RESEARCH

Comparing the Cost-Effectiveness of Disease-Modifying Drugs for the First-Line Treatment of Relapsing-Remitting Multiple Sclerosis

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ABSTRACT

BACKGROUND: Multiple sclerosis (MS) is an inflammatory autoimmune disorder of the central nervous system that primarily afflicts young adults. Approximately 400,000 people in the United States are affected by MS. Although several forms of MS exist, the most common course is known as relapsing-remitting MS (RRMS), which affects about 85% of MS patients. This form of MS is characterized by relapses of neurologic symptoms followed by periods of recovery. Progression of disease can lead to increasingly severe disability. Since the introduction of immunomodulatory biologic agents, such as interferon betas and glatiramer acetate, treatment has helped to change the course of the disease. Under budgetary constraints, health services payers are challenged to differentiate the economic value of these agents for formulary selection and/or placement.

OBJECTIVE: The primary objective of this analysis was to evaluate the 2-year cost-effectiveness of 4 disease modifying drugs (DMDs) used as first-line treatment of RRMS: glatiramer acetate, interferon (IFN) β-1a IM injection, IFN β-1a SC injection, and IFN β-1b SC injection.

METHODS: An Excel-based model was developed to compare the relative effectiveness and cost components of relapses, disability progression, and DMDs in the treatment of RRMS over a 2-year time horizon. The relative risk reduction (RRR) method was used to compare reduction in relapse rates and disease progression data from pivotal randomized double-blind placebo-controlled clinical trials of the DMDs. RRRs for relapses and disability progression, respectively, were calculated as the relative difference (treatment vs. placebo) in relapse rates and disease progression rates from placebo-controlled clinical trials. These RRRs were applied to the weighted average rates of relapse and number of disability progression steps seen in the placebo arms of the pivotal studies. The evaluation was conducted from the perspective of a U.S. health care payer (only direct medical costs considered). Medical savings were calculated as costs saved due to relapses avoided and prevention in disability progression steps. In the base case analysis, we assumed 89.4% persistence, a cost per relapse of $4,682, and a cost per disability progression step of $1,788. Monthly cost of therapy was defined as wholesale acquisition cost ($0 contractual discounts and $25 patient copayment assumed in the base case analysis) plus routine monitoring costs as assessed by an expert panel. The primary economic endpoint was cost per relapse avoided. Costs and outcomes occurring in the second year were discounted 3% to bring to 2008 present values. One-way and multiway probabilistic (Monte Carlo) sensitivity analyses were conducted on key input variables to assess their impact on cost per relapse avoided.

RESULTS: Without DMD treatment, patients were predicted to experience 2.55 relapses and 0.44 disability progression steps over a 2-year period (discounted values). The 2-year reductions in clinical relapses for treatment with glatiramer acetate, IFN β-1a IM injection, IFN β-1a SC injection, and IFN β-1b were 0.66, 0.42, 0.74, and 0.70, respectively. The 2-year reductions in disability progression steps for treatment with glatiramer acetate, IFN β-1a IM injection, IFN β-1a SC injection, and IFN β-1b were 0.05, 0.15, 0.12, and 0.11, respectively. In the base case analysis, IFN β-1a SC injection, IFN β-1b SC injection, and glatiramer acetate had the most favorable costs per relapse avoided ($80,589; $87,061; and $88,310; respectively) and IFN β-1a IM injection had the least favorable cost-effectiveness ratio ($141,721 per relapse avoided). Sensitivity analyses showed that these results were robust to changes in key input parameters, such as the number of relapses and disease progression steps in untreated patients, the RRR in clinical relapse and progression rates, the rate of persistence, the average cost of relapse, and the average cost of a disease progression step.

CONCLUSION: This evaluation suggests that IFN β-1a SC injection, IFN β-1b SC injection, and glatiramer acetate represent the most cost-effective DMDs for the treatment of RRMS, where cost-effectiveness is defined as cost per relapse avoided, assuming that (a) the RRR in relapses and disease progression steps calculated from multiple DMD placebo-controlled clinical trials reflect real differences among DMDs over 2 years; and (b) resource unit costs derived from published sources reflect economic consequences of relapses and disease progression.

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What is already known about this subject

- The economic burden associated with relapsing-remitting multiple sclerosis (RRMS) is substantial. Patients with MS incur medical costs 2 to 3 times those of all enrollees in a managed care organization.
- The majority of total costs incurred by patients with MS are direct medical costs. In a cross-sectional study of U.S. patients with MS (94% of whom were using disease-modifying drugs [DMDs]), Kobelt et al. (2006) found that 34% of total costs (direct and indirect) were attributable to DMDs.
- The reduction in the frequency and severity of MS relapses may have substantial short-term budgetary impact that partially offsets the costs of DMDs. O'Brien et al. (2003) showed that the average cost per person for a high-intensity management level relapse (defined as hospitalization and subsequent care) was $12,870 (2002 U.S. dollars). The average cost per moderate episode (use of emergency room, an observational unit, or administration of acute treatments in an outpatient or home setting) was $1,847, and the average cost of a mild episode (physician office visits and symptom-related medications) was $243.
- DMDs currently available have different efficacy and safety profiles that may produce different economic outcomes. Published retrospective database analyses comparing clinical and economic effects of DMDs have not adequately adjusted for baseline differences among treatment groups. Previous economic models comparing DMDs have typically extrapolated 2-year pivotal trial results over long time horizons and have used preference-based endpoints (i.e., quality-adjusted life years [QALYs]).

What this study adds

- This economic model, constructed using data from pivotal randomized placebo-controlled clinical trials, predicted that patients with RRMS would experience 2.55 relapses and 0.44 disability progression steps over a 2-year period without DMD treatment.
- Over 2 years, for treatment with glatiramer acetate, IFN β-1a IM injection, IFN β-1a SC injection, and IFN β-1b, respectively, reductions in number of clinical relapses were estimated at 0.66, 0.42, 0.74, and 0.70, respectively. Reductions in number of disability progression steps were estimated at 0.05, 0.15, 0.12, and 0.11, respectively.
- IFN β-1a SC injection, IFN β-1b SC injection, and glatiramer acetate have the most favorable estimated costs per relapse avoided ($80,589; $87,061; and $88,310; respectively), and IFN β-1a IM injection has the least favorable cost-effectiveness ratio ($141,721 per relapse avoided).
- This model differs from those previously published because it (a) used a 2-year time horizon based on 2-year pivotal, randomized, double-blind, placebo-controlled clinical trial data without extrapolating to a 5-year or lifetime time horizon; and (b) measured as the primary endpoint relapses averted rather than endpoints that rely on the perception and measurement of preference, such as QALYs.

