Cost-effectiveness of Four Immunomodulatory Therapies for Relapsing-Remitting Multiple Sclerosis: A Markov Model Based on Long-term Clinical Data

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ABSTRACT

BACKGROUND: Before the introduction of the immunomodulatory therapies for multiple sclerosis (MS), treatment options for MS consisted of symptomatic management (physical therapy and pharmacological treatment for symptom management). Symptomatic management for MS has been supplemented in the past decade by 2 new classes of immunomodulatory therapies that have been approved as first-line treatments for relapsing-remitting multiple sclerosis (RRMS): subcutaneous glatiramer acetate (SC GA) and 3 β -interferons: intramuscular interferon β -1a (IM IFN β -1a), SC IFN β -1a, and SC IFN β -1b.

OBJECTIVE: To estimate the economic outcomes of 5 treatment strategies: symptom management alone, symptom management combined with SC GA, IM IFN β -1a, SC IFN β -1a, or SC IFN β -1b in patients diagnosed with RRMS.

METHODS: A literature-based Markov model was developed to assess the cost-effectiveness of 5 treatment strategies for managing a hypothetical cohort of patients diagnosed with RRMS in the United States—4 immunomodulatory drug therapies and symptom management alone. Health states were based on the Kurtzke Expanded Disability Status Scale (EDSS), a widely accepted scale for assessing RRMS (higher EDSS scores = increased disease severity). Baseline relapse and disease progression transition probabilities for symptom management were obtained from natural history studies. Treatment effects of the immunomodulatory therapies were estimated by applying a percentage reduction to the symptom management transition probabilities for relapse (27% reduction) and disease progression (30% reduction). Transition probabilities were subsequently adjusted to account for (1) the effects of neutralizing antibodies, specifically on relapse rates by assuming no additional therapy benefits after the second year of continuous therapy, and (2) treatment discontinuation. Therapy-specific data were obtained from clinical trials and long-term follow-up observational studies. Transitions among health states occurred in 1-month cycles for the lifetime of a patient. Costs (2005 US\$) and outcomes were discounted at 3% annually.

RESULTS: The incremental cost per quality-adjusted life-year for the 4 immunomodulatory therapies is \$258,465, \$303,968, \$416,301, and \$310,691 for SC GA, IM IFN β -1a, SC IFN β -1a, and SC IFN β -1b, respectively, compared with symptom management alone. Sensitivity analyses demonstrated that results were sensitive to changes in utilities, disease progression rates, time horizon, and immunomodulatory therapy cost.

CONCLUSIONS: The pharmacoeconomic model determined that SC GA was the best strategy of the 4 immunomodulatory therapies used to manage MS and resulted in better outcomes than symptom management alone. Sensitivity analyses indicated that the model was sensitive to changes in a number of key parameters, and thus changes in these key parameters would likely influence the estimated cost-effectiveness results. Head-to-head randomized clinical trials comparing the immunomodulatory therapies for the treatment of MS are necessary to validate the projections from the pharmacoeconomic analyses, particularly since the results available today from the clinical trials do not account adequately for treatment dropouts.

KEYWORDS: Multiple sclerosis, Immunomodulatory therapy, Markov model, Cost-effectiveness

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Multiple sclerosis (MS) is a chronic, neurodegenerative inflammatory disease of the central nervous system. In the United States, the prevalence rate of MS is estimated to range between 85 and 177 cases per 100,000, translating to an overall prevalence of approximately 400,000.¹⁻³ In a majority of patients (70%), the onset of MS occurs during early adulthood (age 15-45 years), making MS one of the most common causes of neurological disability in young and middle-aged adults.^{4,5} Common symptoms of MS include fatigue, walking difficulties leading to reduced mobility, bowel/bladder disturbances, optic neuritis and other visual changes, changes in cognitive function, pain, sensory loss, and depression.⁶ Three main types of MS are generally recognized: (1) relapsing-remitting MS (RRMS), (2) secondary progressive MS (SPMS), and (3) primary progressive/relapsing MS (PPMS or PRMS).^{7,8} At disease onset, RRMS is diagnosed in approximately 80% to 85% of MS patients, with the remaining proportion of patients diagnosed with the primary progressive forms of MS (PPMS or PRMS).^{4,9,10} Among RRMS-diagnosed patients, a majority will progress to SPMS (50% of patients will experience a gradual progression of disability within 10 years of the initial attack and 90% of patients will have progressive disease after 25 years).¹¹

Note: An editorial on the subject of this article appears on pages 287-89 of this issue.

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TABLE 1 Table of Immunomodulatory Therapy Clinical Trials in Relapsing-Remitting Multiple Sclerosis

	CIMSSG (1995)	MSCRG (1996)	EIFNBDCS (2002)	PRISMS (1998)	IFNBMSSG (1995)	INCOMIN (2002)	EVIDENCE (2002)
Reference	Johnson ¹²	Jacobs ¹³	Clanet ¹⁴	PRISMS ¹⁵	IFNB MS Study Group ^{16,17}	Durelli ¹⁸	Panitch ¹⁹
Intervention	GA 20 mg PLA	IFNβ-1a 30 µg PLA	IFNβ-1a 30 µg IFNβ-1a 60 µg	IFNβ-1a 22 µg IFNβ-1a 44 µg PLA	IFNβ-1b 1.6 MIU IFNβ-1b 8 MIU PLA	SC IFNβ-1b 8 MIU IM IFNβ-1a 30µg	SC IFNβ-1a 44 µg IM IFNβ-1a 30 µg
Dosing	SC once daily	IM once weekly	IM once weekly	SC 3 times weekly	SC every other day	SC every other day IM once weekly	SC 3 times weekly IM once weekly
Study design	RCT, DB United States 24-months	RCT, DB United States 24 months	RCT, DB Europe 36 months	RCT, DB 9 countries 24 months	RCT, DB United States/ Canada 24 months	RCT Italy 24 months	RCT Europe/Canada/ United States 48 weeks
Number of patients	Total: 251 GA: 125 PLA: 126	Total: 301 30 µg: 158 PLA: 143	Total: 802 30 µg: 402 60 µg: 400	Total: 560 22 µg: 189 44 µg: 184 PLA: 187	Total: 372 1.6 MIU:125 8 MIU: 124 PLA:123	Total: 188 8 MIU: 96 30 µg: 92	Total: 677 44 µg: 339 30 µg: 338
Patient characteristics	EDSS 0.0-5.5 Mean (SD) EDSS: GA: 2.8 (1.2) PLA: 2.4 (1.3) 2 relapses in previous 2 years	EDSS 1.0-3.5 Mean (SE) EDSS: 30 µg: 2.4 (0.05) PLA: 2.3 (0.05) 2 relapses in previous 3 years	EDSS 2.0-5.5 Mean (SD) EDSS: 30 µg: 3.6 (1.0) 60 µg: 3.6 (1.0) 2 relapses in previous 3 years	EDSS 0.0-5.0 Mean (SD) EDSS: 22 µg: 2.5 (1.2) 44 µg: 2.5 (1.3) PLA: 2.4 (1.2) 2 relapses in previous 2 years	EDSS 0.0-5.5 Mean (SE) EDSS: 1.6 MIU: 2.9 (0.1) 8 MIU: 3.0 (0.1) PLA: 2.8 (0.1) 2 relapses in previous 2 years	EDSS 1.0-3.5 Mean (SD) EDSS: 8 MIU: 1.9 (0.6) 30 µg: 2.0 (0.7) 2 relapses in previous 2 years	EDSS 0.0-5.5 Mean (SD) EDSS: 44 µg: 2.3 (N/R) 30 µg: 2.3 (N/R) 2 relapses in previous 2 years
Number (%) of patients who completed the study and contributed to clinical outcomes	Total: 215/251 (85.7%) GA: 106/125 (84.8%) PLA: 109/126 (86.5%)	Total: 129/301 (57.1%) 30 µg: 85/158 (53.8%) PLA: 87/143 (60.8%)	Total: 559/802 (69.7%) 30 µg: 281/402 (69.9%) 60 µg: 273/400 (69.5%)	Total: 526/560 (93.9%) 22 µg: 167/189 (88.4%) 44 µg: 165/184 (89.7%) PLA: 170/187 (90.9%)	Total: 338/372 (90.9%) 1.6 MIU:111/125 (88.8%) 8 MIU: 115/124 (92.7%) PLA: 112/123 (91.1%)	Total: 158/188 (84.0%) 8 MIU: 85/96 (88.5%) 30 µg: 73/92 (79.3%)	Total: 649/677 (95.9%) 44 µg: 325/339 (95.9%) 30 µg: 324/338 (95.9%)
Primary endpoint	Number of relapses	Time to confirmed EDSS progression (increase of 1.0 point on EDSS sustained for 6 months)	Sustained disability progression	Relapse rate	Annual relapse rate and the proportion of relapse-free patients	Number of relapse-free patients and the number of patients with no new T2 lesions on MRI	Proportion of patients relapse-free at 24 weeks
Summary of results	Compared with PLA, GA is effective in reducing relapse rates.	Compared with PLA, 30µg is effective in prolonging the time to disability and reducing relapse rates; initial results based on non- ITT principles.	No difference in relapse or sustained disability progression between treatment groups.	Compared with PLA, 22 µg and 44 µg are effective in reducing relapses and delaying the progression of disability.	Compared with PLA, 1.6 MIU and 8 MIU are effective in reducing relapses and on measures of MRI activity.	Compared with 30 µg, 8 MIU had a greater percentage of patients who remained relapse- free and was more effective in terms of reducing MRI disease activity.	Compared with 30 µg, 44 µg is more effective in preventing relapses and reducing MRI disease activity.

