Volume 7 • Number 5 • 2004
VALUE IN HEALTH

Cost-Effectiveness of Interferon Beta-1a, Interferon Beta-1b, and Glatiramer Acetate in Newly Diagnosed Non-primary Progressive Multiple Sclerosis

Lisa A. Prosser, PhD,[1] Karen M. Kuntz, ScD,[2] Amit Bar-Or, MD, FRCPC,[3] Milton C. Weinstein, PhD[2]

[1]Department of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care, Boston, MA, USA;
[2]Harvard Center for Risk Analysis, Department of Health Policy and Management, Harvard School of Public Health, Boston, MA, USA;
[3]Department of Neurology and Neurosurgery, Montreal Neurological Institute and McGill University, Montreal, QC, Canada

ABSTRACT

Objective: To perform a cost-effectiveness analysis of three immunomodulatory treatments for newly diagnosed nonprimary progressive MS: interferon beta-1a, interferon beta-1b, and glatiramer acetate.

Methods: We developed a state-transition model to estimate the health effects and costs associated with interferon beta-1a, interferon beta-1b, glatiramer acetate, and no treatment for hypothetical cohorts of men and women with non-primary progressive MS. We used the Expanded Disability Status Scale as the measure of disability and included both relapses and disease progression in the model. We evaluated treatment strategies assuming a 10-year treatment duration using the societal perspective. We elicited preferences for disability and treatment states using standard-gamble questions and modeled the disutility associated with treatment administration and side effects explicitly. Main outcome measures were net gains in quality-adjusted life expectancy and incremental cost-effectiveness ratios in dollars per quality-adjusted life year (QALY) gained.

Results: For treatment duration of 10 years for newly diagnosed non-primary progressive MS, interferon beta-1a yielded the largest gain in quality-adjusted life expectancy with an incremental cost-effectiveness ratio of $2,200,000/QALY for women and $1,800,000/QALY for men, compared with no treatment. For a 5-year treatment duration, a "no treatment" strategy yielded more quality-adjusted life years than any of the treatment strategies. Cost-effectiveness ratios were similar for all three immunomodulatory treatments evaluated.

Conclusions: Cost-effectiveness results for all three immunomodulatory treatments for MS were unfavorable in the simulated study population under a wide range of assumptions. For treatment duration less than or equal to 5 years, expected benefits of treatment may not outweigh disutility associated with side effects and treatment discomfort.

Keywords: beta interferon, cost-effectiveness, glatiramer acetate, multiple sclerosis.

Introduction

Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system characterized by bouts of neurologic symptoms (or relapses) and often increasing disability [1]. MS affects approximately 350,000 people in the United States, and annual costs of the disease including costs of lost wages and informal care are estimated to exceed $9 billion [2].

Address correspondence to: Lisa A. Prosser, Department of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care, 133 Brookline Avenue, 6th floor, Boston, MA 02215 USA. E-mail: lprosser@hms.harvard.edu

The introduction of immunomodulatory treatments (interferon beta-1a, interferon beta-1b, and glatiramer acetate) represented a critical advance in available treatments for MS, offering benefits to a patient population with few treatment alternatives. These treatments have been shown both to reduce the number of relapses and slow the progression of disease [3–7]. At the same time, these treatments are expensive (annual drug costs of $10,000 to $13,000) and are associated with uncomfortable side effects (flu-like symptoms and injection-site reactions) that place a burden on patients who initiate treatment. Given these treatment characteristics, we performed a cost-effectiveness analysis to gain insight into the tradeoffs between the costs and health effects of available treatments for newly

 1098-3015/04/$15.00/554 554–568

diagnosed patients with non-primary progressive, or "bout onset," MS.

Methods

The Simulation Model

We developed a state-transition model to simulate the natural history, treatment effects, and costs of four strategies for hypothetical cohorts of patients with non-primary progressive MS: 1) treatment with interferon beta-1a (Avonex); 2) treatment with interferon beta-1b (Betaseron); 3) treatment with glatiramer acetate (Copaxone); and 4) no treatment. Natural history is defined as progression of disease in the absence of immunomodulatory treatments. For example, this assumes that relapses are treated with steroids but that this treatment does not alter the long-term course of the disease. The model includes the costs and health outcomes associated with treatment of relapses and accumulated disability, as defined by Expanded Disability Status Scale level. We simulated separate cohorts of newly diagnosed 30-year-old women and men with non-primary progressive MS, which includes patients with relapsing remitting, secondary progressive, and progressive relapsing MS. We used a time frame of 10 years for the base case analysis, although the simulation model can be run for any length of time up to 40 years. We assumed a societal perspective for the base case analysis and adhered to the recommendations for a reference case analysis as described by the US Panel on Cost-effectiveness in Health and Medicine [8].

A recently developed classification system for MS separates patients into four groups: relapsing remitting, secondary progressive, primary progressive, and progressive relapsing [9]. While physicians use these categories to describe individual patients, a prevailing view is that MS should be treated as a broad spectrum of disease activity [10]. This view is supported by the natural history data on rates of disease progression; disability survival curves do not differ by MS type at the time of diagnosis. Because patients with primary progressive MS are the only group that can be identified in early stages of the disease as having a worse prognosis and are therefore treated differently, these patients are excluded from the current analysis. Base case assumptions in the model reflect the characteristics of a cohort with newly diagnosed MS. Sensitivity analyses can be run to evaluate cohorts of patients with secondary progressive MS.

Long-term natural history studies have shown disease progression to be correlated with a number of prognostic factors: age at onset, gender, relapse frequency, and type of symptoms at onset [11]. Because sufficiently detailed data are available only for modeling the effect of gender on disease progression, our analysis incorporated only gender-specific rates of disease progression.

A simplified schematic of the model is presented in Figure 1. We defined disease status based on the most widely used scale for categorizing patients with MS, the Expanded Disability Status Scale (EDSS). EDSS levels were grouped into five health states for modeling disease progression (Table 1). These five EDSS levels are generally regarded as the key markers of disability for patients with MS [11]. The distribution of EDSS levels among the MS population is bimodal with peaks at 1 and 6 [11].

For the base case analysis, all patients start out in the model with No/Few Limitations (EDSS level 0–2.5). Additional analyses simulated a treatment strategy of delaying initiation of treatment until patients progressed to Moderate Limitations (EDSS level 3–5.5). In these analyses, all patients start out in the model with Moderate Limitations. In any given month (cycle length) in the model, a patient can either remain in their EDSS-defined health state or progress to the next disability level. We assumed

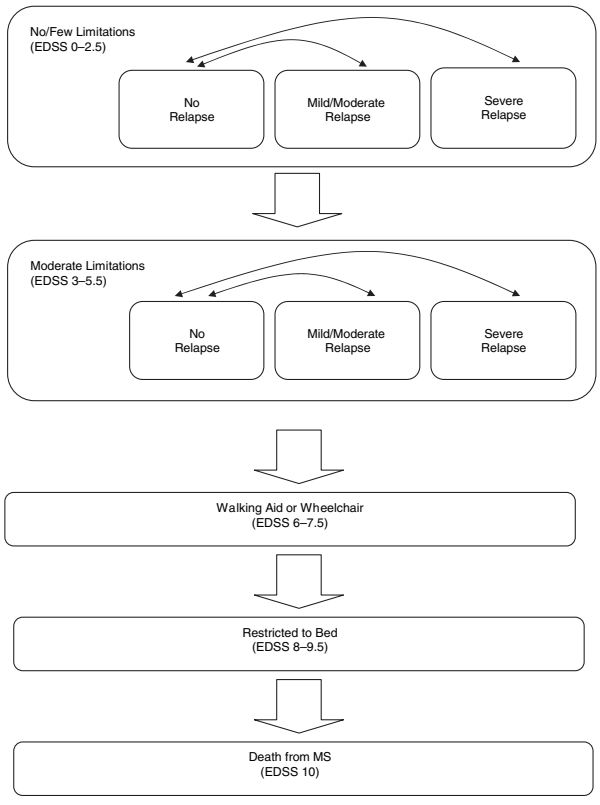

Figure 1 Model overview.