Multiple sclerosis (MS) affects approximately 400,000 people in the United States. Every week about 200 people are diagnosed with this inflammatory autoimmune disorder of the nervous system.[1] MS, which primarily afflicts young adults, can present in 4 different clinical forms: relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), primary-progressive MS (PPMS), and progressive-relapsing MS (PRMS). Approximately 85% of patients with MS present with RRMS.[1] This form of MS is characterized by episodic acute neurologic events that improve over a time period of days to weeks; improvement may be complete or partial.[2]

The economic burden associated with MS is substantial. One study estimated that the mean total lifetime direct and indirect cost per patient with MS was approximately $2.2 million in 1994 U.S. dollars.[3] This same study estimated annual national costs of $2.5 billion (in 1994 U.S. dollars) to manage this condition.[3] From the perspective of managed care organizations, MS contributes to higher per member costs. Pope et al. determined that the mean direct medical costs generated by members with MS (roughly $7,000 to $13,000 per member per year) are 2 to 3 times those generated by all insured enrollees.[4] A more recent study based on data from the North American Research Committee on Multiple Sclerosis patient registry (NARCOMS) estimated that the total mean annual indirect and direct cost per patient was $47,215 (in 2004 U.S. dollars), of which $29,634 (63%) were direct costs.[5] Ninety-four percent of patients in this registry were using disease-modifying drugs (DMDs), which accounted for 34% of total costs.

Reduction in the frequency and severity of MS relapses can have a substantial short-term budgetary impact.[6] O'Brien et al. (2003) found that the average cost per person for a high management level relapse (defined as hospitalization and subsequent care) was $12,870 (2002 U.S. dollars); the average cost per moderate episode (use of emergency room, an observational unit, or administration of acute treatments in an outpatient or home setting) was $1,847; and the average cost of a mild episode (physician office visits and symptom-related medications) was $243.[6] Deceleration of disease progression can also result in longer-term savings, since the direct costs of treatment rise with disability progression.[7] Furthermore, evidence suggests that MS relapses are associated with sustained disability progression, although the exact relationship is controversial.[2]

Operating under constrained resources, health care decision makers must determine the relative value of available first-line DMDs, given their cost and clinical effectiveness. Two published retrospective claims database evaluations have compared the clinical and economic outcomes of patients treated with different DMDs.[8,9] The limitations of nonrandomized analyses are well documented.[10] Randomization is the only method for controlling for unknown or unmeasured prognostic factors among comparison groups.[10] Despite the efforts of the authors of these observational studies to address potentially important between-group differences in baseline characteristics,[8,9] it is still possible that unmeasured confounding factors affected study results.

Previous economic models comparing multiple first-line DMDs have typically extrapolated 2-year pivotal trial results over long time horizons[11-13] and have used preference-based endpoints (i.e., quality-adjusted life years [QALYs]).[11-13] The objective of this study was to develop an evidence-based economic model to assess relative cost-effectiveness of the 4 first-line DMDs using results from randomized placebo-controlled clinical trials (RCTs) in RRMS.[14-19]

Methods

Model Overview

A Microsoft Excel-based model was designed to compare the relative effectiveness and cost components of relapses, disability progression, and DMD therapy in the treatment of RRMS. Four first-line DMDs were included in the evaluation: glatiramer acetate 20 milligram (mg) daily subcutaneous (SC) injection, interferon (IFN) β-1a 30 microgram (mcg) weekly intramuscular (IM) injection (IFN β-1a IM), IFN β-1a 44 mcg 3 times weekly SC injection (IFN β-1a SC), and IFN β-1b 250 mcg every other day SC injection (IFN β-1b). The reference group in the evaluation was defined as RRMS patients not treated with a DMD.

The model was constructed from the perspective of health care payers in the United States. Direct medical costs and outcomes were modeled over a 2-year time horizon because this

TABLE 1 *Clinical Trials[a] and Effectiveness Measures Used in the Model*

First Author and Year	Treatment	Entry Criteria	Relapse Definition[b]	Mean Baseline Relapse Rate, EDSS	N (Placebo, Treatment)	2-Year Relapse Rates (Placebo, Treatment [Absolute Difference, Percent Difference])	2-Year Disability Progression Rates (Placebo, Treatment, [Absolute Difference, Percent Difference][c]
Johnson 1995[14]	Glatiramer acetate, 20 mg SC daily	Aged 18-45 years, ambulatory, EDSS 0-5.0, history of 2 relapses in past 2 years	More restrictive	2.9, 2.8	126, 125	1.68, 1.19 [0.49, 29.2%]	24.6%, 21.6%[d] [0.03, 12.2%]
Jacobs 1996[15]	IFN β-1a, 30 mcg IM weekly	Aged 18-55 years, EDSS 1.0-3.5, history of 2 relapses in past 3 years	More restrictive	1.2, 2.4	143, 158	1.64, 1.34 [0.30, 18.3%]	34.9%, 21.9% [0.13, 37.2%]
PRISMS 1998[16,17]	IFN β-1a, 44 mcg SC 3 times weekly	Aged 18 years or older, EDSS 0-5.0, history of 2 relapses in past 2 years	Less restrictive	3.0, 2.5	187, 184	2.56, 1.73 [0.83, 32.4%]	38.3%, 26.8% [0.12, 30.0%]
IFNB 1993[18,19]	IFN β-1b, 250 mcg SC every other day	Aged 18-50 years, EDSS 0-5.5, history of 2 relapses in past 2 years	Less restrictive	3.4, 3.0	123, 124	2.62, 1.81 [0.81, 30.9%]	28.0%, 20.0%[d] [0.08, 28.6%]

[a]All studies were 2-year, double-blind, placebo-controlled randomized controlled trials.

[b]Less restrictive: consistent with the Schumacher definition of relapse; the appearance of a new symptom or worsening of an old symptom persisting over at least 24 hours, preceded by stability or improvement for at least 30 days, and confirmed by a neurologist to be attributed to MS activity within 7 days.[30] More restrictive: neurological abnormality persists for at least 48 hours, is preceded by a stable or improving state for 30 days, and produces specific symptom changes in system function scores.

[c]Mean disease progression rates for the placebo groups in trials of glatiramer acetate, IFN β-1a IM, and IFN β-1a SC were 0.21, 0.74, and 0.48, respectively.

[d]Differences in number of disease progression steps between DMD and placebo were not statistically significant.

DMD = disease-modifying drug; EDSS = Expanded Disability Status Scale; IFN = interferon; IFNB = interferon beta; IM = intramuscular; mcg = micrograms; mg = milligram; MS = multiple sclerosis; PRISMS = Prevention of Relapses and Disability by IFN-1a Subcutaneously in Multiple Sclerosis; SC = subcutaneous..

was the duration of all pivotal randomized, placebo-controlled studies for the 4 DMDs.[14-19] Cost-effectiveness was expressed as cost per relapse avoided because (a) the original pivotal studies of DMDs were all 2 years in duration; (b) disease progression in MS is a slow process; and (c) U.S. payers typically prefer shorter time periods (e.g., 1 to 3 years) when conducting economic analyses. While some audiences are interested in a longer time horizon and cost-utility analyses based on QALYs, others perceive greater value in shorter-term analyses based on more concrete outcome measures.[20]

Second-line therapies (e.g., mitoxantrone and natalizumab) were not included in the model because use of these products is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate MS therapies.[21-23] In 2008, new information was added to the prescribing label of natalizumab (Tysabri) warning of the risk of liver damage and progressive multifocal leukoencephalopathy (PML).[22] Thus, the purpose of this model was to evaluate the self-injectable DMDs as first-line therapies.

