,18,19 One such U.S. study of employees with MS and at least 1 DMT claim versus untreated employees with MS found that the risk-adjusted total annual medical costs ($4,393 vs. $6,187; \( P < 0.001 \)) and indirect costs ($2,252 vs. $3,053; \( P < 0.001 \)) were significantly lower for employees with at least 1 DMT claim.65

With regard to differences between DMTs in MS-associated absenteeism, Brook et al. (2009) found that patients receiving IM IFNβ-1a had lower sick-leave costs ($969 vs. $523, respectively; \( P = 0.047 \)) and fewer sick-leave days (2.98 vs. 7.18 days, respectively; \( P = 0.01 \)) versus those receiving GA.61 Similarly, Rajagopalan et al. (2011) reported that patients treated with IM IFNβ-1a demonstrated a significant improvement in the number of missed work days, with a decrease of 1.3 days (from 5.6 to 4.3 days) versus an increase of 2 days (from 2.3 to 4.3 days), in GA-treated patients (\( P < 0.05 \)).38 Only patients receiving IM IFNβ-1a showed a reduction in sick-leave absence days with therapy, while sick leave increased with SC IFNβ-1a, IFNβ-1b, and GA. In contrast, Lage et al. (2006) found that GA, compared with IM IFNβ-1a or IFNβ-1b, was associated with significantly fewer days missed for work for any reason. Compared with those not receiving a DMT, GA, IM IFNβ-1a, and IFNβ-1b were associated with 53.70 (\( P = 0.003 \)), 20.73 (\( P = 0.09 \)), and 8.28 (\( P = 0.71 \)) fewer days away from work, respectively.83 In a prospective study, GA was associated with a significant improvement in fatigue symptoms and a marked reduction in absence from work compared with patient baseline status.84

Overall, these results suggest that DMTs are likely to have a positive impact on employment and work productivity, although it is not possible to conclusively determine if certain DMTs have particular benefits. Furthermore, data are lacking on fingolimod and on natalizumab.

Study Limitations

Several study limitations should be considered when evaluating the study results presented here. The Total Resource Utilization Benchmarks analysis was a retrospective, descriptive study; that the study was not inferential; and that the analyses could not control for potential confounding factors. Also, a targeted rather than systematic literature review was performed, and while an effort was made to collect all relevant studies, certain studies may have been inadvertently excluded from the review. Additionally, the cost-effectiveness analyses were not comprehensively discussed, and the quality of the reports was not assessed.

Gaps in Knowledge: Where Is Future Research Required?

Oral Therapies. A key gap in our current knowledge regarding the cost-effectiveness of current therapies for MS relates to new oral therapies. Fingolimod was recently approved for use in RRMS by the FDA and within Europe and has been shown to produce greater reductions in annualized relapse rates compared with current DMTs (but no difference in disability progression vs. IM IFNβ-1a).13,20 Further, other oral therapies such as laquinimod, teriflunomide, and BG-12 have recently completed phase 3 trials and may receive future approval. Given that these therapies are administered orally, it is possible that they could be associated with better adherence due to the greater ease of administration and avoidance of injection anxiety that can occur with other DMTs. However, there are currently no studies demonstrating better adherence with oral therapies in MS. Demonstration of improved adherence with oral agents could lead to certain cost advantages versus some injectable therapies (in particular, lower out-of-pocket expenses for patients in the United States).85

There are still other uncertainties regarding fingolimod that clinicians and managed care organizations may need to consider. In particular, long-term safety data, monitoring practices, experience with the drug in clinical practice, and cost-effectiveness data are lacking. Furthermore, the impact of this oral agent on patient work productivity and absenteeism is currently unknown. In terms of medication costs alone, an annual course of fingolimod is more expensive than other agents. Although this direct cost does not consider DMT effectiveness and the benefits of related improvements in patient outcomes, it is of interest that the poster report of a recent Markov risk-benefit model indicated that the net health benefit of treatment, taking into account treatment efficacy and adverse effects, was similar between fingolimod and IM IFNβ-1a over 5 years (3.76 vs. 3.73 QALYs, respectively).86 Additionally, a recent study indicated that natalizumab is more cost-effective than fingolimod in terms of costs per relapse avoided.89 However, further cost-effectiveness research is required.