Table 1 Description of health states for disease progression

Health states	Description
No/Few Limitations (EDSS 0–2.5)	No MS symptoms (0) to minimal disability in two functional systems (2.5).
Moderate Limitations (EDSS 3–5.5)	Moderate disability in one area, or mild disability in up to four areas, but still able to walk unassisted and accomplish full daily activities (3) to disability which precludes full daily activities, but still able to walk unassisted (5.5).
Walking Aid or Wheelchair (EDSS 6–7.5)	Requires walking aid such as cane, crutch, or brace to walk 100 meters (6) to restricted to wheelchair (7–7.5).
Restricted to Bed (EDSS 8–9.5)	Restricted to bed with some ability to self-care (8) to requiring assistance for all activities of daily living (9–9.5).
Death (EDSS 10)	Death due to MS
No Relapse	Diagnosed with multiple sclerosis but not currently experiencing a relapse
Mild/Moderate Relapse	Experiencing a mild relapse (defined as a change of 0–14 points on the NRS)
Severe Relapse	Experiencing a severe relapse which can require hospitalization (defined as a change in more than 14 points on the NRS)

that patients progress in only one direction on the disability status scale. Although some patients will spontaneously improve in the short term, one-way progression is consistent with the long-term natural history data for MS [11]. In addition to disability status, patients with an EDSS level less than six have a probability of experiencing a relapse (an episode of MS symptoms and signs), that can be categorized into mild/moderate or severe according to their rating on the Neurological Rating Scale (Table 1) [3]. Each relapse is assumed to last for 1 month based on data from two published studies [1,3]. Patients can die from MS or from other causes.

The Data

Disease progression. We performed a literature review to identify natural history studies with data on disease progression in MS [11–17]. We identified two studies that report changes in disability levels over time and did not contain study populations with significant selection bias [13,14]. Excluding data for patients with primary progressive MS, the combined data from those two studies represented a sample of more than 400 patients with a mean age at onset of 30 years and an average follow-up of more than 20 years. The resulting base case estimates for monthly transition probabilities derived from those studies are listed in Table 2. Estimates of disease progression for sensitivity analysis in secondary progressive patients also used these studies [13,14].

Relapses. Relapse rates from three natural history studies were combined to estimate the monthly transition probability for experiencing a relapse (Table 2) [12,18,19]. The probability that a relapse is severe was estimated from published clinical trials (Table 2) [3].

We assumed that relapse rates were the same for patients in the less disabled chronic states (i.e., EDSS < 6) and equal to zero for more-disabled patients (EDSS ≥ 6). While data show that relapse rates decrease as chronic disability increases [19], we simplified this relationship by assuming that less-disabled patients experience relapses and more-disabled patients do not.

Mortality. We assumed that patients die from MS (EDSS 10) only after progressing through all previous EDSS levels. While there will be some patients for whom this is not the case, 89% of MS patients are significantly disabled (unable to walk) prior to death [20]. Patients can also die from competing causes of death throughout the progression of MS. Non-MS mortality rates vary by year of age in the model so that as age increases, non-MS mortality also increases. Mortality rates were stratified by age and gender using data from the 1998 US life tables [21]. Consistent with natural history data, MS patients in the model experience only a small decrease in life expectancy (less than 2 years) as compared with the general population [13,14].

Treatment Effects

The effects of treatment were simulated by a percent reduction in the probabilities of relapse and disease progression (Table 2). Estimates of the effects were derived from clinical trial results for interferon beta-1a, interferon beta-1b, and glatiramer acetate [3–7]. Treatment effects reported in clinical trials were adjusted to account for patients who discontinued treatment during the trial. In other words, our treatment estimates are for patients who maintained treatment for the duration of the trial.

Discontinuation rates reported for these treatments are high and were modeled separately in the analysis. For the base case analysis, we estimated discontinuation rates from those reported in clinical trials and open-label studies (Table 2) [1,4,6,7,22–26]. Patients were assumed to discontinue at a

Table 2 Transition probabilities

Variable	Base case estimate	Range for sensitivity analysis	Sources
Estimated monthly transition probability for progressing to next level of disability (per 1000):			
EDSS 0–2.5			
Men	4.6117	+/– 50% base case	13, 14
Women	4.2642		
EDSS 3–5.5			
Men	9.5498		13, 14
Women	8.8283		
EDSS 6–7.5			
Men	3.7231		13, 14
Women	3.4425		
EDSS 8–9.5			
Men	0.9897		13, 14
Women	0.9151		
Monthly probability of a relapse*	0.0755	0.0325, 0.12	12, 18, 19
Probability of a severe relapse, given that a relapse has occurred	0.23	0, 0.5	3
Probability that a severe relapse is treated on an inpatient basis	1	0, 1	Expert opinion
Treatment effects			
Glatiramer acetate (20 mg SC, every day)			
Percent reduction in relapse rates	34.98	30.17, 40.74	7
Percent reduction in probability of disease progression†	13.20	9.24, 17.16	7
Interferon beta-1a (30 μg IM, 1 ×/week)			
Percent reduction in relapse rates	19.14	13.40, 24.89	4, 5
Percent reduction in probability of disease progression†	38.72	27.11, 50.34	4, 5
Interferon beta-1b (8 miu SC, every other day)			
Percent reduction in relapse rates	37.64	26.34, 48.93	3, 6
Percent reduction in probability of disease progression†	31.00	21.70, 40.29	3, 6
Monthly probability of discontinuing treatment‡			
Glatiramer acetate	0.0154	0.0108, 0.0200	7
Interferon beta-1a	0.0125	0.0087, 0.0162	15, 22
Interferon beta-1b	0.0183	0.0128, 0.0238	1, 6, 23–26

*Weighted average of relapse rates from the three referenced studies.
†Based on 2-year clinical trial data.
‡First 3 years on treatment only.

constant rate during the first 3 years of treatment. After 3 years, the discontinuation rate was assumed to be zero (i.e., all patients who discontinue treatment will have done so by the end of the third year of treatment).