Clinical Input Parameters

Clinical input parameters were derived from 4 pivotal placebo-controlled clinical trials of the comparators.[14-19] The trials were double-blind, placebo-controlled randomized trials of relapsing patients treated with either a recombinant interferon, given by the SC or the IM route, or glatiramer acetate. These treatments decreased the recurrence of exacerbations and the progression of the disease at 2 years after randomization compared with patients receiving placebo (Table 1).[24,25]

Treatment Persistence. Individuals with MS might not be fully aware of the importance of continuing treatment with DMDs in the absence of feeling better (and often feeling worse) while taking therapy.[26] The clinical trial data that were used for effectiveness in the model do not reflect "real-world" discontinuation of therapy. Drop-out rates from clinical trials tell us how many patients stopped participating in the trial, not how many completed the course of therapy. Two recent long-term observational studies documented rates of persistence and discontinuation of DMDs in the "real world."[27,28] We used these rates of persistence (weighted by number of patients in each trial) to adjust the rates of effectiveness down for the comparators and account for the discontinuation of therapy. This adjustment assumed that DMD clinical effectiveness was directly proportionate to persistence. Specifically, the relapse rate reductions taken directly from the randomized controlled clinical trials were adjusted downward by 10.6% based on the weighted average 89.4% persistence rate seen in the 2 observational studies.[27,28] Equal persistence for all DMDs was assumed because adequate data differentiating the persistence of DMDs do not exist. Studies have shown that persistence is affected by effectiveness and tolerability experienced by patients in general,[27-29] but studies presenting persistence rates stratified by DMD treatment did not randomize patients nor account for patient baseline differences, and therefore inferences about actual differences cannot be made.[27,29] A complete listing of the key default input parameters utilized in the model is presented in Table 2.

TABLE 2 Default Input Parameters: Base Case, Undiscounted

Parameter	Base Case Value	Reference
Clinical Inputs		
DMD persistence rate (glatiramer acetate, IFN β-1a IM, IFN β-1a SC, IFN β-1b SC)	89.4%	Nonpersistence rates: O'Rourke et al. 2005 (14.2%, n=394),[27] Rio et al. 2005 (8.3%, n=632)[28]
Rate of untreated events (i.e., "no treatment" option): • # relapses in an untreated patient over 2 years • # disability progression steps in an untreated patient over 2 years	 2.58 relapses 0.45 steps	 PRISMS 1998,[16] IFNB Multiple Sclerosis Study Group 1995[19] Johnson et al. 1991,[14] Jacobs et al. 1996,[15] PRISMS 1998[16]
Cost Inputs		
Monthly cost of therapy[a] (WAC) • Glatiramer acetate SC (20 mg QD) • IFN β-1a IM (30 mcg QW) • IFN β-1a SC (44 mcg TIW) • IFN β-1b SC (250 mcg QOD)	 $2,322 ($2,283) $2,294 ($2,243) $2,384 ($2,334) $2,461 ($2,411)	WAC derived from Red Book, April 2009.[32] Cost of monitoring was calculated from expert opinion by neurologists (unit frequency)[b] and 2008 CMS fee schedule[33] (unit cost).
Cost of relapse by severity • Mild (relative incidence) • Moderate (relative incidence) • Severe (relative incidence) Average cost of relapse[c]	 $243 inflated to $313 (0.33) $1,847 inflated to $2,381 (0.46) $12,870 inflated to $16,589 (0.21) $4,682	O'Brien et al. 2003 (cost),[6] Panitch et al. 2002 (relative incidence),[35,36] U.S. Department of Labor Statistics 2008 (inflation)[34]
Average cost of disability step[d]	$1,788	Kobelt et al. 2006[5]
Monthly costs of therapy monitoring/adverse events: • Glatiramer acetate SC (20 mg QD) • IFN β-1a IM (30 mcg QW) • IFN β-1a SC (44 mcg TIW) • IFN β-1b SC (250 mcg QOD)	 $64 $75 $75 $75	Cost of monitoring was calculated from expert opinion by neurologists (unit frequency),[b] and 2008 CMS fee schedule[33] (unit cost).

[a]*Monthly cost of therapy includes one-twelfth of the annual cost of DMD (based on 80% of AWP, April 2009)[32] offset with a $25 member copayment, net discounts (default set at 0%), and monitoring (i.e., LFT, CBC, MRI, and outpatient visits).*

[b]*Number of units associated with monitoring was based on the opinions of an expert panel of 5 neurologists who were colleagues of the principal author. They were not paid for their expert opinion. Multiple exchanges with the experts were used to obtain a consensus on the type and frequency of monitoring. Annual tests were estimated as follows: LFT—1 for glatiramer acetate, 3 for interferons; CBC—1 for glatiramer acetate, 1.5 for interferons; MRI—0.5 for all DMDs. It was also estimated that all DMD patients would have 2 Level 3 outpatient visits and 1 Level 4 outpatient visit per year for monitoring.*

[c]*Relapse costs reported by O'Brien et al.[6] were adjusted for inflation to U.S. 2008 dollars.*

[d]*Based on slope of line plotting cost by EDSS level by Kobelt et al. (2006).[5]*

CBC = complete blood count; CMS = Centers for Medicare & Medicaid Services; DMD = disease-modifying drug; EDSS = Expanded Disability Status Scale; IFN = interferon; IFNB = interferon beta; IM = intramuscular; LFT = liver function test; mcg = microgram; mg = milligram; MRI = magnetic resonance imaging; PRISMS = Prevention of Relapses and Disability by IFN-1a Subcutaneously in Multiple Sclerosis; QD = every day; QOD = every other day; QW = every week; SC = subcutaneous; TIW = three times per week; WAC = wholesale acquisition cost.