Combination Therapy. MS is a highly heterogeneous disease, and combination therapy strategies that target a range of disease mechanisms might be more effective than agents used as monotherapy. Currently, there is no FDA-approved combination MS therapy regimen. DMTs have been administered in combination with drugs approved for other indications, such as corticosteroids, methotrexate, azathioprine, and cyclophosphamide, with varying degrees of success.87 With the arrival of oral therapies, it is possible that DMT combination therapy could be used more frequently in MS, particularly since these new agents have different proposed mechanisms of action than the IFNβs and GA. Combining drugs with different mechanisms of action has the potential to produce greater efficacy, increased patient benefits, and improved employment rates. However, drug combinations also have the potential to cause an
increased incidence of adverse events and will lead to greater direct medication costs. Perhaps surprisingly, a recent National Institutes of Health (NIH) study (http://www.clinicaltrials.gov/ct2/results?term=NCT00211887&Search=Search) found that the combination of IFNβ with GA was no more effective than either therapy alone. Cost-effectiveness analyses will be a factor for consideration when weighing the risks and benefits of future combination regimens.

Clinical, Imaging, and Biochemical Markers of Disease Activity. Although markers of disease activity are beyond the scope of this article, they may prove useful in predicting which patients are most likely to respond to certain medications. Individualizing treatments in this way has the potential to help avoid patients’ receiving an unsuitable therapy, leading to potential cost benefits. In terms of clinical markers, current information suggests that higher EDSS or Multiple Sclerosis Functional Composite scores at baseline; incomplete recovery from the first neurological attack; shorter time to second attack; sphincter, bladder, or bowel symptoms at disease onset; cerebellar involvement; relapse frequency prior to study enrollment; male sex; and older age are all associated with increased risk of disability progression in patients with RRMS. The imaging markers—“black holes” on magnetic resonance imaging at baseline, baseline or early CNS atrophy, and baseline activity with T2 lesions, active T2 lesions, and/or gadolinium-enhancing lesions—appear to be associated with disability progression. Less is known about biochemical markers. Potential biochemical marker candidates were recently reviewed in an article by Graber and Dhib-Jalbut (2011). Although the potential biochemical markers cerebrospinal fluid neurofilament chains, tumor necrosis factor alpha, and the cell surface ligands Fas/Fasl have been correlated with patient disability, there are currently no reliable, validated MS biomarkers available for widespread clinical use. Prospective evaluations of potential candidates are needed to confirm that biochemical markers reliably predict disability progression during MS therapy.

Conclusions: Implications for Managed Care Organizations and Payers

Retrospective claims analyses can be useful to organizations ascertaining plan-specific disease management efforts versus national and regional norms. Data from the literature and the Total Resource Utilization Benchmarks analysis suggest that DMTs account for a substantial proportion of the total costs of MS. To evaluate this possibility, a review of the literature was conducted to profile the cost-effectiveness of the approved DMTs. Findings from cost-effectiveness research indicate that there are advantages for starting DMT treatment early in the disease course. This is in line with efficacy findings from clinical trials of IFNβ formulations and GA that have shown clear benefits, measured as reported delays in patient conversion to CDMS, when these agents are administered to patients after their first neurologic episode. Therefore, in line with the recommendations of the National Clinical Advisory Board of the National MS Society (http://www.nationalmssociety.org/for-professionals/healthcare-professionals/publications/expert-opinion-papers/download.aspx?id=8), the literature suggests initiating treatment with IFNβ or GA for patients who are at high risk of MS (i.e., patients with CIS).

On the basis of the available evidence, there is little evidence to separate the effectiveness or costs of IFNβ and GA formulations, which are typically used as first-line therapies. Despite the limitations of cross-study comparisons, this review found that these agents produced generally comparable cost-effectiveness, although research to date has been conflicting. Therefore, when considering a first-line agent, current therapy decisions will most likely be made based on preference, adherence, convenience, and tolerability.

Natalizumab is clinically effective and has been shown to be potentially more cost-effective than other DMTs in certain analyses, particularly in patients with more advanced disease. However, risk-benefit considerations are warranted due to the risk of PML as a possible rare adverse event. In the United States, natalizumab is approved for use as monotherapy for the treatment of relapsing forms of multiple sclerosis to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations in patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy, although its recommended use is not restricted to second-line therapy. With the recent development of an assay that detects antibodies against JCV, clinicians can now stratify patients who may be at higher and lower risk of developing PML based on anti-JCV antibody status, prior immunosuppressant use, and duration of natalizumab exposure. However, the impact of this assay on the overall cost-effectiveness of natalizumab has not been established.

Finally, fingolimod has shown promising efficacy in MS and has recently gained FDA approval for treatment of patients with RRMS. However, as discussed, questions remain about the long-term safety and cost-effectiveness of this drug. Addressing these questions will facilitate a more confident placement of this agent in the treatment algorithm.
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REFERENCES


