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Cost-Effectiveness of Disease-Modifying Therapies in the Management of Multiple Sclerosis for the Medicare Population

Paul Tappenden, MSc,[1] Christopher McCabe, PhD,[2] Jim Chilcott, MSc,[1] Emma Simpson, PhD,[1] Richard Nixon, PhD,[3] Jason Madan, MSc,[1] John D. Fisk, PhD,[4] Murray Brown, PhD[5]

[1]School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK; [2]Institute of Health Sciences, University of Leeds, Leeds, UK; [3]Medical Research Council Biostatistics Unit, Cambridge, UK; [4]Department of Psychiatry, Capital District Health Authority, Halifax, NS, Canada; [5]Community Health and Epidemiology, Dalhousie University, Halifax, NS, Canada

ABSTRACT

Objective: To evaluate the cost-effectiveness of disease-modifying therapies (DMTs) for the management of multiple sclerosis (MS) compared to best supportive care in the United States.

Methods: Cost-effectiveness analysis was undertaken using a state transition model of disease natural history and the impact of DMTs for the representative Medicare beneficiary with MS. Costs and outcomes were evaluated from the health-care payer perspective using a 50-year time horizon. Natural history data were drawn from a longitudinal cohort study. The effectiveness of the DMTs was evaluated through a systematic review. Utility data were taken from a study of patients with clinically definite MS in Nova Scotia. Resource use and cost data were derived from the Sonya Slifka database and associated literature.

Results: When based on placebo-controlled evidence, the marginal cost-effectiveness of interferon beta (IFNβ) and glatiramer acetate compared to best supportive care is expected to be in excess of $100,000 per quality-adjusted life-year gained. When evidence from head-to-head trials is incorporated into the model, the cost-effectiveness of 6 MIU IFNβ-1a is expected to be considerably less favorable. Treatment discontinuation upon progression to Expanded Disability Status Scale 7.0 is expected to improve the cost-effectiveness of all DMTs.

Conclusions: Further research is required to examine the long-term clinical effectiveness and cost-effectiveness of these therapies. There is no definitive guidance in the United States concerning discontinuation of DMTs; this study suggests that the prudent use of a treatment discontinuation rule may considerably improve the cost-effectiveness of DMTs.

Keywords: cost-utility analysis, decision analysis model, economic analysis, multiple sclerosis.

Introduction

Multiple sclerosis (MS) is one of the most common neurological conditions affecting young adults, and is two to three times more common in women than men [1,2]. Around 400,000 people in the United States suffer from MS, and its prevalence in the northern states is reported to be higher than in the southern states [2]. The underlying early pathogenic mechanisms include inflammation, demyelination, and axonal loss, whereas chronic axonal degeneration predominates later. The disease is characterized by a variety of symptoms including pain, fatigue, impaired muscle control, balance and postural problems, cognitive impairments, and optic neuritis [1,3]. The disease has a considerable impact upon a patient's quality of life, and the costs of disease management are substantial.

Progressive neurological disability resulting from MS is commonly measured using the Expanded Disability Status Scale (EDSS), an ordinal scale ranging from EDSS 0 (normal neurological examination) to EDSS 10 (death due to MS) [4]. Disease management focuses on slowing progression and preventing relapse as well as controlling symptoms. Interferon beta (IFNβ-1a and IFNβ-1b) and glatiramer acetate (GA), which are known as "disease-modifying therapies" (DMTs), are thought to slow the progression of the disease and reduce the number and severity of relapses experienced. IFNβ-1a, IFNβ-1b, and GA have been approved for the treatment of relapsing–remitting MS (RRMS). IFNβ-1b has also been approved for secondary progressive MS (SPMS). Until 2002, Medicare coverage for these therapies to treat MS was sporadic, varying by carrier depending on their interpretation of whether a drug was usually self- or physician-administered. In 2002, the Centers for Medicare and Medicaid Services (CMS) clarified the definition of self-administered drugs, allowing for coverage of IFNβ-1a for treatment of MS if administered intramuscularly by a physician. Subcutaneous IFNβ-1a administered by the patient was not covered. The Medicare Replacement Drug Demonstration (MRDD) expanded coverage to all self-administered treatments nationwide on a temporary basis before the new prescription drug benefit was introduced [5].