Treatment Response (Relapse Rate and Disability Progression). Treatment response was defined as the number of relapses and disability progression steps avoided by a patient over the 2-year time horizon. Based on the 2-year trends observed in placebo-treated groups of the IFNβ-1a SC and IFNβ-1b SC trials (weighted by number of patients in each of the placebo arms),[16,19] it was assumed that an average untreated patient would experience 2.58 relapses over a 2-year period (nondiscounted values). The IFNβ-1a SC and IFNβ-1b SC trials[16,19] were selected for provision of untreated relapse rate information because the definition of relapse used in these trials is more clinically and economically meaningful than the definition used in the placebo-controlled studies of glatiramer acetate and IFNβ-1a IM.[14,15] The definition of a relapse that was used in the IFNβ-1a SC and IFNβ-1b SC trials is consistent with the Schumacher definition of relapse[30]—the appearance of a new symptom or worsening of an old symptom persisting over at least 24 hours. The abnormality is preceded by stability or improvement for at least 30 days and is confirmed by a neurologist to be attributed to MS activity within 7 days.[30] The definition used in the glatiramer acetate and IFNβ-1a IM studies[14,15] required that the abnormality persist for at least 48 hours, is preceded by a stable or improving state for 30 days, and produces specific symptom changes in system function scores. This more restrictive definition of relapse[14,15] would not adequately capture some meaningful clinical outcomes experienced by MS patients. Furthermore, it is expected that resources would be consumed (and costs would be incurred) for the more mild relapses captured by the Schumacher definition.[30]

Disability progression is often assessed using the 10-point Kurtzke Expanded Disability Status Score (EDSS) scale (0 = no disability; 10 = death from MS).[31] Data about the average number of disease progression steps experienced by patients over a 2-year period were also obtained from the DMD RCTs that had this information available.[14-16] The overall number of disease

progression steps for untreated patients was obtained by weighting the mean disease progression that occurred in each of the 3 trials by the number of patients in that trial's placebo arm.[14-16] Although the *percentage* of patients with disease progression was reported in the IFNβ-1b SC trials, the *mean number* of disease progression steps per patient was not reported.[18,19]

Since there were no randomized controlled trials comparing the 4 DMDs directly, the products were compared indirectly through a common (placebo) comparator.[14-19] It was important to calibrate the efficacy of DMDs seen in the clinical trials, since the trials differed in their design and patient baseline characteristics (Table 1). The IFNβ-1a IM trial[15] included patients with 2 or more relapses in 3 years, whereas the other trials required patients to have 2 or more relapses within 2 years.[14,16-19] Patients in the IFNβ-1a IM trial[15] were required to have a baseline EDSS score between 1.0 and 3.5, whereas patients in the other trials could have baseline EDSS scores between 0 to 5 or 5.5.[14,16-19] On average, patients enrolled in the IFNβ-1a IM trial[15] were younger and had a shorter disease duration, lower baseline relapse rate, and lower baseline EDSS compared with the other IFN trial patients.[14,16-19] The rate of study completion with IFNβ-1a IM,[15] 57.1%, was also considerably lower than that seen with the other DMDs—85.7%, 89.6%, and 90.9% for glatiramer acetate, IFNβ-1a SC, and IFNβ-1b SC, respectively.[14,16-19]

To account for differences in trial design among the studies, the numbers of relapses avoided and rate of reduction in disability progression steps by each DMD were calculated as the relative difference between the placebo and DMD groups. The number of relapses avoided was estimated using the relative risk reduction of relapse with each of the DMDs from each DMD pivotal trial. The relative risk reduction of relapse was obtained by subtracting the rate of relapse with the DMD from the rate of relapse with placebo and dividing this difference by the rate of relapse with placebo. The calculated relative risk reduction of relapse with the DMD was then multiplied by the persistence rate (89.4%) and by the number of relapses over 2 years obtained from placebo pivotal trial data (2.58)[16,19] to obtain the number of relapses avoided with the DMD over 2 years. This number of relapses avoided with the DMD was then subtracted from the placebo pivotal trial number of relapses (2.58)[16,19] to obtain the number of relapses with the DMD.

The absolute reductions in clinical relapses during a 2-year period for glatiramer acetate, IFN β-1a IM, IFN β-1a SC, and IFN β-1b were calculated to be 0.49, 0.30, 0.83, and 0.81, respectively. The relative risk reductions of relapse for glatiramer acetate, IFN β-1a IM, IFN β-1a SC, and IFN β-1b SC were calculated to be 29.2%, 18.3%, 32.4%, and 30.9%, respectively. Thus, for example, before discounting the assumed relapses avoided for patients treated with glatiramer acetate were 29.2% X 89.4% X 2.58 = 0.67; subtracting 0.67 from 2.58 yields 1.91 relapses before discounting and 1.88 after discounting for a 2-year period.

The number of disability progression steps avoided was estimated using the relative risk reduction of progression with each of the DMDs from each DMD pivotal trial. Because mean change in disability progression steps was not reported for all the trials, the calculation was based on the reported rate of disability progression, defined as the percentage of patients experiencing a change of at least 1 disability step on the EDSS. The relative risk reduction of progression for each DMD was obtained by subtracting the rate of disability progression with the DMD from the rate of progression with placebo and dividing this difference by the rate of progression with placebo. The calculated relative risk reduction of progression with the DMD was then multiplied by the persistence rate (89.4%) and the number of disability progression steps over 2 years obtained from placebo pivotal trial data (0.45)[14-16] to obtain the number of disability progression steps avoided with the DMD over 2 years. This number of disability progression steps avoided with the DMD was then subtracted from the placebo pivotal trial number of disability steps (0.45)[14-16] to obtain the number of disability steps with the DMD.

Note that all DMD treatment groups were numerically observed in the RCTs to reduce the proportion of patients progressing compared with placebo. However, in the studies of IFN β-1b and glatiramer acetate, the differences did not reach statistical significance. Nonetheless, the rates of progression were utilized as reported in the studies. The absolute reductions in rates of disability progression for glatiramer acetate, IFN β-1a IM, IFN β-1a SC, and IFN β-1b, were calculated to be 0.03, 0.13, 0.12, and 0.08, respectively. The relative risk reductions of progression for glatiramer acetate, IFN β-1a IM, IFN β-1a SC, and IFN β-1b were calculated to be 12.2%, 37.2%, 30.0%, and 28.6%, respectively. Thus, for example, before discounting the assumed disability progression steps avoided for patients treated with glatiramer acetate were 12.2% X 89.4% X 0.45 = 0.049; subtracting 0.049 from 0.45 yields disability progression steps of 0.40 before discounting and 0.40 after discounting (discounted difference too small to detect with 2 decimal places).

Cost Input Parameters

Index Reporting Year. All costs were reported as U.S. dollars in 2008 value (base year). Year 2 costs and clinical outcomes were discounted at 3%.

Cost of DMD Therapy (monthly). Cost of therapy was based on the monthly cost of DMD therapy and duration of treatment. Monthly cost of therapy included cost of the agent (based on one-twelfth of the annual wholesale acquisition cost [WAC], April 2009)[32] offset by a $25 member copayment, a base case net discount (i.e., rebates) of 0%, and any costs associated with resource use for office visits and laboratory and/or diagnostic testing performed to monitor for adverse events (i.e., liver function tests [LFTs], complete blood count [CBC], and magnetic resonance imaging [MRI]; Table 2). Unit costs associated with monitoring of DMDs were based on the 2008 Medicare fee schedule.[33]

Recommendations for type and frequency of monitoring units for RRMS patients were based on a review of the package inserts for all DMDs and consultation with an expert panel of 5 neurologists who were colleagues of the principal author. They were not paid for their expert opinion. Multiple exchanges with the experts were used to obtain a consensus on the type and frequency of monitoring. The following formula was applied to the calculation of the monthly cost of DMD:

Cost of DMD therapy (monthly) = DMD WAC price − net discount − copay + resource use due to monitoring for adverse events

Thus, for example, the total monthly cost of treatment with glatiramer acetate was assumed to be $2,283 - $25 + $64 = $2,322 (Table 2).