Quality of life

Health outcomes were measured in the model using quality-adjusted life years (QALYs). The quality-adjusted life year is a preference-based measure that incorporates both morbidity and mortality effects [8]. Quality-of-life adjustments were made for each level of chronic disability (MS health states), type and presence of relapse, and discomfort associated with treatments (Table 3). Treatment-related quality adjustments were assumed to last for the first 6 months of treatment only [24,27]. Quality adjustments were based on health- and treatment-state

Table 3 Quality-of-life adjustments

Quality adjustments	Base case estimate	Range for sensitivity analysis*	Sources
By disability level (in utilities)			
No/few limitations	0.954	0.971, 0.936	28
Moderate limitations	0.870	0.917, 0.823	28
Walking aid or wheelchair	0.769	0.858, 0.680	28
Restricted to bed	0.491	0.609, 0.372	28
Dead from MS	0		
By relapse severity (in disutilities)†			
Mild/moderate	–0.091	–0.063, –0.119	28
Severe	–0.302	–0.238, –0.366	28
By treatment (in disutilities)†,‡			
Glatiramer acetate	–0.066	–0.020, –0.113	28
Interferon beta-1a	–0.115	–0.045, –0.185	28
Interferon beta-1b	–0.204	–0.061, –0.346	28
Pooled	–0.130	–0.072, –0.188	28

*Ranges based on 95% confidence intervals.
†Reduction from utility for each disability level.
‡Quality adjustments applied for first 6 months on treatment only, assumed to be zero for treatment beyond the first 6 months [25,28].

utilities elicited from members of the community using the standard-gamble method [28]. Community-based rather than patient utilities were used in the base-case analysis to be consistent with recommendations from the US Public Health Service Panel on Cost-Effectiveness in Health and Medicine [8]. Subjects for the utility assessments were a convenience sample from San Diego, CA, USA. Utilities for described MS health states were assessed during a 30-minute computer-administrated interview using U-Titer II software with an interviewer present (LAP) [28]. QALYs were discounted at 3% per year.

Costs

Costs included direct health care costs, including costs of physician visits, hospital stays, drugs, home care, and equipment, as well as costs of informal care, and patient time costs for administering treatment. Costs of lost work productivity were not included in the base case analysis, under the assumption that lost income is reflected in the disutility weights, and in keeping with the reference-case criterion of the US Panel on Cost-Effectiveness in Health and Medicine [8]. All costs have been adjusted to 1999 dollars using the GDP price index [29] and were discounted at 3% per year.

Treatment costs. Treatment costs included the costs of medication, laboratory tests, and patient time required to administer medication (Table 4). Medication costs were calculated using 1999 average wholesale price [30]. Mean time for administering an injection was 15 minutes. We estimated the value of patient time for administering medication by multiplying the time by average US hourly wage rates [31]. Laboratory tests to monitor liver function were assumed to occur every 3 months for interferon beta-1a and interferon beta-1b [32].

Relapse-related costs. For the base case analysis, mild/moderate relapses were assumed to require one physician outpatient visit with no additional treatment [33]. We assumed that all severe relapses were treated on an inpatient basis for intravenous steroid

Table 4 Cost inputs

Health states or events	Base case estimate (in 1999 US dollars)	Range for sensitivity analysis	Sources
*Monthly treatment costs**		+/– 50% of base case	
Glatiramer acetate			
Men	$1006		
Medication Costs	$877		30
Laboratory Costs	$0		32
Patient Time Costs	$129		31
Women	$973		
Medication Costs	$877		30
Laboratory Costs	$0		32
Patient Time Costs	$96		31
Interferon beta-1a			
Men	$956		
Medication Costs	$923		30
Laboratory Costs	$16		32
Patient Time Costs	$17		31
Women	$952		
Medication Costs	$923		30
Laboratory Costs	$16		32
Patient Time Costs	$13		31
Interferon beta-1b			
Men	$1175		
Medication Costs	$1095		30
Laboratory Costs	$16		32
Patient Time Costs	$65		31
Women	$1159		
Medication Costs	$1095		30
Laboratory Costs	$16		32
Patient Time Costs	$48		31
Relapse:			
Outpatient treatment of mild/moderate relapse	$57.50	$0, $100	33
Inpatient treatment of severe relapse	$5270	+/– 50% of base case	†
Monthly costs associated with each disability level			
No/few limitations	–	$0, $50	2, 36
Moderate limitations	$10	$0, $100	2, 36
Walking aid or wheelchair	$310	$260, $1,500	2, 36
Restricted to bed	$860	$530, $10,000	2, 36

*Includes costs of medication, laboratory tests, and patient time.
†Confidential cost data from large teaching hospital in Boston, MA.

treatment. Using data from the cost-accounting system of a large teaching hospital in Boston, MA, we found that the mean cost of treating a relapse on an inpatient basis was $5270 (Table 4).

Chronic MS-related costs. Ongoing MS-related health care costs were accounted for separately from relapse-related costs. Separate monthly costs were assigned to each disability level (Table 4). Although data available on costs of MS in the US are limited [2,34–37], we used two studies, Inman [36] (1987) and Whetten-Goldstein et al. [2] (1998), to derive cost estimates by EDSS level. These were cross-sectional national surveys that reported data on costs of multiple sclerosis including direct medical costs, informal care, and lost earnings.

Cost-effectiveness analysis. Methods of incremental cost-effectiveness analysis were used [8]. The incremental cost-effectiveness ratio is the difference in time-discounted costs between the evaluated strategy and the comparison strategy divided by the difference in time-discounted QALYs between the two strategies. Results are reported in dollars per QALY.

Sensitivity Analysis

One-way sensitivity analyses were performed on all variables listed in Tables 2 to 4 as well as on treatment duration (0–40 years), duration of side effects (0–60 months), discontinuation time frame (0–60 months), and rate of time preference (0–10%). Ranges for the sensitivity analyses were developed using 95% confidence intervals when primary data were available or guided by ranges in the literature if primary data were not available. Additional sensitivity analyses were performed to explore the effects of delaying treatment until higher levels of disability are reached, delaying treatment until secondary progressive disease has been diagnosed, including patient preferences instead of community values for health states, and the inclusion of lost wages as a cost of illness.

A key set of sensitivity analyses was performed to evaluate the assumption regarding persistence of treatment benefits. In the base-case analysis, the time horizon of the analysis is equal to the treatment duration. In an alternate analysis, we evaluate the cost-effectiveness of specific treatment durations (5 and 10 years) over longer time horizons of up to 30 years beyond the end of treatment. Once patients have discontinued treatment, they are expected to follow the natural history of the disease. Benefits due to delayed progression accrued during treatment are retained, but probabilities of disease progression following treatment are assumed to be the same as those prior to treatment (i.e., simulated patients will "return" to the natural history submodel at a less-disabled EDSS level than without treatment). In this set of analyses we evaluate the cost-effectiveness of 1) 5-year treatment duration; 2) 10-year treatment duration; and 3) discontinuation of treatment after a patient has reached EDSS level 6, when the benefits persist up to 30 years beyond treatment.

Two- and three-way sensitivity analyses were performed on variables for which the results were sensitive in the one-way sensitivity analysis. A probabilistic sensitivity analysis was performed using Monte Carlo simulation in which variables were simultaneously varied. Probability distributions for the parameters in the Monte Carlo sensitivity analysis were assumed to be lognormal for costs and to follow a beta distribution for effects and quality adjustments. Ranges in Tables 2 to 4 were used to derive 95% confidence intervals.

Results

Base Case Analysis

Under base-case assumptions, interferon beta-1a (IFNB-1a) provided more health benefits and was more costly than no treatment for both men and women, with resulting cost-effectiveness ratios of $1,838,000/QALY for men and $2,218,000/QALY for women (Table 5). Ten-year treatment with IFNB-1a provided an additional 0.030 QALYs, or 11 additional quality-adjusted life days, for women and 0.036 QALYs, or 13 additional quality-adjusted life days, for men. IFNB-1b was less effective and more costly than no treatment (i.e., strongly dominated), and glatiramer had a higher incremental cost-effectiveness ratio but lower cost compared with IFNB-1b (i.e., glatiramer acetate was ruled out through extended dominance).