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TABLE 1 Table of Immunomodulatory Therapy Clinical Trials in Relapsing-Remitting Multiple Sclerosis (continued)

	C1MSSG (1995)	MSCRG (1996)	EIFNBDCS (2002)	PRISMS (1998)	IFNBMSG (1995)	INCOMIN (2002)	EVIDENCE (2002)
Relapse results ⁶	Mean number of relapses over 2 years: GA: 1.19 PLA: 1.68 RR (vs. PLA): GA = 0.71	Annual relapse rate (all patients): 30 µg: 0.67 PLA: 0.82 RR (vs. PLA): 30 µg = 0.82 Annual relapse rate (2-year completers): 30 µg: 0.61 PLA: 0.90 RR (vs. PLA): 30 µg = 0.68	Annualized relapse rate: 30 µg: 0.77 60 µg: 0.81	Relapse rate over 2 years: 22 µg: 1.82 44 µg: 1.73 PLA: 2.56 RR (vs. PLA): 22 µg = 0.71 44 µg: 0.68	Annual relapse rate over 2 years: 1.6 MIU: 1.17 8 MIU: 0.84 PLA: 1.27 RR (vs. PLA): 1.6 MIU = 0.92 8 MIU = 0.66 Relapse-free patients after 2 years: 1.6 MIU: 23% 8 MIU: 36% PLA: 18%	Relapse-free patients after 2 years: 8 MIU: 51% 30 µg: 36%	Relapse-free patients after 24 weeks: 44 µg: 75% 30 µg: 63% Relapse-free patients after 48 weeks: 44 µg: 62% 30 µg: 52%
Disease progression results ⁶	Patients with increase of 1.0 point on EDSS (unsustained): GA: 20.8% PLA: 28.8%	Sustained progression (all patients): 30 µg: 21.9% PLA: 34.9%	Sustained progression by 36 months (increase of 1.0 point on EDSS sustained for 6 months): 30 µg: 37% 60 µg: 37%	Time (months) to progression of disability (increase of 1.0 point on EDSS sustained for 3 months): 22 µg: 18.5 44 µg: 21.3 PLA: 11.9	N/A	Confirmed progression of disability (increase of 1.0 point on EDSS sustained for 6 months): 8 MIU: 30% 30 µg: 15%	Confirmed progression of disability (increase of 1.0 point on EDSS sustained for 6 months): 8 MIU: 6% 30 µg: 8%
Study extensions (% of patients initially randomized to study drug completing extension)	35 months (77.6%) ²⁰ 6 years (61.6%) ²⁴ 8 years (57.6%) ²⁵ 10 years (51.2%) ²⁸	8 years (N/A, LTFU) ⁹⁴	4 years (55.6%) ²¹	4 years (78.8%) ²² 6 years (50.1%) ²⁶ 8 years (N/A, LTFU) ²⁷	5 years (44.2%) ²³ 16 years (N/A, LTFU) ⁹⁵	N/A	N/A

C1MSSG = Copolymer-1 Multiple Sclerosis Study Group; DB = double blind; EDSS = Expanded Disability Status Scale (Kurtzke); EIFNBDCS = European IFNβ-1a Dose-Comparison Study; EVIDENCE = Evidence of Interferon Dose-Response: European North American Comparative Efficacy; GA = glatiramer acetate; IFN = interferon; IFNBMSG = Interferon Beta Multiple Sclerosis Study Group; IM = intramuscular; INCOMIN = Independent Comparison of Interferon; ITT = intent to treat; LTFU = long-term follow-up visit; MIU = million international units; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSCRG = Multiple Sclerosis Collaborative Research Group; N/A = not available; N/R = not reported; PLA = placebo; PRISMS = Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis; RCT = randomized clinical trial; RR = relative risk; SC = subcutaneous; µg = micrograms.

Before the immunomodulatory therapies for MS were introduced, treatment options for MS consisted of symptomatic management (physical therapy and pharmacological treatment for symptom management). Symptomatic management for MS has been supplemented in the past decade by 2 new classes of immunomodulatory therapies that have been approved as first-line treatments for RRMS: subcutaneous glatiramer acetate (SC GA) (Copaxone) and 3 β-interferons: intramuscular interferon β-1a (IM IFNβ-1a [Avonex]), SC IFNβ-1a (Rebif), and SC IFNβ-1b (Betaseron). Evidence from randomized clinical

trials (1-2 years)¹²⁻¹⁹; prospective extensions of the clinical trials (2-5 years)²⁰⁻²³; and long-term follow-up studies of patients initially enrolled in clinical trials²⁴⁻²⁷ (one of which extends beyond 10 years²⁸) have shown that there is good evidence demonstrating the benefits of immunomodulatory therapies in reducing relapse rates, slowing the progression of disability, and reducing MS disease activity (Table 1).

However, the use of the immunomodulatory therapies in everyday clinical practice has been a topic of substantial debate. The National Institute for Clinical Excellence (NICE) determined

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FIGURE 1 Schematic Representation
of the Markov Model

EDSS = Expanded Disability Status Scale (Kurtzke).

that "...on the balance of their clinical and cost-effectiveness, neither beta interferon nor glatiramer acetate is recommended..." and those therapies were provided to patients only after the Department of Health and the respective manufacturers agreed to a risk-sharing scheme.^{29,30} In contrast to NICE's guidance, some clinical practice guidelines have recommended the immunomodulatory therapies for the treatment of MS.³¹ The selection of specific therapies is based on individual patient characteristics (e.g., disease severity, patient compliance) and treatment characteristics (e.g., efficacy, incidence of neutralizing antibodies [NABs], side effects).