Cost of Relapse. The costs associated with relapse were obtained from a published 2003 study by O'Brien et al. that stratified cost of relapse by severity (i.e., low, moderate, and high intensity).[6] The O'Brien et al. study[6] used net payer cost data whenever available and adjusted any costs using a cost-to-charge ratio when any charges were used as inputs. These published costs were inflated to year 2008 U.S. dollars using the medical care component of the Consumer Price Index (CPI) for all urban consumers.[34]

The average cost of relapse ($4,682) was calculated as the sum of costs of mild, moderate, and severe relapse events that were weighted by the relative incidence ratios derived from the EVidence for Interferon Dose-response: European North American Comparative Efficacy (EVIDENCE) trial data reported by Panitch et al. (2002, 2005)[35,36] This trial was selected for provision of this information because it was rich in information about the nature of relapses that occurred and because the definition of relapse used in the EVIDENCE trial was clinically and economically meaningful. The definition used by Panitch et al., like the definition used in the IFNβ-1a SC and IFNβ-1b SC randomized, placebo-controlled trials,[16-19] is consistent with the Schumacher definition of relapse.[30] It was assumed that the severity of relapse was the same for all medications.

Cost of Disability Step. The average cost of increasing a disability step ($1,788) was calculated using data from the U.S. MS costing study by Kobelt et al. (2006).[5] These authors presented mean annual costs per MS patient by levels of functional capacity. Their study showed that mean annual costs per patient increased linearly by EDSS level. By calculating the slope of the line of direct medical costs, we were able to estimate the direct medical cost per increase in disability step for the current economic model. Since Kobelt et al. included the cost of DMDs and the cost of relapses in direct medical costs,[5] we subtracted these costs from the total costs to estimate the direct medical costs related to disability. Although the cost of DMDs per patient per year was presented in Kobelt et al.'s study, the cost of relapses was not shown. Therefore, we approximated the cost of relapses per year for our model input by averaging the annual number of relapses per DMD patient in our study and multiplying this average by the cost of relapse that we estimated from O'Brien et al.[6]

Model Outputs

The results of the model were expressed in 4 different metrics:

1. *Medical cost*—defined as the cost associated with the stated event rates of relapses and progression in steps of disability.

   Medical Cost = (number of relapses X average cost of relapse) + (number of disability steps X average cost of disability step)

2. *Cost of DMD therapy*—defined as the cost of DMD therapy reflecting the stated treatment persistence rate of 89.4%.

   Cost of DMD therapy = (monthly cost of DMD therapy) X 24 months X persistence rate

3. *Medical savings*—defined as the direct medical costs (related to relapses and progression in steps of disability) not incurred as compared with no DMD treatment.

   Medical savings = medical cost without DMD therapy – medical cost with DMD therapy

4. *Cost per relapse avoided*—defined as the primary model outcome.

   Cost per relapse avoided = (medical cost + cost of DMD therapy)/(number of relapses without DMD therapy – number of relapses with DMD therapy)

Model Assumptions

The following assumptions were made during model development:

1. The costs of treating or further investigating adverse events for the products were not included because most adverse events seen in DMD clinical trials are typically mild, requiring minimal or no medical intervention (e.g., injection-site reactions and flulike symptoms). Evidence has shown that liver function abnormalities are typically reversible, either spontaneously or with dose reduction. Furthermore, some patients experiencing adverse events would likely discontinue therapy (and therefore this effect would be captured by including a rate of persistence) and no further resource utilization would occur.
2. DMD effects on disability progression were included in the model regardless of statistical significance.
3. Health plan member attrition and mortality were not accounted for because these factors were assumed to have similar effect across all comparison groups over the study period.
4. The possible impact of neutralizing antibodies (NAbs) on treatment efficacy was not considered because the effect should be reflected in the differences in treatment efficacy seen in the RCTs.

TABLE 3 Base-Case Results: Discounted Per Patient Clinical Outcomes, Costs, and Savings Over 2 Years

	Glatiramer Acetate	IFN β-1a IM	IFN β-1a SC	IFN β-1b SC	No DMD Treatment
Clinical outcomes					
Relapses	1.88	2.13	1.84	1.81	2.55
Relapses avoided[a]	0.66	0.42	0.74	0.70	-
Disability progression steps	0.40	0.30	0.33	0.33	0.44
Disability progression steps avoided[b]	0.05	0.15	0.12	0.11	-
Costs and savings					
Medical cost: relapses and disease progression[c]	$9,537	$10,513	$9,060	$9,231	$12,733
Medical savings[d]	$3,196	$2,221	$3,673	$3,502	-
Cost of DMD therapy[e]	$49,068	$48,473	$50,389	$52,010	$0
Total MS-related cost[f]	$58,605	$58,986	$59,449	$61,241	
Cost per relapse avoided[g]	$88,310	$141,721	$80,589	$87,061	-

[a]*Relapses avoided = (number of relapses for no DMD treatment) – (number of relapses for placebo in DMD trial - number of relapses for DMD), reduced by 10.6% to account for an assumed persistency rate of 89.4%.*

[b]*Disability progression step avoided = (number of disability progression steps for no DMD treatment) – (% placebo patients progressing in DMD trial - % of DMD patients progressing), reduced by 10.6% to account for an assumed persistency rate of 89.4%.*

[c]*Medical cost = (number of relapses x average cost per relapse) + (number of disability progression steps x average cost per disability progression step).*

[d]*Medical savings = cost of disease with no DMD therapy ($13,301) – Medical cost of individual DMD.*

[e]*Cost of DMD therapy = cost of DMD treatment + cost of monitoring of adverse events for DMD (monthly monitoring cost of $64.06 for glatiramer acetate and $75.37 for the interferons).*

[f]*Total MS-related cost = cost of DMD therapy + medical cost for relapses and disease progression.*

[g]*Cost per relapse avoided = (medical cost + cost of DMD therapy) / (number of relapses avoided). Results may not match exactly to numbers shown because of rounding.*

DMD = disease modifying drug; IFN = interferon; IM = intramuscular; MS = multiple sclerosis; SC = subcutaneous.

Sensitivity Analyses

One-way and multiway probabilistic (Monte Carlo) sensitivity analyses were performed to evaluate the impact of variations in a number of input parameters. Specifically, input parameter values were varied to assess their impact on the cost-effectiveness ratio (cost per relapse avoided).