Sensitivity Analysis

In one-way sensitivity analyses, the results were most sensitive to changes in treatment duration, disability level at initiation of treatment, drug costs, rate of disease progression, disutility and duration of treatment side effects, and treatment effects on disease progression (Table 6).

Treatment duration. The cost-effectiveness ratio varied substantially with the duration of treatment (Fig. 2); however, the cost-effectiveness exceeded $200,000/QALY under the most favorable scenario. If treatment duration was extended to 40 years, the

Table 5 Results of base case analysis, 10-year treatment duration

Strategy	Total cost	Incremental cost	QALY increase due to treatment benefits	QALYs lost due to treatment side effects	Total QALYs	Incremental QALYs		$/QALY
All strategies								
Women								
No treatment	$11,290				7.926			
Glatiramer acetate	$72,356	$61,066	0.053	0.029	7.950	0.024	Dominated	
IFNB-1a	$76,959	$4,603	0.080	0.051	7.955	0.005		
IFNB-1b	$78,134	$1,175	0.073	0.088	7.911	(0.045)	Dominated	
Men								
No treatment	$11,169				7.855			
Glatiramer acetate	$74,023	$62,854	0.056	0.029	7.882	0.027	Dominated	
IFNB-1a	$76,645	$2,622	0.086	0.051	7.891	0.009		
IFNB-1b	$78,611	$1,966	0.078	0.088	7.845	(0.046)	Dominated	
Undominated strategies								
Women								
No treatment	$11,290				7.926			
IFNB-1a	$76,959	$65,669			7.955	0.030		$2,217,736
Men								
No treatment	$11,432				7.855			
IFNB-1a	$76,879	$65,447			7.891	0.036		$1,838,227

cost-effectiveness ratios for IFNB-1a decreased to $250,000/QALY for women and $235,000/QALY for men. For treatment duration of less than or equal to 6 years, not treating was the least costly and most effective option because the disutility associated with treatment side effects outweighed the benefits of treatment. For treatment duration between 6 and 9 years, treatment with glatiramer acetate was the most effective strategy. For treatment duration of 10 years or more, treatment with IFNB-1a was the most effective strategy.

Disability level at initiation of treatment. The base-case analysis assumed that treatment was initiated

Table 6 Sensitivity analyses for interferon beta-1a

	Parameter	Range of cost-effectiveness ratios ($/QALY) Women	Men
Base case		2,218,000	1,838,000
One-way sensitivity analyses:			
Cost of treatment	50% of base case	1,112,000	924,000
Cost of treating a severe relapse	50% of base case	2,236,000	1,852,000
Monthly costs for each disability level	Low	2,226,000	1,845,000
	High	2,043,000	1,670,000
	30 × base case	1,178,000	870,000
	Lost earnings included*	2,185,000	1,808,000
Disease progression	50% higher	888,000	776,000
	50% lower	10,132,000	8,798,000
Side effect duration (months)	0 (No treatment disutility)	819,000	759,000
	60	No treatment preferred	No treatment preferred
Probability of treatment discontinuation (monthly probability)	0.87%	2,148,000	1,806,000
	1.62%	2,311,000	1,884,000
Treatment effects on			
Percent reduction in disease progression	27.11%	2,526,000	2,337,000
	50.34%	1,480,000	1,267,000
Percent reduction in relapse rate	13.40%	2,494,000	2,023,000
	24.89%	1,994,000	1,683,000
Quality adjustments			
Disability levels	Lower bound	4,516,000	4,070,000
	Upper bound	1,245,000	1,080,000
	Medians	4,832,000	4,286,000
Relapse severity	Lower bound	2,241,000	1,970,000
	Upper bound	2,046,000	1,722,000
Patient-based preference weights		4,020,000	3,273,000
Discount rate	0%	1,632,000	1,403,000
	10%	6,442,000	5,359,000

*Based on estimates from Sweden by Kobelt et al. (2003). This sensitivity analysis assumes that lost earnings are not captured in the utility weights and that some proportion of patients at each EDSS level can not work.

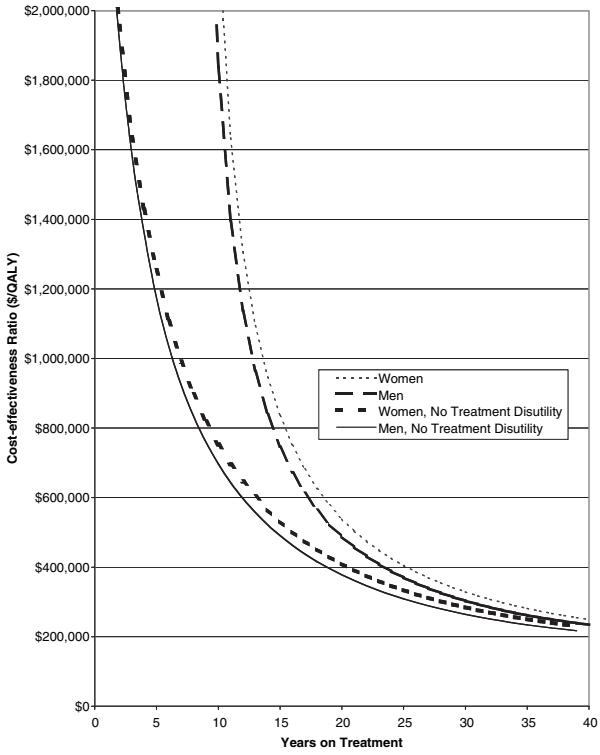

Figure 2 Cost-effectiveness of undominated strategies (IFNB-Ia) with and without treatment disutility by treatment duration.

during early stages of the disease, corresponding to an EDSS level of 0, 1, or 2. An analysis assuming that treatment does not begin until patients have reached EDSS 3 to 5.5 resulted in cost-effectiveness ratios for IFNB-1a that were 90% lower than those in the base-case analysis, or approximately $180,000/QALY for both women and men (Fig. 3 shows results for women). Extending treatment duration to 30 or 40 years, in addition to deferring treatment until EDSS 3 to 5.5, resulted in even lower cost-effectiveness ratios between $80,000/QALY and 90,000/QALY.

Treatment benefits persist beyond treatment period. Assumptions regarding the effect of treatments on future disease progression have a dramatic impact on cost-effectiveness results (Fig. 3). For both 5 and 10 years of treatment, cost-effectiveness ratios drop to less than $350,000/QALY if benefits accrued during the treatment period persist for 20 years or more following the discontinuation of treatment. For 5 years of treatment, cost-effectiveness ratios drop to less than $100,000/QALY if benefits accrue for 25 or more years following treatment. A "best-case" analysis in which treatment initiation is delayed until EDSS levels 3 to 5.5 and benefits persist for many years beyond treatment duration is shown for both 5- and 10-year treatment durations in Figure 3. The cost-effectiveness ratios for this scenario dropped to less than $100,000 per QALY for both 5 and 10 years of treatment for both men and women if benefits persist for 5 or more years beyond treatment duration. Similarly, cost-effectiveness ratios for treatment in secondary progressive patients fall below $100,000/QALY if benefits persist for 5 or more years beyond treatment duration (Fig. 4).