The socioeconomic burden of MS is substantial given the debilitating nature of this chronic, progressive, and lifelong condition that affects individuals in the most productive years of life. Drug acquisition cost for the immunomodulatory therapies was estimated to exceed \$16,000 per patient per year in 2006, a significant expenditure for health care payers.³²⁻³⁴ The annual cost of illness of MS (in 1994 US\$) is estimated to be between \$6.8 and \$13.6 billion, composed largely of indirect costs for

formal/informal care and lost earnings.³⁵ Patwardhan et al.³⁶ assessed the link between disability levels and costs and found that costs rose at an exponential rate with increasing MS disability levels, a finding that was consistent with previously published studies.³⁷⁻³⁹ Given this evidence of increasing costs (direct and indirect) with increasing disease severity, we believe the ability of the immunomodulatory therapies to reduce relapse rates and slow the progression of the MS may assist in reducing resource use and may, in turn, help to offset the cost of these therapies.

Cost-effectiveness and cost-utility analyses (CEA/CUAs) are useful tools to assess the tradeoff between the added costs and potential benefits (e.g., improved patient outcomes) of new therapies. In the current environment of cost-consciousness and limited health care resources, CEA/CUA affords decision makers an opportunity to evaluate new therapies from an economic perspective and quantify the budgetary implications of adopting such therapies. A majority of the published CEA/CUA evaluations of immunomodulatory therapies for MS have been conducted from perspectives outside the United States.^{30,40-45} In a recent U.S.-based CUA evaluation, immunomodulatory therapy for the treatment of nonprimary, progressive MS (e.g., RRMS and SPMS) was compared with no treatment over a 10-year time horizon.⁴⁶ Cost-effectiveness results from this analysis, as well as previously published CUA evaluations, were considerably higher than the arbitrary and commonly referenced benchmark of \$50,000 per quality-adjusted life-year (QALY).⁴⁷

Recent published literature on the impact of the immunomodulatory therapies in MS has provided key data that have not been previously used in CEA/CUA evaluations. Specifically, long-term follow-up data of patients initially enrolled in clinical trials have been published,²⁴⁻²⁸ one of which, for SC GA, extended beyond 10 years.²⁸ In previous CEA/CUA evaluations, long-term treatment outcomes (e.g., treatment effects and discontinuation rates) were extrapolated over time based primarily on data from short-term clinical trials. In addition to long-term follow-up data, there has been focus on the development of NABs among patients prescribed β -interferons, which may inhibit or "neutralize" the effectiveness of β -interferon treatment.⁴⁸

Because of data limitations, previous models have made assumptions regarding the impact of β -interferons on treatment effects (e.g., constant treatment effects over time), which, in turn, made it difficult to examine the impact that NABs might have on cost-effectiveness. With the availability of long-term data, cost-effectiveness analysis of various therapies in the presence of these clinical markers can be made more appropriately. In this regard, we examine the cost-effectiveness of 5 treatment strategies in patients diagnosed with RRMS (symptom management alone and in combination with SC GA, IM IFN β -1a, SC IFN β -1a, or IM IFN β -1b). Cost-effectiveness results (symptom management vs. the 4 immunomodulatory therapies) were reported in terms of cost per QALY gained as well as cost per outcome achieved

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(e.g., cost per year spent relapse free or cost per year spent in less severe disease health states), thus providing decision makers relevant data with which to evaluate the cost-effectiveness of the 4 immunomodulatory therapies versus symptom management in treating RRMS.

Methods

Model Description

We developed a Markov model to assess the cost-effectiveness of 5 treatment strategies to manage a hypothetical cohort of patients diagnosed with RRMS in the United States. The strategies were symptom management alone (e.g., physical therapy/exercise and pharmacological treatment [e.g., corticosteroids for relapse, tizanidine for spasticity, and modafinil for fatigue]) and symptom management in combination with 1 of the following immunomodulatory therapies: SC GA, IM IFN β -1a, SC IFN β -1a, or SC IFN β -1b. The clinical course of RRMS (e.g., disease progression and relapse) was modeled in terms of the Kurtzke Expanded Disability Status Scale (EDSS).⁴⁹ Specifically, 7 EDSS health states were modeled (Figure 1):

1. EDSS 0.0-2.5: no or few limitations in mobility
2. EDSS 3.0-5.5: moderate limitations in mobility
3. EDSS 6.0-7.5: walking aid or wheelchair required
4. EDSS 8.0-9.5: restricted to bed
5. Death (natural causes or EDSS 10)
6. Relapse EDSS 0.0-2.5: relapse with a change in disability within EDSS 0.0-2.5
7. Relapse EDSS 3.0-5.5: relapse with a change in disability within EDSS 3.0-5.5

Transitions among the health states occurred in 1-month cycles. The baseline time horizon of the model was assumed to be lifetime in order to capture the full benefits of immunomodulatory therapy. Costs and outcomes were estimated from the societal perspective and were discounted at 3% per annum.⁵⁰ All costs were reported in 2005 U.S. dollars. The natural history of MS disease progression, clinical efficacy of MS therapies, mortality, resource use, costs, and utilities were obtained from the published literature. The model calculated the following outcomes: average number of years spent in EDSS 0.0-5.5; average number of years spent relapse free; life-years; QALYs; total costs and costs by component (i.e., immunomodulatory therapy cost, MS-related medical costs [e.g., drugs for symptom management], and lost worker productivity costs); and incremental cost-effectiveness ratios comparing symptom management alone with symptom management combined with each of the 4 immunomodulatory therapies. Model parameters were varied in sensitivity analyses.

A number of underlying assumptions were adopted for the base-case model:

1. A Web survey of patients (aged ≥ 18 years) treated with immunomodulatory therapy in the United States and enrolled in a patient support program was used to determine the percentage of patients entering the model among the 4 nonrelapse EDSS

health states⁵¹ (Table 2). The survey, based on previous surveys conducted in the United States and Europe,^{52,53} was completed by 711 MS patients and collected data such as disease information (e.g., type of MS, therapy used), quality of life, resource use, and associated costs (direct and indirect). The majority of surveyed patients were in the lower EDSS health states (e.g., EDSS < 6.0), which represents RRMS patients eligible for immunomodulatory therapy, and the overall distribution was relatively consistent with previously published surveys among patients diagnosed with MS.⁵⁴⁻⁵⁷ Sensitivity analyses were conducted to assess varying patient distributions (e.g., 100% of patients start in EDSS 0.0-2.5 health state).

2. The point at which patients transformed from RRMS (characterized by clearly defined relapses with at least partial recovery of deficits and lack of disease progression between relapses) to SPMS (characterized by less frequent relapses and deficits that begin to progress even between relapses) was not specified in the model, as the precise time at which this transformation takes place is not clearly defined. Rather, the model assumed that this transformation took place between EDSS 3.0-5.5 and EDSS 6.0-7.5. Corresponding to this assumption, the model assumed that relapses occurred only in patients in the lower EDSS health states (EDSS 0.0-5.5) and that the rate of disease progression increased in the higher EDSS health states (EDSS 6.0-9.5).