For the one-way sensitivity analyses, the method of calculating effectiveness was changed to the absolute risk reduction method (i.e., calculating effectiveness as the absolute difference between treatment and placebo) rather than the relative risk reduction method. The number of relapses and disease progression steps in untreated patients, the relative risk reduction in clinical relapse rate and progression rate, the rate of persistence, the cost of DMD therapy, the cost of disease progression, and the cost of relapse were varied by ± 25% of base value to determine the sensitivity of model results to these individual inputs. An analysis using no copayment was also conducted.

For the multiway probabilistic (Monte Carlo) sensitivity analyses, the number of relapses and disease progression steps in untreated patients (assumed normal distribution), the number of relapses and disease progression steps avoided (assumed normal distribution), the rate of persistence (assumed uniform distribution from 89.6% to 100%), and the costs of relapse and disease progression (assumed lognormal distribution) were simultaneously varied to better evaluate the robustness of the model.

Results

Base Case

According to the base case assumptions and after discounting second-year outcomes, it was determined that the "no treatment" option in a given patient was associated with 2.55 relapses and 0.44 disability progression steps over a 2-year period (Table 3). IFN β-1a SC was estimated to result in the greatest effect in terms of avoiding relapses and disability progression. In comparison with no DMD treatment during a 2-year period, patients treated with IFN β-1a SC would avoid 0.74 relapses and 0.12 disability progression steps. In contrast, patients treated with IFN β-1a IM would avoid 0.42 relapses and 0.15 disability progression steps.

Reduced number of relapses and disability progression steps over the 2-year period translated into medical cost savings compared with the no DMD treatment group. Considering that the 2-year medical cost without treatment was calculated to be $12,733, 2-year per patient medical savings with use of DMDs ranged from $3,673 with IFN β-1a SC to $2,221 with IFN β-1a IM. Including drug cost, cost of monitoring for adverse events ($64.06 for glatiramer acetate and $75.37 for the interferons) and net of patient copayment ($25 in the base case), the total cost of DMD treatment over 2 years for the 4 comparators was $49,068 for glatiramer acetate, $48,473 for IFN β-1a IM injection, $50,389 for IFN β-1a SC injection, and $52,010 for IFN β-1b SC. Ranked in order based on the cost per relapse avoided (most to least cost-effective), first-line DMDs were IFN β-1a SC ($80,589), IFN β-1b SC ($87,061), glatiramer acetate ($88,310), and IFN β-1a IM injection ($141,721).

TABLE 4 Sensitivity Analyses of the Effect of Key Input Parameters on Cost Per Relapse Avoided

Parameter	Glatiramer Acetate	IFN β-1a IM	IFN β-1a SC	IFN β-1b SC
Base Case	$88,310	$141,721	$80,589	$87,061
One-way analyses				
Clinical inputs				
Absolute risk reduction in relapse and progression	$138,388	$226,152	$81,406	$85,880
Number of relapses in untreated patients				
-25%	$113,506	$181,199	$103,764	$112,140
+25%	$73,193	$118,035	$66,684	$72,013
Number of disease progression steps in untreated patients				
-25%	$88,036	$141,394	$80,387	$86,845
+25%	$88,584	$142,049	$80,792	$87,277
RRR in clinical relapse rate				
-25%	$119,247	$190,450	$108,968	$117,594
+25%	$69,748	$112,484	$63,562	$68,741
RRR in disease progression rate				
-25%	$88,344	$141,885	$80,663	$87,135
+25%	$88,277	$141,558	$80,515	$86,987
Persistence rate				
-25%	$94,644	$151,838	$86,294	$93,043
+25%	$86,295	$138,500	$78,773	$85,156
Cost inputs				
Cost of DMD				
-25%	$70,335	$113,562	$64,052	$69,142
+25%	$106,285	$169,881	$98,780	$104,979
No copayment	$89,106	$142,991	$81,305	$87,812
% distribution of low, moderate, and high relapses equal (33.3%)	$93,053	$150,403	$84,713	$91,468
Cost of relapse				
-25%	$85,130	$135,899	$77,823	$84,105
+25%	$91,491	$147,544	$83,355	$90,016
Cost of disease progression				
-25%	$88,036	$141,394	$80,387	$86,845
+25%	$88,584	$142,049	$80,792	$87,277
Multiway probabilistic (Monte Carlo) analyses (95% simulation interval)	$74,999-$107,261	$119,456-$174,644	$68,266-$98,398	$73,783-$105,819

DMD = disease-modifying drug; IFN = interferon; IM = intramuscular; RRR = relative risk reduction; SC = subcutaneous.

Sensitivity Analyses

The results of one-way sensitivity analyses are shown in Table 4. Although model results were sensitive to using absolute risk reduction rather than relative risk reduction, the overall rank order of results did not change. Sensitivity analyses around the number of relapses and disease progression steps in untreated patients showed that the model was more sensitive to the untreated relapse rate, but again, the overall rank order results were robust to changes in the values of these input parameters. Increasing the number of relapses in untreated patients by 25% decreased the cost-effectiveness ratio, thereby increasing the cost-effectiveness. Increasing the number of disability steps had the opposite effect—the cost-effectiveness ratio increased, and products were less cost-effective than in the baseline analysis. Changing the relative risk reduction in clinical relapse rate had a similar effect on model results. Again, the rank order of cost-effectiveness of the products did not change with this analysis. Decreasing the persistence increased the cost-effectiveness ratio of all the products, making them all less cost-effective to varying degrees. Increasing the persistence rate had the opposite effect.

Sensitivity analyses on the cost of DMD therapy revealed that IFN β-1a SC, IFN β-1b SC, and glatiramer acetate yielded the most favorable estimates of cost per relapse avoided over the range of costs tested. Removing the $25 member copayment made the cost-effectiveness ratios of the products slightly less favorable. Distributing the frequency of the types of relapses equally increased the cost of relapse, in effect, and thereby increased the cost-effectiveness ratios of the products. Varying the cost of relapse or a step in disease progression did not affect results significantly.

Multiway probabilistic (Monte Carlo) sensitivity analyses showed that simultaneously varying multiple input parameters did not affect overall model findings. The 95% simulation intervals around the cost per relapse avoided demonstrated the robustness of findings.

Discussion

Because of the risk of irreversible disability progression and the emerging evidence suggesting that MS relapses may produce a measurable sustained effect on disability, patients with MS are treated aggressively in earlier stages.[2,7] Costs of long-term MS therapy are prompting payers to look for effective measures that can control MS-related spending. Health care decision makers must determine the relative value of available first-line DMDs given their costs and clinical effectiveness.