For an alternative treatment strategy in which patients initiate treatment at EDSS levels of 0 through 2.5 and treatment is discontinued once a patient reaches EDSS level 6, cost-effectiveness ratios also drop but remain above $200,000/QALY

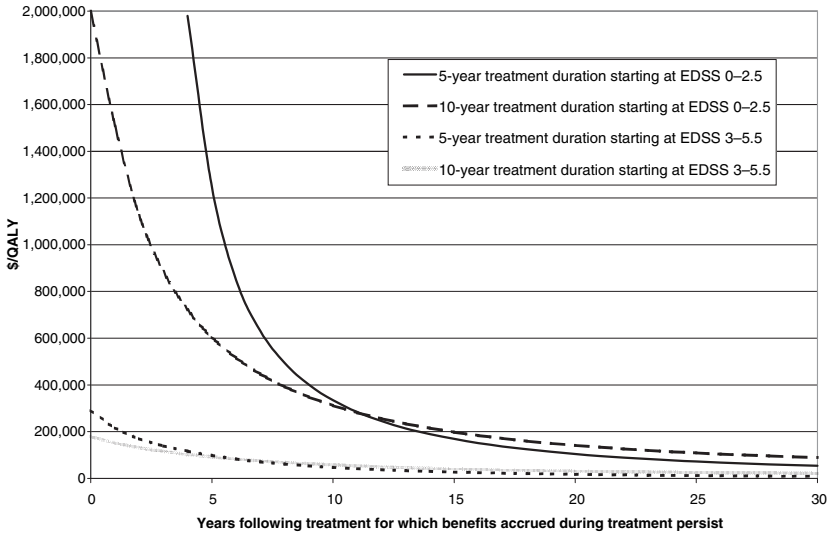

Figure 3 Cost-effectiveness of IFNB-1a assuming treatment benefits extend beyond treatment duration for 5 and 10 years of treatment for different disability levels at initiation of treatment, women only.

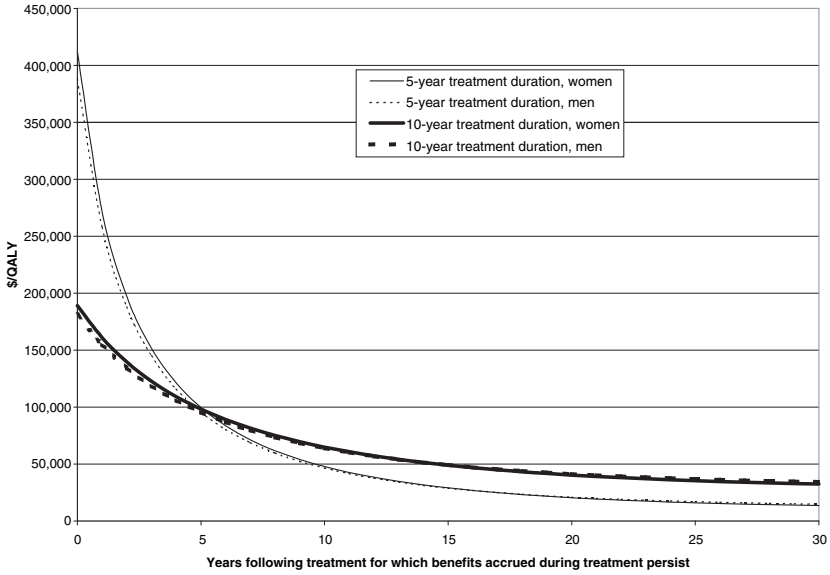

Figure 4 Cost-effectiveness of IFNB-1a assuming treatment benefits extend beyond treatment duration for 5 and 10 years of treatment in patients with secondary progressive MS.

even when treatment benefits accrued during treatment persist for up to 30 years (Fig. 5).

Side effects. If we allowed side effects to persist beyond 10 to 12 months, then no treatment became the optimal strategy. Results were also sensitive to the amount of disutility assumed for each treatment. Since treatment effects were similar, as treatment disutilities were varied the treatment with the lowest disutility became the dominant strategy. If treatments had no disutility associated with them (i.e., there are no side effects from any of the treatments), cost-effectiveness ratios decreased by about 60% to $820,000/QALY for women and $760,000 for men, assuming 10 years of treatment. When treatment disutility was included in the analysis, even treatments that completely halt disease progression and eliminate relapses have unfavorable cost-effectiveness ratios ($350,000/QALY).

Costs. Our results were quite sensitive to changes in drug costs; therefore substantially reducing the cost of the drug may bring the cost-effectiveness ratios for treatment closer to a range considered favorable. Varying the medication cost results in an almost proportionate change in the cost-effectiveness ratio for IFNB-1a. For example, reducing the cost of IFNB-1b from $1095 per month to

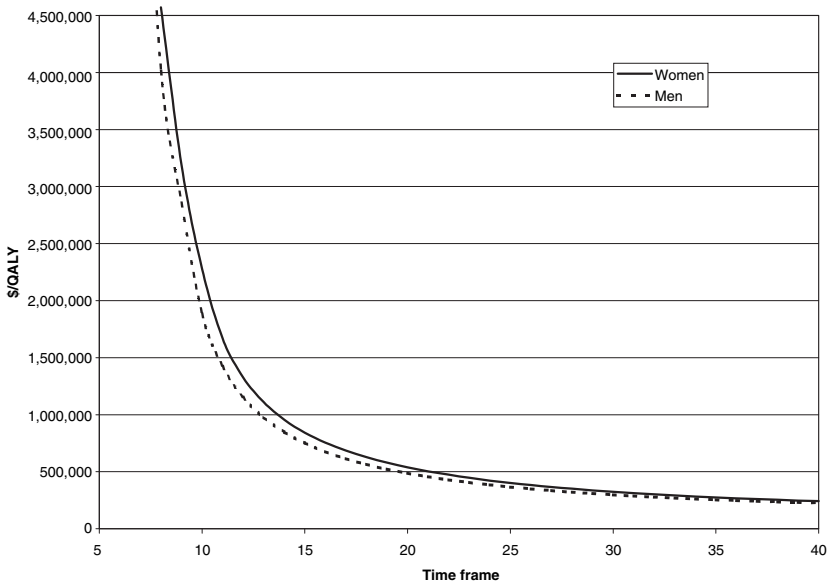

Figure 5 Treatment discontinued once patient reaches EDSS 6, benefits accrued during treatment persist beyond treatment duration.

approximately $100 per month results in a cost-effectiveness ratio of $200,000/QALY for men and $240,000/QALY for women.

Results were not sensitive to changes in the cost of treating a relapse or probability of treating a relapse. Alternative assumptions for MS health state costs also did not significantly affect results. Scenarios assuming chronic MS-related costs of as much as 10 times those in the base case resulted in cost-effectiveness ratios within 30% of the base case. Results also varied little with the inclusion of lost earnings; cost-effectiveness ratios were only slightly lower at $2,185,000/QALY for women and $1,808,000/QALY for men.

Disease progression. Increasing the base-case estimates of disease progression by 50% resulted in cost-effectiveness ratios that were approximately 60% lower than in the base case. Decreasing the base case estimates of disease progression by 50% increased the cost-effectiveness ratios by a factor of 4.

Treatment effects. Changes in treatment effects regarding disease progression affected the cost-effectiveness ratios more than treatment effects on relapse rates. A large increase or decrease of the baseline treatment effect on disease progression resulted in cost-effectiveness ratios 25% below to 50% above base case results. Similar changes for the treatment effect on relapse rate resulted in cost-effectiveness ratios within 10% of the base case (Table 6).

Results were also not sensitive to the probability of discontinuing treatment. Assuming no patients discontinue treatment, resulting ratios were within 10% of the base case.

Quality adjustment. Using the 95% confidence interval upper and lower bound estimates for health state utilities caused ratios to increase by up to 100% or decline by 35%. Changing relapse-related utility weights, however, did not affect results much. Using median instead of mean utility weights caused the cost-effectiveness ratios to double.