3. The model assumed that, per product labeling, only RRMS patients were eligible for and received immunomodulatory therapy, corresponding to patients in the lower EDSS health states (i.e., EDSS 0.0-5.5).

4. Switching among the immunomodulatory therapies was not permitted in the model. Patients discontinuing immunomodulatory therapy were assigned the transition probabilities for relapse and disease progression used in the symptom management arm. Patients who discontinued therapy were not permitted to reinstate therapy.

5. The model assumed that nonrelapse-related EDSS scores do not improve over time; therefore, patients transitioned to the next, more severe health state, 1 health state at a time, corresponding to a progression in disease severity (e.g., EDSS 0.0-2.5 to EDSS 3.0-5.5).

The base-case parameter inputs, values, and additional assumptions are detailed in the next sections and are summarized in Table 2.

Clinical Course of MS

Relapse and disease progression transition probabilities within the symptom management arm were obtained from published natural history studies (relapse rates,^{4,58,59} disease progression^{11,60}), as reported in a previous MS cost-effectiveness model.⁴⁶ Mortality due to natural causes was assumed to occur at any cycle in the model based on age-specific, all-cause mortality rates.⁶¹ Mortality due to MS was assumed to occur only after patients had progressed through all EDSS health states

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TABLE 2 Summary of Parameters and Values Used in the Base-Case Markov Model

Parameter Description	Estimate for Base-Case Model	Range for Sensitivity Analysis (±25% Unless Indicated Otherwise)		Reference
Initial patient distribution among EDSS health states		Scenario 1	Scenario 2	Oleen-Burkey [abstract] ⁵¹
EDSS 0.0-2.5	26.4%	100.0%	25.0%	
EDSS 3.0-5.5	58.7%	0.0%	25.0%	
EDSS 6.0-7.5	13.8%	0.0%	25.0%	
EDSS 8.0-9.5	1.1%	0.0%	25.0%	
Monthly probability of disease progression (symptom management)		N/C		Weinshenker ¹¹ ; Runmarker ⁶⁰ ; Prosser ⁴⁶
EDSS 0.0-2.5 to 3.0-5.5	0.004438			
EDSS 3.0-5.5 to 6.0-7.5	0.009189			
EDSS 6.0-7.5 to 8.0-9.5	0.003583			
EDSS 8.0-9.5 to 10 (death)	0.000952			
Monthly probability of relapse (symptom management)	0.075500	N/C		Goodkin ⁵⁸ ; Weinshenker ^{4,59} ; Prosser ⁴⁶
Treatment effects of SC GA and β-interferons, % reduction in:				
Probability of disease progression	30%	12.5%-47.5%		Filippini ⁶⁴ ; Simpson ⁹⁰ ; Khan ⁶⁶
Probability of relapse	27%	8.8%-45.2%		
Incidence of NABs				Rossman ⁴⁸ ; IFNB MS Study Group ¹⁶ ; European Study Group ⁹⁶ ; PRISMS ¹⁵ ; SPECTRIMS ⁹⁷ ; Panitch ¹⁹ ; Jacobs ^{13,98} ; Clanet ¹⁴ ; Cohen ⁹⁹
IM IFNβ-1a	2.2%	1.7%-2.8%		
SC IFNβ-1a	17.4%	13.1%-21.8%		
SC IFNβ-1b	36.4%	27.3%-45.5%		
Monthly drug acquisition costs (WAC), 2005 U.S.\$				Red Book ³³
SC GA	\$1,258.20	\$943.65-\$1,572.75		
IM IFNβ-1a	\$1,275.00	\$956.25-\$1,593.75		
SC IFNβ-1a	\$1,469.64	\$1,102.23-\$1,837.05		
SC IFNβ-1b	\$1,264.85	\$948.64-\$1,581.06		

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(i.e., only patients in the EDSS 8.0-9.5 health state could transition to EDSS 10, which is death). This assumption was consistent with a previous model⁴⁶ that was based on data indicating that nearly 90% of MS patients were significantly disabled (e.g., unable to walk) before death.⁶² These data are presented in Table 2.

Treatment Effects of SC GA and the β -Interferons

Treatment effects associated with the immunomodulatory therapies were estimated by adjusting (via a percentage reduction) the probabilities of relapse and disease progression used in the symptom management arm of the model. Relapse and disease progression rates over time were obtained from randomized clinical trials (SC GA,¹² IM IFN β -1a,^{13,14,63} SC IFN β -1a,¹⁵ SC IFN β -1b^{16,17}); prospective extensions of the clinical trials (SC GA,²⁰ IM IFN β -1a,²¹ SC IFN β -1a,²² SC IFN β -1b²³); and long-term follow-up studies (SC GA,²⁸ SC IFN β -1a²⁶).

Relapse and disease progression rates were then mapped and fitted to prediction curves over time to estimate the long-term treatment effects of SC GA and the β -interferons (relapse: Figure 2; disease progression: Figures 3 and 4).

To account for the inherent differences between the randomized clinical trials (e.g., patient population, primary endpoint), a fixed patient population was assumed for the base-case model. In particular, all patients entered the model on the basis of a fixed EDSS distribution (Table 2). Furthermore, short-term outcomes were modeled by assuming, for all immunomodulatory therapies, a single percentage reduction for relapse and disease progression in the first 2 years of therapy (Table 2). This assumption was based on data from several published review papers⁶⁴⁻⁶⁶ that indicated annual relapse and disease progression rates in the randomized clinical trials were similar among therapies. In subsequent years of the model, treatment effects were estimated based on the long-term, immunomodulatory-specific prediction

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TABLE 2 Summary of Parameters and Values Used in the Base-Case Markov Model (continued)

Parameter Description	Estimate for Base-Case Model	Range for Sensitivity Analysis (±25% Unless Indicated Otherwise)			Reference
Health state-specific MS-related costs (monthly)					Oleen-Burkey [abstract] ⁵¹
EDSS 0.0-2.5	\$433.26	\$324.95-\$541.58			
EDSS 3.0-5.5	\$838.8.3	\$629.12-\$1,048.54			
EDSS 6.0-7.5	\$1,990.02	\$1,492.52-\$2,487.53			
EDSS 8.0-9.5	\$3,499.59	\$2,624.69-\$4,374.49			
Relapse EDSS 0.0-2.5	\$427.98	\$320.99-\$534.97			
Relapse EDSS 3.0-5.5	\$1,094.80	\$821.10-\$1,368.50			
Monthly cost of lost worker productivity (no. of days missed x hourly wage x % of patients employed)		Scenario 1		Scenario 2	Lichtenberg ⁷⁴ ; Lage ⁷⁵ ; Busche ⁷⁶
Symptom management	\$154.74	N/C		\$116.06-\$193.43	
SC GA	\$109.39	\$84.94-\$133.82		\$82.05-\$136.74	
IM IFNβ-1a	\$167.40	\$158.04-\$176.77		\$125.55-\$209.26	
SC IFNβ-1a	\$167.40	\$158.04-\$176.77		\$125.55-\$209.26	
SC IFNβ-1b	\$162.63	\$159.47-\$165.79		\$121.97-\$203.29	
Utility weights		Scenario 1	Scenario 2	Scenario 3	
EDSS 0.0-2.5	0.824	0.618-1.000	0.710	N/C	
EDSS 3.0-5.5	0.679	0.509-0.849	0.590	N/C	
EDSS 6.0-7.5	0.533	0.400-0.666	0.420	N/C	
EDSS 8.0-9.5	0.491	0.368-0.614	0.125	N/C	
Utility decrement associated with relapse	0.094	0.071-0.118	N/C	0.071-0.118	

EDSS = Expanded Disability Status Scale (Kurtzke); EDSS 0.0-2.5 = no MS symptoms to minimal disability in 2 functional areas; EDSS 3.0-5.5 = moderate disability in 1 functional area or mild disability in up to 4 areas to disability severe enough to preclude full daily activities; EDSS 6.0-7.5 = intermittent or unilateral constant assistance required to walk 100 meters to restricted to wheelchair; EDSS 8.0-9.5 = restricted to bed with many self-care functions retained to requiring assistance for all activities of daily living; GA = glatiramer acetate; IFN = interferon; IM = intramuscular; MS = multiple sclerosis; N/A = not applicable; NAb = neutralizing antibodies; N/C = no change; SC = subcutaneous; symptom management = symptomatic management alone; WAC = wholesale acquisition cost.

curves. Sensitivity analyses were performed to assess the impact of varying the percentage reduction adjustments.