It is challenging to make comparisons of the relative effects of DMDs across clinical trials because of heterogeneity in inclusion criteria and baseline disease severity. Most, if not all pivotal clinical trials in MS report clinical efficacy in terms of relative risk reduction.[14-19] This is the method we employed in our economic evaluation for the base-case scenario. The relative risk reductions in relapse and disease progression rates of 4 DMDs were assessed over a 2-year period in this evaluation. The relative efficacies of the 4 DMDs were assumed to have a direct effect on their cost-effectiveness. When considering reduction in clinical relapses, the rank order of decreasing effectiveness (number of relapses avoided, from most effective to least effective) was the following: INF β-1a SC (0.74), INF β-1b SC (0.70), glatiramer acetate (0.66), and INF β-1a IM (0.42). Data from the EVIDENCE trial and from the work of Etemadifar et al. (2006), who directly compared INF β-1a SC with INF β-1a IM, corroborate the ranking of these 2 agents in this evaluation.[35-37] Furthermore, 2 trials that directly evaluated INF β-1b SC and INF β-1a IM found higher rates of patients who were relapse free at 2 years with INF β-1b SC.[38] Again, these findings validate the ranking between these 2 agents estimated in the current model. Khan et al. (2001) also support these findings in an open-label observational study, by showing that after 18 months of treatment, the mean annualized number of relapses was significantly reduced only in patients treated with glatiramer acetate and INF β-1b SC, not in patients treated with INF β-1a IM.[39] Measured as reduction in disability progression, the rank order of decreasing effectiveness (from most effective to least effective) found in this study was as follows: INF β-1a IM (0.15), INF β-1a SC (0.12), INF β-1b SC (0.11), and glatiramer acetate (0.05).

In the assessment of relative cost-effectiveness, cost per relapse avoided was selected as the primary outcome primarily because the financial impact of relapses is more immediate than that of disability progression. According to O'Brien et al, the cost of a relapse can be as high as $16,589 (adjusted to U.S. 2008 dollars).[6] Secondarily, over a 2-year period, it is unlikely that patients considered in the model, assumed to have similar disability as patients from the source clinical trials, would have experienced much disability progression. Note that all trials selected for this model included populations with mean baseline EDSS scores below 3.

Results from this evaluation showed a difference in the cost-effectiveness ratio among the DMDs. IFN β-1a SC injection had the most favorable cost-effectiveness ratio, measured as cost per relapse avoided ($80,589), followed by IFN β-1b SC injection ($87,061), glatiramer acetate ($88,310), and IFN β-1a IM injection ($141,721). Differences in cost-effectiveness were primarily driven by the assumed net clinical benefit in relative reduction in relapse rates for each of the 4 self-injectable DMDs. This model is suited to the U.S. health care payer perspective because it compares 4 first-line DMDs to one another, uses an appropriate time horizon (2 years), uses a simple and transparent approach (decision analysis using data from 2-year trials directly without extrapolation beyond 2 years), includes only direct medical costs (productivity loss and caregiver costs not considered), and evaluates clinical outcomes that are relevant for the U.S. health care payer audience (relapses and disease progression rather than utilities or QALYs).

Sensitivity analyses across the range of inputs demonstrated that the model results were robust to changes in a range of input parameters. Because of the heterogeneity in the design of the various studies, we conducted sensitivity analyses around clinical effectiveness inputs. In recognition of the limitations inherent in measures of relative effect, the U.S. Food and Drug Administration recently issued guidance that encourages industry sponsors to report both relative and absolute differences between the treatment groups.[40] In formulary policy situations, the absolute risk reduction technique may be more meaningful, since it reflects both the underlying risk without treatment and the risk reduction associated with treatment.[41] From an economic perspective, the net clinical benefit derived from the relative risk reduction technique is a key driver in the cost-effectiveness calculation as it represents the denominator in the average cost-effectiveness ratio calculation. We included a sensitivity analysis examining the effect of using absolute rather than relative risk reduction. The 2 methods resulted in similar findings: IFN β-1a SC injection, IFN β-1b SC injection, and glatiramer acetate had the most favorable cost-effectiveness ratios per relapse avoided, and IFN β-1a IM injection had the least favorable cost-effectiveness ratio. This same finding was observed with all remaining one-way sensitivity analyses and was confirmed with the multiway probabilistic (Monte Carlo) analysis. This finding also corresponds to recent findings of 3 randomized clinical trials comparing glatiramer acetate with IFN β-1a SC and IFN β-1b SC that found no significant differences in the primary clinical outcomes.[42-45]

It is difficult to equate or contrast the results of this investigation with published studies comparing cost-effectiveness of DMD therapies in MS. This is largely because of differences in comparators, methodological design, model assumptions, context, and settings among these evaluations. A study by Prosser et al. (2004)[12] evaluated patients who were newly diagnosed with nonprimary progressive MS using a 10-year MS treatment cost-utility model that evaluated societal outcomes extending up to 40 years. IFN β-1a SC was not included in the evaluation. Using a relative risk reduction method similar to that used in the present study, the advantage of IFN β-1a IM with respect to

relative disease progression was carried out over 40 years. For this reason, IFN β-1a IM was found to yield the largest gain in QALYs compared with glatiramer acetate and IFN β-1b SC, with an incremental cost-effectiveness ratio of $2,200,000 per QALY for women and $1,800,000 per QALY for men compared with no treatment. Using the relative risk reduction method for the calculation of relapse rates is favorable towards IFN β-1a IM because the placebo rate of relapse of IFN β-1a IM[15] patients was lower than the placebo rate of relapse in trials of other DMDs,[14,18,19] resulting in a smaller denominator in the relative risk reduction calculation for relapse, thereby magnifying the benefits of IFN β-1a IM. Utilities used to derive QALYs in the Prosser model[12] relied on a sample of 67 residents in a single apartment complex in San Diego, California.[46]

Chilcott et al. (2003)[13] assessed costs for managing relapses and disability using a UK-based patient database and conducted a cost-utility analysis that reported cost per QALY gained for the same 4 DMDs evaluated in this study over a 20-year time horizon. The base case cost per QALY gained by using any of the 4 treatments ranged from £42,000 to £98,000. Estimates of the utilities for each disability and relapse state were derived from 780 patients based on a generalized linear regression of EQ-5D single index score; however, the analyses were proprietary and are not available in the public domain. The analysis was based on UK treatment patterns and costs and its results may not be applicable to patients treated in the United States.