Rate of time preference. As the annual discount rate was varied from 0% to 10%, cost-effectiveness ratios changed from $1,600,000/QALY for women and $1,400,000/QALY for men to $9,415,000/QALY for women and $5,360,000/QALY for men.

Multi-way sensitivity analyses. Two-way sensitivity analyses resulted in cost-effectiveness ratios from $400,000/QALY to $900,000/QALY for women and men. Scenarios involving faster disease progression or no disutility of treatment resulted in the lower end of the range.

Three-way sensitivity analyses produce results with ratios from $240,000/QALY to 1,245,000/QALY, or 10 to 30% of base case results. The most favorable scenario assumed faster disease progression, a 50% reduction in drug costs, and no treatment disutility and had cost-effectiveness ratios of $260,000/QALY for women and $240,000/QALY for men.

Using preferences for quality adjustments assessed by MS patients [28] resulted in considerably higher cost-effectiveness ratios of $4,020,000 for women and $3,273,000/QALY for men.

Probabilistic sensitivity analysis. Interferon beta-1a was the optimal strategy in 56% of the trials. Glatiramer acetate was optimal 33% of the time, and IFNB-1b was optimal 7% of the time. In 5% of the trials, no treatment was the best strategy. Because the effects of the treatments are so similar, each of the treatment strategies could be dominated, extended dominated, or preferred in any given trial.

Cost-effectiveness ratios remained unfavorable for most scenarios generated in the probabilistic sensitivity analysis. More than 70% of the scenarios resulted either in dominance by no treatment or in cost-effectiveness analyses greater than $1,000,000/QALY.

Discussion

We used the currently recommended approach to evaluate the cost-effectiveness of treatments for patients with newly diagnosed non-primary-progressive MS. Our results for the three treatment strategies are unfavorable under a wide range of assumptions. Costs, effects, and quality-of-life benefits are quite similar among the three immunomodulatory treatments. Based on the published pivotal clinical trial data, assumptions of slightly better effects of IFNB-1a in slowing disease progression and better effects on relapse reduction for glatiramer acetate and IFNB-1b drive which treatment strategy dominates the others in our analysis. With these assumptions, IFNB-1a was the best strategy in terms of health outcome. IFNB-1b was disadvantaged relative to the other two because of the higher disutility associated with treatment. Of note, the quality of the efficacy data differs between treatments, since the pivotal clinical trials for these therapies focused on different primary endpoints. Small changes in reported treatment effects, as additional

data become available, will likely affect which treatment is most effective in a cost-effectiveness analysis. The most effective treatment strategy may change with new data, but the associated cost-effectiveness ratios are likely to remain similar as long as the updated costs, health benefits, and side-effects of the treatments remain similar.

Reports of the cost-effectiveness of IFNB-1b are available from other countries [38–46]. Most evaluated cost-effectiveness for a more disabled population, and all except one evaluated only IFNB-1b. The study by Parkin and others (1998) modeled a more-disabled population (EDSS 3–7) and estimated cost effectiveness at £328,000/QALY for 5-year treatment duration. Their results are similar to those reported in our sensitivity analysis for initiating treatment in patients at later stages of diseases. Forbes et al. reported a cost-effectiveness ratio of £1,024,667/QALY for IFNB-1b treatment in secondary progressive MS for patients in the UK, which is similar to our results [41]. Brown and colleagues did not measure effectiveness in QALYs, which makes a comparison with our results difficult [38,39]. Kendrick and Johnson (2000) reported cost-effectiveness ratios as low as £27,000/QALY, but this analysis evaluated a more disabled population and included markedly different assumptions regarding treatment effectiveness, disease progression, and quality adjustments.

The analyses by Kendrick and Johnson (2000) and Chilcott and others (2003) are the only analyses of the interferon betas to yield favorable cost-effectiveness ratios. The Kendrick and Johnson model included several assumptions which were biased toward more favorable cost-effectiveness ratios for treatment when compared with the assumptions used in our model: larger differences in utility between disability levels, a more favorable interpretation of the clinical trial data on treatment effects on delaying disease progression, a more disabled population, and a sustained effect on disease progression. In contrast, our analysis includes prospectively collected utility inputs and mean treatment effects from the pivotal Phase III clinical trials. Sensitivity analyses evaluate the effect of varying the last two assumptions: a more disabled population at initiation of treatment and sustained effect of treatment benefits. Changing these last two assumptions does indeed result in more favorable cost-effectiveness ratios of less than $100,000/QALY, results similar to those reported by Kendrick and Johnson (2000) (Fig. 4). Once treatment benefits continue to accrue beyond the duration of treatment, cost-effectiveness improves because the benefits of delaying progression to very disabled and more costly (both in terms of dollars and quality-adjusted life years) health states are included. An interesting result of this sensitivity analysis is that cost-effectiveness improves as treatment duration decreases. Kendrick and Johnson model the long-term effects of only 2 years of treatment followed by 18 years of benefit accrual. We have modeled 5 and 10 years of treatment followed by up to 35 years of benefit accrual and find favorable cost-effectiveness results for 5 years of treatment. In our model, modeling the effect of 2 years of treatment followed by 18 years of benefit accrual results in ratios of $110,000/QALY for men and $120,000/QALY for women; however, a treatment duration of only 2 years is unlikely unless the patient does not tolerate treatment or develops neutralizing antibodies to the beta interferons. In clinical practice, patients who tolerate these therapies will often remain on them for 5 or more years of treatment but may discontinue once they start exhibiting signs of progressive disease, for which the effectiveness of these treatments has not been established. Such a treatment strategy, treatment discontinuation once signs of progressive disease are apparent, is approximated in our model by having patients discontinue treatment once they have reached EDSS level 6. The cost-effectiveness of this treatment strategy remains above $200,000/QALY even if benefits accrue for the remaining life expectancy of the patient (Fig. 5). Results from the analysis performed by Chilcott and others on behalf of the UK National Institute for Clinical Excellence show cost-effectiveness ratios of under $100,000/QALY for the beta interferons but are difficult to compare to our results since key modeling inputs such as costs and quality of life adjustments for the Chilcott model are not available (classified as "commercial in-confidence"). Using the qualitative description of their quality adjustments provided in their paper, we attempted to model a scenario in which there was a larger difference in utility values between EDSS health states. The clinical strategy in their model is most similar to the scenario shown in our Figure 5 for a 20-year time horizon. If we adjust for larger differences in quality adjustments between health states, the cost-effectiveness ratios drop to about $200,000 per QALY for IFNB-1a.

Our results for patients with secondary progressive MS are much more favorable than those for patients with newly diagnosed MS (Fig. 5). They are slightly higher than those presented by Kobelt and colleagues which were $39,250/QALY using clinical trial data and $25,700/QALY using natural history

data [44,45]. Their analysis differs from ours in that it assumes 33 months of interferon treatment during a 10-year time frame, uses quality-of-life adjustments based on the EQ-5D, and does not include any adjustment for treatment side effects. All of these assumptions would result in more favorable cost-effectiveness results. If patients delay treatment until the onset of secondary progressive MS, cost-effectiveness ratios are much more favorable. The most recent analysis by Kobelt and colleagues evaluates treatment for a mixed population of patients with relapsing-remitting or secondary progressive MS with cost-effectiveness ratios considerably lower than our estimates for a newly diagnosed cohort [46].