To account for the effect of NABs, the probabilities of relapse for patients in the β-interferon arms of the model were subsequently adjusted. The model assumed that NABs would affect the probability of relapse and would occur only after the second year of continuous interferon treatment.⁶⁷⁻⁶⁹ The incidence of NABs was obtained from the published literature⁴⁸ and was used to calculate an adjusted probability of relapse that reflected a weighted average of NAb-positive (NAb+) and NAb-negative (NAb-) patients. A conservative approach to modeling the impact of NABs was adopted, where NAb+ patients (titer ≥20) experienced a probability of relapse equal to that of the year-2 probability in each subsequent year of the model, and NAb- patients experienced a probability of relapse equal to that predicted by the fitted curve described previously. The model did not consider dose escalation of the β-interferons in response to NABs.

The probabilities of relapse (adjusted for NABs) and disease progression associated with the immunomodulatory therapies were also adjusted to account for patients who discontinued therapy. Rates of discontinuation were obtained from the published clinical trials and long-term follow-up studies; a relative 3% annual discontinuation rate was assumed in the event data were not available.³⁰ Patients who discontinued therapy were assigned the probabilities of relapse and disease progression used in the symptom management arm of the model. Similar to the calculation performed for NABs, the adjusted probability of relapse and disease progression reflected a weighted average of patients continuing and discontinuing therapy. The fitted curves for the long-term treatment effects of the immunomodulatory therapies adjusted for NABs and discontinuation are reflected in Figures 2-4. The figures indicate an immediate short-term reduction in relapse and disease progression rates and a stabilization in rates (relapse and disease progression) over the long term.

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FIGURE 2 Prediction Curve of the Long-term Probability of Relapse While on Immunomodulatory Therapy^{12-17,20-23,26,28,63}

GA=glatiramer acetate; IFN=interferon; IM=intramuscular; SC=subcutaneous.

FIGURE 3 Prediction Curve of the Long-term Probability of Disease Progression (EDSS 0.0-2.5: No or Few Limitations in Mobility to EDSS 3.0-5.5: Moderate Limitations in Mobility) While on Immunomodulatory Therapy^{12-17,20-23,26,28,63}

EDSS=Expanded Disability Status Scale (Kurtzke); GA=glatiramer acetate; IFN=interferon; IM=intramuscular; SC=subcutaneous.

Costs

The model accounted for immunomodulatory therapy acquisition costs, health state-specific MS-related medical costs, and the cost of lost worker productivity. Costs were obtained from the published literature and were inflated to 2005 U.S. dollars, where necessary, by the medical component of the Consumer Price Index.⁷⁰ The annual acquisition cost of SC GA and each β -interferon was calculated using wholesale acquisition costs (WACs),³² days supply per prescription, the recommended dosing schedule, patient compliance (assumed 70% in base-case model⁷¹⁻⁷³), patient copayment (\$25 per prescription in base-case model), and the proportion of patients discontinuing therapy as reported in clinical trials (see Table 1).

Health state-specific MS-related medical costs were estimated from the previously described Web survey of 711 RRMS patients in the United States.⁵¹ The resource use and associated costs component of the survey was used in the model and comprised the cost of inpatient care, outpatient care, community services, alterations and equipment, informal care, and medications used to manage the symptoms of MS. Costs were estimated on the basis of Current Procedural Terminology, 4th Edition (CPT-4) codes and corresponding physician fees for each CPT-4 code, diagnosis-related groups, and the Drug Topics *Red Book*³³ (WAC prices). Health state and drug costs are presented in Table 2.

Worker Productivity

Estimates of lost worker productivity were based on the published literature. Specifically, Lichtenberg⁷⁴ estimated the average number of days missed from work for 47 major chronic conditions, including MS. SC GA and β -interferon-specific estimates of the number of days missed from work (all reasons) were derived via regression analyses of retrospective administrative claims data⁷⁵ and were subtracted from the Lichtenberg baseline value to determine the average number of days missed due to MS for each therapy. The cost of lost worker productivity was estimated as the number of work days missed (in hours) multiplied by an hourly wage and adjusted to account for the proportion of patients employed (Table 2).^{75,76}

The model assumed that productivity losses were limited to patients in EDSS 0.0-5.5 and that patients in the later EDSS health states (EDSS >5.5) were not employed. Since the results of the Lage et al. analysis⁷⁵ identified a modest nonsignificant difference in work days missed for the β -interferons relative to no treatment, the base-case model took these modest differences into account even though they were not statistically significant by using the conservative assumption that the absolute reduction in days lost from work was incurred in comparison with symptom management. Furthermore, while providing an estimate of absenteeism (within the context of a small sample size and including paid time off [PTO]), the Lage et al. analysis⁷⁵ did not provide an estimate of overall lost worker productivity, which includes both absenteeism (lost productivity associated

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with missing a work day, excluding PTO) and presenteeism (lost productivity associated with being present at work but performing below expectations). The results reported by Lage et al. provided an estimate of absenteeism that, given the lack of better data, might be used in the model to estimate the impact of MS and its treatments on worker productivity.

Utilities

Utility weights allow an objective measurement of the desirability of a health state. Utility weights range from 0.0 to 1.0, where a utility value of 1.0 represents perfect health and a value of 0.0 represents death. These utility values are used to estimate QALYs by multiplying the number of life-years within a particular health state by that health state's utility weight. Utilities were estimated by health state and were obtained from the published literature (Table 2).^{46,52,77} The relapse health states were associated with a 0.094 decrement in utility (e.g., utility for relapse EDSS 0.0-2.5 = 0.824 – 0.094 = 0.730).

Model Calculations

The model estimated the following outcomes: average number of years spent in EDSS 0.0-5.5; average number of years spent relapse free; life-years; QALYs; and total costs and costs by component (i.e., immunomodulatory therapy cost, MS-related medical costs, and lost worker productivity costs). Incremental cost-effectiveness ratios (ICERs) were assessed in the model by comparing each of the individual immunomodulatory therapies plus symptomatic management with symptom management. The ICERs were calculated as the difference in costs between 2 treatments divided by the difference in effectiveness: (Cost Drug A – Cost Drug B) / (Effectiveness Drug A – Effectiveness Drug B). The resulting ICERs described the relative cost of purchasing 1 additional unit of relative effectiveness (e.g., cost of 1 additional year spent in the lower EDSS health states). ICERs were calculated for 4 effectiveness measures (cost per QALY; cost per life-year; cost per year spent in the lower EDSS health states [EDSS 0.0-5.5]; and cost per year spent relapse free).