Bell et al. (2007)[11] conducted a lifetime analysis that reported cost per year spent relapse-free, comparing 5 strategies in the United States: (a) symptom management, (b) glatiramer acetate, (c) IFN β-1a SC, (d) IFN β-1a IM, and (e) IFN β-1b SC. Over a lifetime horizon, Bell et al. (2007) estimated that the incremental costs per QALY were. $258,465 for glatiramer acetate; $303,968 for IFN β-1a IM; $310,691 for IFN β-1b SC; and $416,301 for IFN β-1a SC, compared with symptom management alone. These investigators assumed no difference among DMDs in relapse rate and disease progression during the first 2 years of therapy. This assumption contradicts with results from the EVIDENCE study that directly compared IFN β-1a IM with IFN β-1a SC.[35,36] At 48 weeks, the proportions of patients who were relapse-free were 56.3% for IFN β-1a SC and 48.2% for IFN β-1a IM. This difference corresponds to an odds ratio of 1.5 (95% confidence interval [CI] = 1.1-2.0, $P = 0.023$) for remaining relapse-free in favor of IFN β-1a SC.[36]

Bell et al. also conducted a lifetime analysis that relied on a prediction curve for the probability of relapse (adjusted for the impact of NAbs and treatment discontinuation) that extended well beyond the experience of actual patients on DMD therapy (i.e., up to 50 years). Based on these prediction curves, it would take more than 20 years before the curve for glatiramer acetate to become more favorable than IFN β-1a SC. As shown in the sensitivity analyses conducted by Bell et al., the model results were sensitive to the time period of the analysis; therefore, the underlying evidence supporting each time interval should be evaluated carefully.

A recently published modeling study by Guo et al. (2009)[47] reported results of a discrete event simulation comparing the cost-effectiveness of IFN β-1a IM and IFN β-1a SC in the United States. Libraries of data from the head-to-head, randomized EVIDENCE trial[35,36] and published literature sources were used to populate the model. Based on the results observed in EVIDENCE, the model predicted that, compared with IFN β-1a IM, IFN β-1a SC would prevent 0.50 relapses and save 23 relapse-free days per patient over 4 years at an incremental cost-effectiveness ratio of $10,755 per relapse prevented and $232 per relapse-free day gained.[47]

Two retrospective database analyses compared the costs and effectiveness of DMDs. Ollendorf et al. (2002)[8] reported costs of glatiramer acetate versus interferon beta therapy among patients with MS in a managed care setting. Their study was based on a retrospective claims database reflecting older (January 1996 to June 2001) treatment patterns prior to the launch of IFN β-1a SC. Clinical and economic outcomes of glatiramer acetate and IFN β-1a SC were also evaluated in a retrospective claims database evaluation by Castelli-Haley et al. (2008).[9] The results of both studies were in favor of glatiramer acetate, but analyses of baseline differences in both studies showed that patients receiving glatiramer acetate had less severe disease progression. Ollendorf et al. used propensity scores as a measure of patient severity and found that glatiramer acetate patients had less severity of illness and disease progression. Castelli-Haley et al. found that patients receiving IFN β-1a SC had a greater number of diagnoses, greater use of musculoskeletal agents, greater frequency of 6-month pre-treatment hospitalizations, greater relapse, and greater cost compared with patients treated with glatiramer acetate.[8,9] In the multivariate analyses conducted in both studies, the investigators did not adequately control for disease severity. Ollendorf et al. based their propensity scores (which were used to adjust for severity of illness and disease progression) on age, geographic region, a flag for the presence of at least 1 relapse during the pre-treatment and follow-up periods, physician specialty, and plan type. Castelli-Haley et al. controlled only for the proportion of patients hospitalized with a diagnosis of MS in the 6 months prior to the index date. They did not specify whether the hospitalization was for MS (primary diagnosis) or due to another cause (MS as a secondary diagnosis). They also did not take the frequency of hospitalization into consideration. Furthermore, the authors did not control for the number of relapses in the pre-treatment period (even though differences were observed), and the 6-month pre-treatment period window was likely inadequate to ascertain severity (most trials present information about events 2 years prior to baseline).

Limitations

First, the model was built by combining data from multiple sources to identify inputs for rates, severity, and costs of relapses and disability progression. Because the placebo control groups differed in baseline characteristics and behavior during the DMD 2-year trials, the relative effectiveness of the DMDs may have differed among the trials for reasons other than therapeutic efficacy. It is well known that even placebo groups "improve" during a clinical trial.[48] This lack of comparability is a common critique of economic evaluation based on modeling technique, which is why this study attempted to control for these differences using relative risk reduction, comparing the relative differences among products. It is possible that this technique still did not capture exact differences among comparators, but no randomized, blinded, direct head-to-head comparisons of all first-line DMDs exist, and this was the method of adjustment chosen given the available evidence.

Overall, this evaluation was conducted using a limited number of assumptions and relied on high level of evidence for comparison. Where feasible, the ranking of relative efficacy established by the model was substantiated by a limited number of head-to-head clinical studies. Extensive one-way sensitivity analyses were performed on the model. The objective was to conduct a straightforward, easily interpretable analysis of the input parameters to which the model was most sensitive (i.e., what were the key cost drivers in the model and how did uncertainty around these parameter estimates affect the key results and conclusions).

Second, data obtained from a retrospective claims analysis might have provided a better representation of actual costs and utilization; however, as was observed in the Castelli-Haley et al.[9] and Ollendorf et al.[8] studies, it is difficult to control for disease severity and disability progression using administrative claims.

Third, the impact of NAbs was not included in this evaluation primarily because it was assumed that their effects would be reflected in the trial results. The role of NAbs also remains controversial. There is evidence to suggest that NAbs could attenuate the efficacy of interferon betas,[49] however, some patients with NAbs lose them over time, and there are differences among studies in how the impact of NAbs was assessed.[50] In the Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis (PRISMS) trial, patients who were to become NAb+ had trends toward lower relapse rates during the first 6 months on therapy than those who remained NAb- throughout.[16,17] Furthermore, 2-year data from the PRISMS study did not show a difference between NAb+ and NAb- patients, but 4-year data from the study showed a higher relapse rate in NAb+ patients (0.81 vs. 0.50, respectively in years 3 and 4, $P=0.002$), suggesting that the clinical impact of NAbs may be delayed. While the potential differential impact of NAbs on DMD therapies may impact treatment preferences, there currently is insufficient information on the utilization of NAb testing to provide specific recommendations regarding when to test, which test to use, how many tests are necessary, or which cutoff titer to apply.[50]

Fourth, indirect costs were not included in this analysis primarily because the evaluation was conducted from the perspective of payers. An assessment of both direct and indirect costs would have been more comprehensive, especially since MS is one of the most common causes of neurological disability in young adults.[1] Often, costs related to earnings loss and informal care are not reported, even though they represent major components of the total cost of MS.[3,5] If the magnitude of indirect medical costs is correlated with the frequency of relapses and the extent of disability progression, it is conceivable that the cost-effectiveness ranking from this evaluation will still hold.

Conclusion

This evaluation of the cost-effectiveness of DMDs was based on RCT evidence and was conducted with a minimum number of assumptions. Assuming that (a) the relative risk reduction in relapses and disease progression steps calculated from multiple DMD placebo-controlled clinical trials reflect real differences among DMDs over 2 years; and (b) resource unit costs derived from published sources reflect economic consequences of relapses and disease progression, modeling results suggest that the use of IFN β-1a SC, IFN β-1b SC, and glatiramer acetate represent the most cost-effective approaches for treatment of RRMS in terms of minimizing drug costs per relapse avoided and maximizing medical savings.

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DISCLOSURES

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