This article reports a study requested by the CMS to evaluate the cost-effectiveness of expanded drug coverage to Medicare. We report the methods and results of a mathematical model developed to estimate the marginal cost-effectiveness of IFNβ and GA as compared to best supportive care for RRMS and SPMS from the perspective of the US health-care payer. The cost-effectiveness of these therapies from the perspective of the CMS was also examined.

Methods

Model Scope and Structure

The model estimates the costs and health outcomes for seven active treatment options as compared to best supportive care. For RRMS only, the following interventions are evaluated: IFNβ-1a 6 MIU (physician-administered), IFNβ-1a 6 MIU (self-administered), IFNβ-1a 22 μg, IFNβ-1a 44 μg, IFNβ-1b 8 MIU, and GA 20 mg. For these six options, management of SPMS is assumed to include best supportive care only. The cost-effectiveness of a combined option of IFNβ-1b 8 MIU for the

Address correspondence to: Paul Tappenden, Health Economics and Decision Science, School of Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA, UK. E-mail: p.tappenden@sheffield.ac.uk

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treatment of both RRMS and SPMS is also evaluated. Other DMTs such as natalizumab and mitoxantrone were excluded from the analysis on two grounds. First, natalizumab and mitoxantrone were not covered by the MRDD at the time of the analysis and therefore were not relevant to the CMS' decision problem. Second, natalizumab is used in patients with rapidly evolving MS who have high disease activity; this subgroup of MS patients is likely to have a very different natural history to the broader RRMS population.

Details of the model structure have been reported in detail elsewhere [6–8]. Briefly, the model simulates the natural history of MS using the state transition methodology, modeling individual EDSS states from 0 through 10 in RRMS, and from EDSS 2.0 through 10 in SPMS. Disease course, cost, and utilities with and without treatment are assessed using an annual cycle length over a time horizon of 50 years (the remaining lifetime of the model cohort irrespective of treatment option). Patients enter the model aged 51 years, with a baseline distribution across the RRMS EDSS states based on a sample of patients from the Sonya Slifka data set who represented the Medicare MS population [9,10]. All patients subsequently experience progressive disability as measured on the EDSS according to the transition probabilities derived from the London Ontario Cohort natural history data set [11,12]. The model assumes that disease progression is independent of time since onset, while the age-specific risk of death is modeled using time-dependent probabilities. EDSS-specific relapse rates without DMT were derived from an analysis of a long-term observational study of MS relapse [13].

During any given model cycle, patients can remain in their current EDSS state, progress one or more EDSS states, transit to an SPMS health state, discontinue therapy, or die. At the point of treatment cessation, patients are assumed to retain any previously accrued benefits of DMT in terms of delayed disease progression (rather than reverting to their expected EDSS had they never received treatment) and subsequently progress according to the natural history transition rates [11]. Disease management costs are associated with spending one cycle in each individual EDSS health state. Each EDSS state is also assigned a specific utility score which describes the mean level of health-related quality of life (HRQoL) associated with that degree of disability. Within any EDSS state, patients may also experience relapse, which has a temporary detrimental impact upon HRQoL and incurs additional medical management costs. The "on treatment" and "best supportive care" cohorts progress at different rates, as determined by instantaneous hazard rates estimated using current clinical effectiveness evidence. Consequently, the two cohorts accrue different costs and quality-of-life profiles; the marginal cost-effectiveness of each option is estimated as the additional total costs divided by the additional quality-adjusted life-years (QALYs) gained for each treatment strategy as compared to best supportive care.