Sensitivity Analyses

To test the robustness of the model assumptions and specific parameters, univariate sensitivity analyses were performed by increasing and decreasing values for key parameters in the model. Plausible ranges of values were obtained from the published literature or by varying the estimates by up to 25% in each direction. Parameters analyzed included health state and relapse state utilities; symptomatic treatment costs, health state costs, and drug costs; percentage employed and work days saved; percentage reductions in relapse and disease progression rates in the first 2 years of therapy; changes in relapse and disease progression over time; change in treatment discontinuation over time; EDSS distribution; incidence of NABs; change in NABs over time; and discount rates. Sensitivity results for each model input

FIGURE 4 Prediction Curve of the Long-term Probability of Disease Progression (EDSS 3.0-5.5: Moderate Limitations in Mobility to EDSS 6.0-7.5: Walking Aid or Wheelchair Required) While on Immunomodulatory Therapy^{12-17,20-23,26,28,63}

EDSS = Expanded Disability Status Scale (Kurtzke); GA = glatiramer acetate; IFN = interferon; IM = intramuscular; SC = subcutaneous.

assessed were ranked from most sensitive to least sensitive and plotted on a tornado diagram. Results (Figure 5) indicated that changes in health state utilities were the most sensitive model parameter. To further test the sensitivity of the model to changes in health state utilities, 3 analyses were performed: (1) changing all utility values by a relative $\pm 25\%$; (2) replacing the utility values in the base-case model with European-derived utilities used in previous economic evaluations⁷⁸; and (3) changing only the disutility values associated with the relapse health states by a relative $\pm 25\%$. Additional scenario-based sensitivity analyses were performed to evaluate the impact on model results of changes to multiple parameters (e.g., simulating assumptions used in previously published MS models). Ranges used in sensitivity analyses (univariate and scenario) are presented in Table 2.

Results

Total costs per patient over the time horizon of a patient's lifetime were estimated at \$295,586, \$352,760, \$364,267, \$377,996, and \$358,509 for symptom management, SC GA, IM IFN β -1a, SC IFN β -1a, and SC IFN β -1b, respectively (Table 3). MS-related medical costs were the largest cost component (approximately 95% of total costs in the symptom management arm and 70%-75% of total costs in the immunomodulatory arms), followed by the cost of immunomodulatory therapy (approximately

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FIGURE 5 Sensitivity Analyses Results

Note: Sensitivity analyses were based on two methods of changing values: (1) by +25% and -25%; and (2) by prespecified values. The gray bars present results from method #1 and the white bars represent results from method #2. The asterisks are specific to the white bars:

* Time horizon: base case = lifetime; sensitivity analysis = 5 years.

** Compliance: base case = 70%; sensitivity analysis = 100%.

*** Utility values: base case = U.S.-based values; sensitivity analysis = European-based values.

**** EDSS distribution: base case = across all EDSS health states; sensitivity analysis = all patients start in first EDSS health state (EDSS 0.0-2.5).

EDSS = Expanded Disability Status Scale (Kurtzke); GA = glatiramer acetate; IFN = interferon; IM = intramuscular; MS = multiple sclerosis; NABs = neutralizing antibodies; SC = subcutaneous.

20%-25% of total costs). Comparing direct medical costs (i.e., MS-related medical costs and immunomodulatory therapy costs) of the symptom management arm with the SC GA, IM IFN β -1a, SC IFN β -1a, and SC IFN β -1b arms of the model (from Table 3), we found the added cost of immunomodulatory therapy was partially offset by savings in MS-related medical costs, and the greatest cost offsets occurred in the SC GA arm (24% of the cost of SC GA was offset by savings in MS-related medical costs versus 17%-22% of the cost of the β -interferons).

Outcomes over the lifetime time horizon assessed in the model were similar across the 4 immunomodulatory therapies and were generally improved compared with outcomes with symptom management (Table 3). The exception was for the estimated life-years gained, as immunomodulatory therapy had little impact on survival other than the slight delay in disease progression to EDSS 10 (death). Comparisons among the 4 immunomodulatory therapies indicated that patients on SC GA had slightly better outcomes relative to patients on the β -interferons.

Overall, the model indicated that patients on SC GA experienced greater cost benefits compared with patients on any of the 3 β -interferons. The incremental cost per QALY was \$258,465, \$337,968, \$416,301, and \$310,691 for SC GA, IM IFN β -1a, SC IFN β -1a, and SC IFN β -1b, respectively, compared with symptom management. ICERs comparing symptom management with the 4 immunomodulatory therapies for the other outcomes of interest are presented in Table 3.

Sensitivity Analyses

Overall, univariate sensitivity analyses showed results to be sensitive to changes in health state utilities, the percentage reduction in disease progression rates in the first 2 years of therapy used to estimate immunomodulatory therapy treatment effects, model time horizon, and immunomodulatory therapy acquisition costs (Figure 5). Further assessment of changes to health state utilities revealed that changes to the disutility values associated with the relapse health states had minimal effect on cost-effectiveness results. However, changes to utility values over all health states had a substantial impact. We observed the greatest impact when we changed all utility values by a relative $\pm 25\%$.

In a scenario in which the model assumed no change in SC GA effects on disease progression in the first 2 years and a 25% improvement for the β -interferons, we observed an overall improvement in the cost-effectiveness of the β -interferons compared with symptom management, and the ICERs for the β -interferons (vs. symptom management) were more favorable than those of SC GA (vs. symptom management). However, ICERs for the β -interferons (vs. symptom management) did not improve compared with SC GA (vs. symptom management) when we assumed no change in SC GA effects on relapse in the first 2 years and a 25% improvement for the β -interferons.

As expected, shorter time horizons (e.g., 10-20 years) resulted in larger ICERs when we compared symptom management with each of the 4 immunomodulatory therapy arms of the model, as the shorter time horizons did not fully account for all benefits associated with immunomodulatory therapy. Assuming no change in the acquisition cost of SC GA and a 25% decrease in the acquisition cost of the β -interferons resulted in more favorable ICERs for the β -interferons (vs. symptom management) compared with SC GA (vs. symptom management). Finally, changes in the incidence of NABs had minimal impact on the ICERs of the β -interferons compared with symptom management.

Discussion

The present analysis is the first economic model in MS to (1) incorporate long-term data on treatment effects, (2) include the effect of NABs on the β -interferons, (3) account for the inherent differences among clinical trial study designs of the immunomodulatory therapies (e.g., via fixed EDSS distribution and single percentage reduction in relapse and disease progression rates in the first 2 years of therapy), and (4) present results in terms of cost-utility (cost per QALY gained) and cost-effectiveness (e.g., cost per year spent relapse free or cost per year spent in less severe disease health states). Model results highlight the potential long-term health and economic benefits of treating MS patients with immunomodulatory therapy and indicate that all 4 immunomodulatory therapies are associated with increased benefits compared with symptom management, albeit at higher costs and without consideration of the cost of adverse events. The model indicated that, of the 4 immunomodulatory therapies used to manage MS and in comparison with symptom management, SC GA was the best strategy in terms of outcomes and costs. Sensitivity analysis indicated that the model was sensitive to changes in a number of key parameters, and thus changes in these key parameters would likely influence the estimated cost-effectiveness results.