Time horizon for base case analyses ranges from 2.5 years to 40 years in other studies [38–46]. We selected a base case time horizon of 10 years for our analysis since at the start of our study it was anticipated that new treatments for MS may become available within that time frame. Because results were sensitive to this assumption, we have included sensitivity analyses for 5 to 40 years to allow comparison to other studies.

Explicitly incorporating the loss in quality of life due to treatment side effects and administration provides insight into the high discontinuation rates associated with the immunomodulatory treatments. For treatment duration less than or equal to 6 years, we found that benefits of treatment did not outweigh the disutility associated with the side effects and treatment discomfort. If treatment effects beyond 6 years are not considered, then our model predicts that declining or discontinuing treatment would be the patient's preferred strategy. Although results were quite sensitive to changes in drug costs, substantially reducing the cost of the drug by a factor of 10 would be needed to bring the cost-effectiveness ratios for treatment closer to a range considered favorable when treatment disutility is included in the analysis.

There are some limitations regarding simplifying assumptions made in this analysis. We do not explicitly model the effects of age at onset, relapse frequency, or type of symptoms at onset on disease progression. Being able to stratify by these characteristics could result in more favorable cost-effectiveness ratios for treating subgroups with faster expected disease progression. For example, if a newly diagnosed patient is male, 40 years old, has symptoms and signs of cerebellar dysfunction, and has more frequent relapses that are likely to predict a more progressive course of disease, treatment with immunomodulatory treatments will have more favorable cost-effectiveness ratios. Using data from an analysis that estimates the effect of certain variables on median length of time to reach DSS6 [47], we conducted a "what-if" analysis for this hypothetical patient that resulted in cost-effectiveness ratios approximately 50% lower than base case results. On the other hand, patients presenting with optic neuritis and purely sensory symptoms that are associated with a more benign course of disease would have less favorable cost-effectiveness ratios as compared with our base case analyses.

The frequency of other illnesses that could affect mortality does not appear to be increased in persons with MS, with the exception of suicide [20,47]. The elevated risk of suicide associated with MS was not included in our analysis. While some studies [48,49] have suggested a possible increase in suicide risk in patients treated with interferon-beta therapies, the significance of this may have been overestimated. We did not incorporate this into our assumptions. We also assumed that once patients reach a significant level of disability, it is more difficult to identify individual relapses, and that the costs and quality-of-life effects of a relapse are outweighed by those in the chronic MS state. If this is not the case, the effectiveness of treatments that reduce relapse rate may be somewhat underestimated in this analysis for later stages of disease.

Recent cost data by individual EDSS levels were not available, and costs by EDSS level were approximated by applying weights from 1976 data to 1994 data. Annual costs for the average patient with MS were remarkably similar across three available studies on costs related to MS treatments [2,34–36]. There have been no major advances in MS treatment until the introduction of the drugs evaluated in this analysis, and sensitivity analyses around these estimates resulted in little change in the resulting cost-effectiveness ratios.

Our analysis was based solely on data from the pivotal clinical trials. Inclusion and exclusion criteria differed among trials, potentially limiting the ability to compare results. We chose to model a hypothetical newly diagnosed cohort rather than use data from placebo arms in the clinical trials because of the differences across study populations and concern that these might not reflect the disease progression of a "typical" MS patient. The hypothetical cohort modeled in this analysis (mean age at onset of 30 years, initial EDSS level between 0 and 2.5) differed from the trial populations on several characteristics. The IFNB-1b trial reported a higher relapse rate in the placebo arm when compared with our hypothetical cohort or the IFNB-1a or

glatiramer acetate trials. The IFNB-1b and glatiramer acetate trials were restricted to relapsing-remitting patients while the IFNB-1a trial included both relapsing-remitting and relapsing-progressive MS. The hypothetical cohort included all non-primary progressive MS patients. The primary endpoint for the IFNB-1a trial was disability progression, whereas relapse rate was the primary endpoint for the other two drugs. The study populations in the IFNB-1b and glatiramer acetate trials also included more disabled patients up to and including EDSS level 5.5 and 5, respectively. On this measure, the population in the IFNB-1a trial, which included patients with EDSS levels from 1 to 3.5, matched most closely to our entering hypothetical cohort with EDSS levels from 0 to 2.5. Mean ages were similar across the trials (34–36 years) and slightly higher than for our hypothetical cohort. Given these differences in characteristics, an analysis based on simply extending the trial data beyond 2 years could result in different cost-effectiveness ratios. Our objective in using a hypothetical cohort was to diminish the effect of differences in trial design on cost-effectiveness results. A recent analysis by Kobelt and colleagues clearly demonstrates the differences between placebo arm and natural history data for patients with secondary progressive MS [46].

Our results suggest that strategies of waiting to initiate treatment until a patient has progressed to a more-disabled health state or of limiting the duration of treatment are more cost-effective options. At the same time, recent studies suggest that immunomodulators may have better efficacy when initiated early in the course of disease, providing support for a policy advocating earlier initiation of treatment [50–52]. Although we assumed a constant effect of the treatments over time, early effects would have to be substantial to have an appreciable impact on the cost-effectiveness of treatment.

These results underscore the need for MS treatments that are not just more cost-effective but that are more clinically effective. Benefits provided by currently available immunomodulatory treatments are modest, even if one excludes the disutility of treatment. For all three immunomodulatory treatments, the benefits provided by 10 years of treatment are approximately 30 additional quality-adjusted life days (days in perfect health) or less. Once the disutility of treatment is included, these benefits drop to about 11 to 13 additional days in perfect health for IFNB-1b, and even fewer days for the other treatments. Despite minor differences in the efficacy reported in clinical trial results, the interferon betas and glatiramer acetate are quite similar regarding the modest benefits they provide for patients with MS and their associated cost-effectiveness. New MS drugs will need to be both less costly and more effective than the current options to result in more favorable cost-effectiveness ratios. Oral therapies currently in development are likely to be associated with less discomfort in administration, which would favorably improve their economic profile, but will also need to be more effective than currently available treatments.

This study was funded in part by a dissertation grant from the National Multiple Sclerosis Society, the Harvard Program on the Economic Evaluation of Medical Technology, the Harvard Center for Risk Analysis, and the Thomas O. Pyle Fellowship (Harvard Pilgrim Health Care and Harvard Medical School). The funding sources played no role in the design, methods, data collection, analysis or interpretation of the results of the study.

References

1 Knobler RL, Greenstein JI, Johnson KP, et al. Systemic recombinant human interferon-beta treatment of relapsing-remitting multiple sclerosis: pilot study analysis and six-year follow-up. J Interferon Res 1993;13:333–40.
2 Whetten-Goldstein K, Sloan FA, Goldstein LB, Kulas ED. A comprehensive assessment of the cost of multiple sclerosis in the United States. Mult Scler 1998;4:419–25.
3 IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. Neurology 1993;43:655–61.
4 Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol 1996;39:285–94.
5 Rudick RA, Goodkin DE, Jacobs LD, et al. Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis. Neurology 1997;49: 358–63.
6 The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. Neurology 1995;45: 1277–85.
7 Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial. Neurology 1995;45:1268–76.
8 Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-Effectiveness in Health and Medicine. New York: Oxford University Press, 1996.