The model employs the following key assumptions:

1. Patients enter the model aged 51 years [9,10]
2. The model simulates the lifetime experience of patients with RRMS and SPMS disease courses only. The simulation is continued until all patients within the model have died.
3. All transitions within the model are progressive (patients cannot experience improvements on the EDSS).
4. The effectiveness of DMT is assumed to continue only for the period in which the patient is on therapy.
5. A "retained effect" of treatment on both progression and relapse beyond the duration of the trials included in the clinical effectiveness review is modeled. Any patient who discontinues therapy subsequently progresses according to natural history rates but retains any previously accrued benefits at no additional cost of therapy.
6. The relative hazards of disease progression and the relative risks of relapse attributable to DMTs do not deteriorate or increase over time.
7. The annual risk of "all-cause" mortality for the MS cohort is assumed to be the same as a normal healthy population.
8. Patients may continue to receive DMT until they drop off therapy due to side effects, lack of efficacy or until progression to SPMS or death. The impact of discontinuing therapy upon progression to EDSS 7.0 is explored in the scenario analysis.

Evidence Used to Inform Model Parameters

Effectiveness Evidence

A systematic review was undertaken to identify all studies reporting progression and relapse outcomes for IFNβ and GA in comparison to placebo or another DMT in RRMS and SPMS. The systematic review identified five placebo-controlled trials [14–23] and two head-to-head trials [24,25]; the inclusion and exclusion criteria are summarized in Table 1. The methods and results of this systematic review are available from the full study report [26]. Key clinical outcomes included time-to-disease progression, relapse rates, and the incidence of adverse events. Relative hazard ratios for disease progression were estimated using Kaplan–Meier progression-free survival curves or using relevant narrative data from the trial publications. EDSS progression hazard ratios were estimated assuming that EDSS progression-free survival is exponentially distributed. Relative risks of relapse for the DMTs were estimated from annualized relapse rates for each treatment group.

Evidence on EDSS progression hazards and relapse rates from placebo-controlled and head-to-head trials of the disease modifying therapies were also synthesized within two Bayesian mixed treatment comparison models using WinBUGS software [14–25]. The WinBUGS progression model includes a random effects term which allows for between-trial heterogeneities. The WinBUGs relapse model uses a fixed effect comparison; owing to a lack of published evidence, the relapse model did not allow for between-trial heterogeneities. A summary of key model parameters is presented in Table 2.

Table 1 Systematic review inclusion and exclusion criteria

Inclusion criteria	
Population	Adults with RRMS or SPMS, eligible for treatment with IFNβ or GA.
Interventions	(1) GA 20 mg, daily subcutaneous injection; (2) IFNβ-1a 22 μg subcutaneous injection 3 times a week; (3) IFNβ-1a 44 μg, subcutaneous injection 3 times a week; (4) IFNβ-1a 6 MIU, intramuscular injection once per week; (5) IFNβ-1b 8 MIU, subcutaneous injection every other day.
Comparators	Placebo, or another disease-modifying therapy in instances where head-to-head trials were available.
Outcomes	EDSS disease progression rates; relapse rates; Health-related quality of life; adverse events/treatment-related toxicities; study withdrawals and dropouts.
Study design	Randomized controlled trials.
Exclusion criteria	Studies were excluded if off-label doses or administrations of IFNβ or GA were employed. Studies of other medications for MS not listed as included interventions were excluded. Clinical trials which did not report EDSS progression data were also excluded from the systematic review.

Table 2 Key model parameters

Relative hazard ratios for EDSS progression

Treatment strategy	Distribution	Mean (standard error)		References
		Placebo-controlled evidence only	Mixed treatment comparison model	
IFNβ-1a 6 MIU	Lognormal	0.58 (0.19)	0.79 (0.12)	[14–25]
IFNβ-1a 22 μg	Lognormal	0.72 (0.19)	0.72 (0.19)	
IFNβ-1a 44 μg	Lognormal	0.60 (0.19)	0.70 (0.11)	
IFNβ-1b 8 MIU RRMS	Lognormal	0.71 (0.18)	0.52 (0.09)	
IFNβ-1b 8 MIU SPMS	Lognormal	0.72 (0.18)	0.72 (0.18)	
GA 20 mg	Lognormal	0.86 (0.23)	0.86 (0.23)	