In a previous U.S.-based cost-effectiveness model conducted by Prosser et al.⁴⁶ the authors concluded that IM IFN β -1a compared with no treatment (i.e., symptomatic treatment) yielded the largest gain in QALYs with an ICER between \$1.8 and \$2.2 million per QALY gained. These results were significantly different from that reported in the current analysis and can be attributed to the underlying methodology used to model MS, the most notable aspects of which include assumptions regarding the treatment effects associated with the immunomodulatory therapies, model time horizon, and utility values. In terms of the treatment effects of the immunomodulatory therapies over time, the Prosser model is based on relapse rates and disease progression rates reported in the pivotal clinical trials for the respective drugs. The current analysis supplements the pivotal clinical trials with data from patients initially enrolled in the pivotal trials and followed over time. While both approaches have limitations (pivotal trials in MS are based on a 2-year

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TABLE 3 Base-Case Discounted Costs per Patient (Lifetime Perspective)

Cost Component	Symptom Management	SC GA	IM IFN β -1a	SC IFN β -1a	SC IFN β -1b
Lifetime drug acquisition costs (average no. of years on therapy)	\$0 (N/A)	\$77,340 (13.54)	\$82,635 (13.05)	\$95,208 (12.93)	\$76,957 (13.21)
MS-related medical costs	\$282,950	\$264,351	\$265,366	\$266,839	\$265,940
Productivity costs	\$12,636	\$11,069	\$16,266	\$15,948	\$15,611
Total costs	\$295,586	\$352,760	\$364,267	\$377,996	\$358,509
Average no. of years spent in EDSS 0.0-5.5	12.28	14.92	14.71	14.29	14.54
Average no. of years spent relapse-free*	11.42	14.67	14.24	13.98	14.15
Life years	14.791	14.819	14.818	14.815	14.817
QALYs	9.081	9.303	9.285	9.279	9.284
Incremental cost per year spent in EDSS 0.0-5.5	–	\$21,667	\$28,293	\$41,008	\$27,860
Incremental cost per year spent relapse-free	–	\$17,599	\$24,327	\$32,207	\$23,065
Incremental cost per life-year gained	–	\$2,076,622	\$2,588,087	\$3,378,626	\$2,452,616
Incremental cost per QALY gained	–	\$258,465	\$337,968	\$416,301	\$310,691

* Cumulative number of months spent relapse-free converted to years.

GA=glatiramer acetate; IFN=interferon; IM=intramuscular; MS=multiple sclerosis; N/A=not applicable; QALY=quality-adjusted life-year; SC=subcutaneous; symptom management=symptomatic management alone.

snapshot of a chronic, lifelong condition, and the follow-up studies are nonrandomized), they represent alternative methods for modeling MS outcomes. It should be noted that the published estimate of effectiveness for IM IFN β -1a is based on those subjects who completed 2 years in the trial at the time it was stopped as opposed to being based on the intent-to-treat population. This approach likely overestimates the true effects of IM IFN β -1a in this particular trial, which is apparent in results from head-to-head clinical trials of IM IFN β -1a.^{18,19}

Sensitivity analyses conducted in the Prosser model, the current analysis, and other MS models have clearly indicated that results are influenced by time horizon, with shorter time horizons associated with less favorable ICERs (e.g., Prosser⁴⁶ and other models^{30,44,78}) and longer time horizons associated with more favorable ICERs (e.g., current analysis, Nuijten and Hutton⁴¹). Guidelines for the conduct of cost-effectiveness analyses (e.g., Academy of Managed Pharmacy,⁷⁹ Canadian Coordinating Office for Health Technology Assessment,⁸⁰ NICE⁸¹) recommend that pharmacoeconomic models should be sufficiently long to reflect all relevant costs and outcomes, which would suggest that an MS model should adopt a lifetime perspective, given the chronic nature of MS. While guidelines may suggest that a longer time horizon is more appropriate, the managed care perspective often reflects much shorter time horizons (e.g., 1-3 years), which would translate into increasingly less favorable ICERs as the

time horizon is shortened. However, as the enrollment base of managed care plans shifts over time, plans are likely to gain and lose MS patients across the spectrum of disability levels. Thus, therapies that reduce relapse and disease progression rates, such as the immunomodulatory therapies for MS, may reduce the burden of MS.

A comparison of the utility values used in the current analysis with that of the Prosser model indicated substantial differences, which are reflected in the ICER results of the individual models. Utilities used in the Prosser model were derived from a U.S. sample of MS patients and members of the general community⁸² and were significantly higher than those reported in a subsequent U.S. study,^{52,77} which were used in the current analysis. The higher utilities contributed to the higher ICERs reported in the Prosser model. The Prosser utilities were also significantly higher than those reported in the United Kingdom and Europe^{30,78} (e.g., utility assigned to the initial EDSS health state 0.0-2.5 was 0.95 in the Prosser model compared with 0.71 derived from a European population for the same health state⁷⁸), which is reflected in the more favorable ICERs calculated in analyses from other countries.^{30,40,41} It is also of interest that the percentage reduction in utilities from one health state to the next was smaller in the Prosser U.S.-based analyses (e.g., 9% reduction in utilities from EDSS 0.0-2.5 to EDSS 3.0-5.5 and 12% reduction in utilities from EDSS 3.0-5.5 to EDSS 6.0-7.5^{46,52,77}) compared

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with analyses performed in other countries that estimated a 30% reduction in utilities from EDSS 0.0 to EDSS 3.0 and a similar reduction from EDSS 3.0 to EDSS 7.0.^{30,78}

Overall, the majority of economic evaluations in MS, including the current analysis, resulted in ICERs well above the arbitrary and commonly referenced benchmark of \$50,000 per QALY, even in the “best-case” scenarios used in sensitivity analyses.^{30,40-46,78,83} This was, in part, a reflection of (1) the chronic nature of the disease, (2) survival not being significantly affected by the disease, (3) the modest QALY benefits associated with immunomodulatory therapy in MS versus symptom management, and (4) the high drug acquisition costs of the immunomodulatory therapies. A review of the published cost-effectiveness literature revealed a number of analyses of health care interventions that resulted in ICERs above the \$50,000 per QALY benchmark, including \$1.8 to \$2.2 million per QALY as reported in the Prosser MS model⁴⁶; \$91,000 per QALY for osteoarthritis or rheumatoid arthritis patients using diclofenac versus ibuprofen⁸⁴; \$110,000 per QALY for patients using metformin in a diabetes prevention program⁸⁵; \$200,000 per QALY for osteoarthritis or rheumatoid arthritis patients using diclofenac and a proton pump inhibitor versus celecoxib⁸⁴; \$370,000 per QALY for women with irritable bowel syndrome using alosetron versus no treatment⁸⁶; and \$56,000 to \$840,000 per QALY for the use of high-dose erythropoietin versus normal dosages to maintain increased hemoglobin levels (e.g., 12-14 g/dL).⁸⁷

A review of the cost-effectiveness literature for blood safety interventions (e.g., blood screening and pathogen inactivation) identified a median ICER of \$355,000 per QALY,⁸⁸ with some results exceeding several million dollars per QALY.⁸⁹ While direct comparisons between these studies and the current analysis are limited, the results indicate that not all economic evaluations are bounded by the \$50,000 per QALY benchmark and that numerous interventions with ICERs well above this threshold have been deemed valuable by patients, health care decision makers, and society. Thus, evaluating the cost-effectiveness of the immunomodulatory therapies in terms of the \$50,000 per QALY benchmark may not be appropriate.