9 Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. Neurology 1996;46:907–11.
10 Ebers GC, Koopman WJ, Hader W, et al. The natural history of multiple sclerosis: a geographically based study. 8. Familial multiple sclerosis. Brain 2000;123:641–9.
11 Weinshenker BG. The natural history of multiple sclerosis: update 1998. Semin Neurol 1998;18: 301–7.
12 Goodkin DE, Hertsgaard D, Rudick RA. Exacerbation rates and adherence to disease type in a prospectively followed-up population with multiple sclerosis. Implications for clinical trials. Arch Neurol 1989;46:1107–12.
13 Weinshenker BG, Bass B, Rice GPA, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. Brain 1989;112:133–46.
14 Runmarker B, Anderson O. Prognostic factors in a multiple sclerosis incidence cohort with twenty-five years of follow-up. Brain 1993;116:117–34.
15 Goodkin DS. The Northern California MS Study Group. Survey of multiple sclerosis in northern California. Mult Scler 1999;5:78–88.
16 Jacobs LD, Wende KE, Brownscheidle CM, et al. A profile of multiple sclerosis: the New York State multiple sclerosis consortium. Mult Scler 1999;5: 369–76.
17 Miller DH, Hornabrook RW, Purdie G. The natural history of multiple sclerosis: a regional study with some longitudinal data. J Neurol Neurosurg Psych 1992;55:341–6.
18 Weinshenker BG, Bass B, Rice GPA, et al. The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. Brain 1989;112:1419–28.
19 Weinshenker BG, Ebers GC. The natural history of multiple sclerosis. Can J Neurol Sci 1987;14:255–61.
20 Phadke JG. Survival pattern and cause of death in patients with multiple sclerosis: results from an epidemiological survey in northeast Scotland. J Neurol, Neurosurg Psychiatry 1998;50:523–31.
21 Anderson RN. United States Life Tables, 1998. National Vital Statistics Reports, Vol. 48 No. 18. Hyattsville, Maryland: National Center for Health Statistics, 2001.
22 Mohr DC, Likosky W, Boudewyn AC, et al. Side effect profile and adherence to in the treatment of multiple sclerosis with interferon beta-1a. Mult Scler 1998;4:487–9.
23 Neilley LK, Goodin DS, Goodkin DE, Hauser SL. Side effect profile of interferon beta-1b in MS: results of an open label trial. Neurology 1996;46: 552–4.
24 Logan-Clubb L, Stacy M. An open-labeled assessment of adverse effects associated with interferon 1-beta in the treatment of multiple sclerosis. J Neurosci Nurs 1995;27:344–7.
25 Weinstock-Guttman B, Cohen JA. Newer versus older treatments for relapsing-remitting multiple sclerosis. Drug Saf 1996;14:121–30.
26 Mohr DC, Goodkin DE, Likosky W, et al. Therapeutic expectations of patients with multiple sclerosis upon initiating interferon beta-1b: relationship to adherence to treatment. Mult Scler 1996;2:222–6.
27 Lublin FD, Whitaker JN, Eidelman BH, et al. Management of patients receiving interferon beta-1b for multiple sclerosis: report of a consensus conference. Neurology 1996;46:12–18.
28 Prosser LA, Kuntz KM, Bar-Or A, Weinstein MC. Patient and community preferences for treatments and health states in multiple sclerosis. Mult Scler 2003;9:311–19.
29 US Department of Commerce, Bureau of Economic Analysis. Available from: http://www.bea.doc.gov/bea/newsrel/gdp499p.htm. [Last accessed Mar 3, 2000].
30 Drug Topics Red Book. Montvale, NJ: Medical Economics Co., Inc., 1999.
31 Bureau of Labor Statistics. Available from: http://stats.bls.gov/news.release/wkyeng.nws.htm. [Last accessed Mar 9, 2000].
32 1999 Medicare Clinical Laboratory Fee Schedule. Available from: http://www.cms.hhs.gov/providers/pufdownload/clfdown.asp. [Last accessed March 3, 2000].
33 1999 National Physician Fee Schedule Relative Value File. Available from: http://cms.hhs.gov/providers/pufdownload/rvudown.asp. [Last accessed Mar 3, 2000].
34 Stolp-Smith KA, Atkinson EJ, Campion ME, et al. Health care utilization in multiple sclerosis. A population-based study in Olmsted County, MN. Neurology 1998;50:1594–600.
35 Fishman P, Von Korff M, Lozano P, Hecht J. Chronic care costs in managed care. Health Aff 1997;16:239–47.
36 Inman RP. The economic consequences of debilitating illness: the case of multiple sclerosis. Rev Econ Stat 1987;69:651–60.
37 Bourdette DN, Prochazka AV, Mitchell W, et al. Health care costs of veterans with multiple sclerosis: implications for the rehabilitation of MS. Arch Phys Med Rehabil 1993;74:26–31.
38 Brown MG, Murray TJ, Fisk JD, et al. A Therapeutic and Economic Assessment of Betaseron in Multiple Sclerosis. Ottawa: Canadian Coordinating Office for Health Technology Assessment, 1996. Technology report.
39 Brown MG, Murray TJ, Sketris IS, et al. Cost-effectiveness of interferon beta-1b in slowing multiple sclerosis progression: first estimates. IJTAHC 2000;16:751–67.

40 Parkin D, McNamee P, Jacoby A, et al. A cost-utility analysis of interferon beta for multiple sclerosis. Health Technol Assess 1998;2:1–66.
41 Forbes RB, Lees A, Waugh N, Swingler RJ. Population based cost utility study of interferon beta-1b in secondary progressive multiple sclerosis. BMJ 1999;319:1529–33.
42 Kendrick M, Johnson KI. Long term treatment of multiple sclerosis with interferon-beta may be cost effective. Pharmacoeconomics 2000;18:45–53.
43 Chilcott J, McCabe C, Tappenden P, et al. Modelling the cost effectiveness of interferon beta and glatiramer acetate in the management of multiple sclerosis. BMJ 2003;326:522–6.
44 Kobelt G, Jonsson L, Henriksson F, et al. Cost-utility analysis of interferon beta-1b in secondary progressive multiple sclerosis. Int J Tech Assess Health Care 2000;16:768–80.
45 Kobelt G, Jonsson L, Miltenburger C, et al. Cost-utility analysis of interferon beta-1b in secondary progressive multiple sclerosis using natural history data. Int J Tech Assess Health Care 2002;18:127–38.
46 Kobelt G, Jonsson L, Fredrikson S. Cost-utility of interferon beta-1b in the treatment of patients with active relapsing-remitting or secondary progressive multiple sclerosis. Eur J Health Econom 2003;4:50–9.
47 Weinshenker BG, Rice GPA, Noseworthy JH, et al. The natural history of multiple sclerosis: a geographically based study. 3. Multivariate analysis of predictive factors and models of outcome. Brain 1991;114:1045–56.
48 Sadovnick AD, Eisen RN, Ebers GC, Paty DW. Cause of death in patients attending multiple sclerosis clinics. Neurology 1991;41:1193–6.
49 Koch-Henriksen N, Bronnum-Hansen H, Stenager E. Underlying cause of death in Danish patients with multiple sclerosis: results from the Danish Multiple Sclerosis Registry. J Neurol Neurosurg Psychiatry 1998;65:56–9.
50 Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. N Engl J Med 2000;343:898–904.
51 Beck RW, Chandler DL, Cole SR, et al. Interferon beta-1a for early multiple sclerosis: CHAMPS trial subgroup analyses. Ann Neurol 2002;51:481–90.
52 Comi G, Filippi M, Barkhof F, et al. Early Treatment of Multiple Sclerosis Study Group. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. Lancet 2001;357:1576–82.