Relative risks of relapse

Treatment strategy	Distribution	Mean (standard error)		
		Placebo-controlled evidence only	Mixed treatment comparison model	
IFNβ-1a 6 MIU	Lognormal	0.82 (0.13)	0.83 (0.07)	[14–25]
IFNβ-1a 22 μg	Lognormal	0.71 (0.08)	0.71 (0.08)	
IFNβ-1a 44 μg	Lognormal	0.68 (0.08)	0.68 (0.05)	
IFNβ-1b 8 MIU RRMS	Lognormal	0.70 (0.09)	0.66 (0.07)	
IFNβ-1b 8 MIU SPMS	Lognormal	0.69 (0.09)	0.69 (0.09)	
GA 20 mg	Lognormal	0.70 (0.11)	0.70 (0.11)	

Key cost model parameters

Treatment strategy	Distribution	Mean (standard error)	
Constant parameter for linear EDSS-cost function	Normal	$3,126 ($1,500)	Model based on [9,10]
Gradient parameter for linear EDSS-cost function (per EDSS increase)	Normal	$10,169 ($2,000)	Model based on [9,10]
Cost per relapse	Lognormal	$3,158 ($4,000)	[15,30]
Annual cost IFNβ-1a 6 MIU	n/a	$12,438.57 (n/a)	Provided by CMS
Annual cost IFNβ-1a 22 μg	n/a	$13,965.83 (n/a)	
Annual cost IFNβ-1a 44 μg	n/a	$13,965.83 (n/a)	
Annual cost IFNβ-1b 8 MIU	n/a	$12,344.03 (n/a)	
Annual cost GA 20 mg	n/a	$11,613.38 (n/a)	

EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; IFNβ, interferon beta; MIU, million international units; n/a, not applicable; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

HRQoL

Health utilities associated with individual EDSS states were estimated from a sample of 813 patients with clinically definite MS who, between March 2002 and March 2004, attended the Dalhousie MS Research Unit, the only specialized referral service for MS in Nova Scotia, Canada [27]. Each patient completed the Health Utilities Index Mark 3 (HUI3) questionnaire within 16 days of a clinician-completed EDSS assessment. Previous studies have demonstrated the reliability and validity of the HUI3 for use in cost-effectiveness evaluations of MS therapies [28]. Complete HUI3 and EDSS data were available for 784 patients. A previously described parametric function was fitted to the data using least squares minimization techniques [8]. The empirical and modeled utility data by EDSS are shown in Figure 1; the figure clearly shows that the modeled utility function provides a good

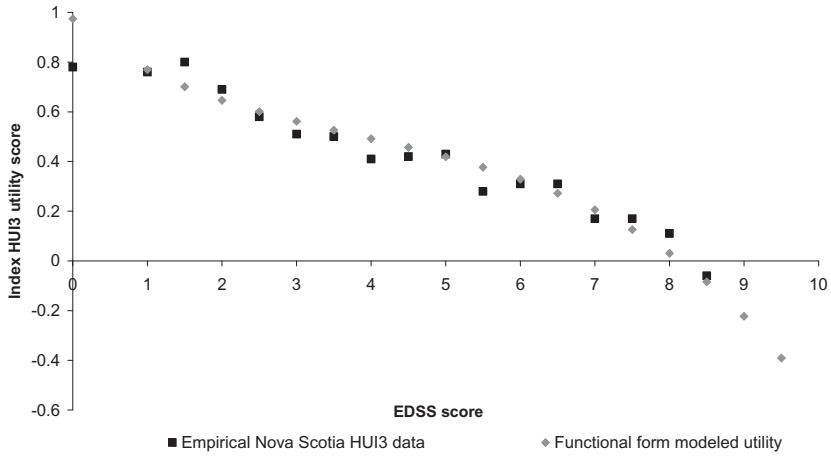

Figure 1 Empirical and modelled Health Utilities Index Mark 3 (HUI3) utility data. EDSS, Expanded Disability Status Scale.

fit to the data. The disutility associated with relapse was assumed to be –0.22 for a mean duration of 46 days, based on the work of Prosser [29]. In addition, treatment-related adverse events were assumed to lead to a further utility decrement of 0.05, also based on the previous work of Prosser [29]. In line with current recommendations, health outcomes were discounted at a rate of 3%.