Limitations

First and foremost among the limitations of this study is its reliance on clinical trial data. While clinical trial data are considered the preferred source for the basis of parameter inputs used in cost-effectiveness analyses, the MS clinical trials have been criticized for a number of methodological issues. For example, in the Cochrane review of the β -interferon randomized, placebo-controlled clinical trials,⁶⁵ Rice et al. commented that the quality of the trials was variable with substantial methodological inadequacies. In its review of all immunomodulatory therapy randomized clinical trials for MS, which included SC GA,²⁹ NICE noted similar methodological issues concerning

randomization,^{30,40} allocation concealment,^{30,36,40} intent-to-treat analysis,^{30,37,40} and last observation carried forward analysis.³⁶ Finally, incomplete description of treatment dropouts in the short-term clinical trials likely affected trial results, where if dropouts were deemed to progress (worst-case scenario), the effect of these drugs on relapse and disease progression rates would likely be lost.⁶⁵

Second, our economic analyses did not include the impact of adverse events (e.g., cost and disutility) except to the extent that these might be captured indirectly in the proportion of patients who discontinue therapy (Table 1). However, the cost of treating adverse events would not likely affect the overall results of this analysis since the most common adverse events reported for all 4 immunomodulatory therapies were injection site reactions and influenza-like symptoms, which were generally self-limiting and significantly decreased over time.^{90,91} Nevertheless, these adverse events would likely have an impact on patient utilities, which would influence the cost-effectiveness results. In the Prosser model, treatment-specific disutilities were assigned to account for patient discomfort associated with each treatment, where values ranged from 0.066 for SC GA to 0.204 for SC IFN β -1b. These disutilities favored SC GA over the β -interferons and thus would not likely have changed the model results.

A third limitation arises from the assumption in the model that patients who discontinued immunomodulatory therapy were not allowed to switch to another therapy nor reinstitute therapy at a later time. It is expected that a proportion of patients will discontinue therapy due to worsening of MS symptoms (e.g., as specified by the Association of British Neurologists' guidelines for stopping therapy: 2 disabling relapses within 12 months, secondary progression with increased disability over 6 months, and loss of ability to walk that persists for 6 months⁹²); however, some patients may discontinue therapy and experience no change in their disability status. On the basis of general clinical practice patterns, these patients would be likely candidates for switching or reinstituting therapy. Had patients been allowed to switch or reinstitute therapy in the model, the calculated ICERs would likely be less favorable for all the immunomodulatory therapies. This assumption (no switching and no reinstitution of therapy) was also adopted in other MS models.^{30,40,41,46} Evidence from real-world observational studies in MS has indicated that from 5%^{73,93} to 13% of patients⁷² switched therapy upon discontinuation.

A fourth limitation arises from the assumption in the model regarding the estimation of relapse and disease progression rates associated with the immunomodulatory therapies. To account for differences in the immunomodulatory clinical trials, a fixed patient population was assumed to enter the model (e.g., based on fixed EDSS distribution), and in the first 2 years of therapy, the model assumed that the probabilities of relapse and disease progression used in the symptom management arm were adjusted by a common percentage reduction (relapse: 27%;

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disease progression: 30%). A fitted prediction curve of treatment effects was used to estimate long-term treatment effects of the immunomodulatory therapies. This is a conservative approach to modeling treatment effects over time that uses both the clinical trial and long-term data to predict future outcomes. Previous CEA/CUA studies for the immunomodulatory therapies relied on data from short-term clinical trials and made assumptions to extrapolate treatment effects over time. At the time of the present economic analyses, SC GA was the only immunomodulatory therapy with long-term data collected in a systematic manner over more than 10 years (although it is important to note that by 10 years, 51.2% of patients eventually withdrew from study follow-up).²⁸ Thus, the fitted prediction curve for SC GA may be a better representation of patient outcomes compared with the curves estimated for the β -interferons, which were based on significantly shorter time horizons (e.g., the longest follow-up was 6 years for SC IFN- β 1a).

Fifth, the data used in the present economic analysis are not from comparative, head-to-head clinical trials of the immunomodulatory therapies. Comparative trials of this type, particularly one in which all 4 therapies were evaluated head to head, would be the ideal source of information for the model, but the similarity in outcomes across the 4 therapies suggests that a very large and expensive randomized clinical trial would be necessary in order to observe significant differences among the therapies. Nevertheless, reviews of the individual randomized clinical trials for the 4 immunomodulatory therapies suggest that the therapies have similar short-term effects on relapse and disease progression rates.⁶⁶

Sixth, clinical trials are designed to specifically test the efficacy and tolerability of a particular therapy in a select patient population. The specified inclusion and exclusion criteria of clinical trials may not result in a population that is representative of all patients (e.g., real-world situations). This is especially relevant in MS clinical trials in which patients are selected on the basis of a number of criteria, including having experienced an average of 2 relapses in the previous 2 years, a rate that is relatively higher than that reported for the general MS population (range of 0.14 to 1.1 relapses per year). From the modeling perspective, the clinical trial population is the best available data; however, cost-effectiveness results based on data derived from this population may or may not comport with population-based care and the projection of average economic costs.

Conclusions

All 4 immunomodulatory therapies used in the treatment of RRMS patients are associated with increased benefits compared with symptom management alone, albeit at higher costs. The pharmacoeconomic model indicated that, of the 4 immunomodulatory therapies used to manage MS and in comparison with symptom management, SC GA was the best

strategy. Sensitivity analysis indicated that the model was sensitive to changes in a number of key parameters, and thus changes in these key parameters would likely influence the estimated cost-effectiveness results. While the results of this analysis provide decision makers with health economic information supporting the use of the immunomodulatory therapies, MS is a heterogeneous disease and physicians must select the most appropriate treatment based on the disease characteristics of individual patients. Comparative head-to-head, randomized clinical trials of the immunomodulatory therapies for the treatment of MS are needed to confirm the results predicted by economic models.

What is already known about this subject

- A number of CEA/CUA evaluations of the immunomodulatory therapies for MS have been published. However, the majority of these evaluations have been conducted from perspectives outside the United States.^{30,40-45} The most recent U.S.-based analysis was the recent CUA evaluation of the immunomodulatory therapies for the treatment of nonprimary, progressive MS (e.g., RRMS and SPMS) over a 10-year time horizon.⁴⁶ Cost-effectiveness results from this analysis, as well as previous evaluations, were considerably higher than the arbitrary and commonly referenced benchmark of \$50,000 per QALY.

What this study adds

- The present analysis is the first economic model in MS to (1) incorporate long-term data on treatment effects, (2) include the effect of NAb on the β -interferons, (3) account for the inherent differences among clinical trial study designs of the immunomodulatory therapies, and (4) present results in terms of cost-utility (cost per QALY gained) and cost-effectiveness (e.g., cost per year spent relapse free).
- Compared with the U.S.-based model published by Prosser et al.⁴⁶ in 2004, the results from the present analysis are significantly different from that reported by Prosser and can be attributed to the underlying methodology used to model MS, the most notable aspects of which include assumptions regarding the treatment effects associated with the immunomodulatory therapies, model time horizon, and utility values.

DISCLOSURES

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Bell served as principal author of the study. Study concept and design were contributed primarily by Bell and Earnshaw, with input from the coauthors. Data collection was the work of Graham, Castelli-Haley, and Bell, with input from Oleen-Burkey and Earnshaw; data interpretation was the work of Bell, Johnson, and Earnshaw with input from the coauthors. Writing of the manuscript was primarily the work of Bell, Oleen-Burkey, and Castelli-Haley, with input from Earnshaw and Graham; its revision was the work of Bell, Graham, and Johnson, with input from the coauthors.

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