Dropouts

Published evidence suggests a dropout rate for all therapies of up to around 30% during the trial durations; however, the evidence on the distribution of dropouts over time is unclear. Evidence from actual usage provided by two of the manufacturers of these therapies suggested a slightly lower level of dropouts; however, this was still over 20% [6]. The dropout estimates reported within the trials and the company-generated dropout estimates cannot be considered robust. The trial data include dropouts for different reasons, some of which are protocol-related, while the data on therapy cessation in clinical practice provide no information on the reasons for dropout. As there appears to be little significant difference between treatment-related averse events or their ease of use, it seems sensible to treat the therapies equally in this regard. Therefore, the model assumes a dropout rate of 10% in each of the first 2 years, followed by a 3% dropout rate for each subsequent year on therapy. The underlying assumption is that there are a group of people who drop out early due to treatment-related adverse events (10%), and a second group of people who drop out later because either they or their doctors feel that the therapy is not helping (10%). After that point, the model assumes a long-term attrition each year in use consistent with treatment compliance seen for the treatment of many chronic conditions.

Resource Use and Costs

Costs included drug acquisition, administration, costs of MS care according to EDSS disability, and costs associated with managing MS relapse. All costs were valued in 2005 US dollars. Annual drug and administration costs for the DMTs were obtained from the CMS at manufacturers' recommended doses. Evidence relating to the relationship between the degree of MS disability and costs of care in the United States is limited. Consequently, EDSS-specific costs of care were obtained from an analysis of data collected within the Sonya Slifka database commissioned specifically for use in this cost-effectiveness analysis. The Sonya Slifka longitudinal study was established to study demographic, clinical characteristics and disease course, resource utilization, health provider and drug usage, as well as neurological, psychosocial, and economic outcomes [10]. At the time of the analysis, the Sonya Slifka study sample consisted of 2156 people with MS who have been shown to be representative of the MS population in the United States [10]. A subset of the wider Sonya Slifka population, which included only those patients who represented the Medicare population receiving these therapies, was included in the analysis. The costs of care for RRMS and SPMS according to the Activities of Daily Living (ADL) scale were obtained from an analysis of a sample of the Sonya Slifka Longitudinal Multiple Sclerosis database [9,10]. Resource use components included hospitalizations, outpatient and emergency room visits, treatments, laboratory tests, health-care professional visits, and medications. For the majority of resource utilization items, unit cost estimates were obtained from Medicare claim files provided by the CMS, while drug costs were obtained from the 2005 Red Book.

The ADL cost profile was mapped onto the EDSS by direct comparison of the dimensions of the ADL and EDSS descriptive systems. The mapping process involved identifying any ADL categories and EDSS states that appeared to be direct or partial matches; this was done independently by two of the study authors (PT and CM). The two assessments were then compared and an agreed descriptive mapping was produced. As the EDSS has 20 states and ADL has only 9 states, it was necessary to map individual ADL categories to more than one EDSS state. As the Sonya Slifka data cover only a proportion of the range of EDSS health states, an EDSS cost model was fitted to the Sonya Slifka data using linear regression techniques. Wide standard errors were used to allow for uncertainty surrounding the Sonya Slifka data itself and uncertainty surrounding the mapping process. Further details of the mapping process are available from the full study report [26].

The cost of managing mild, moderate, and severe relapses was used to estimate a weighted mean cost for MS relapse, based on a US costing study reported by O'Brien et al. [30] and the relapse severity data observed within the clinical evidence base [15]. All costs were discounted at a rate of 3%. The absence of robust evidence on the relationship between the EDSS and the costs of care in the United States is clearly a limitation of this health economic analysis.

Initially, we intended to undertake the cost-effectiveness analysis purely from the perspective of the CMS. Nevertheless, the CMS perspective excludes the substantial nursing home costs in later EDSS states, which would lead to an underestimate of the cost savings attributable to delayed progression. Adopting the CMS perspective would also lead to an imbalance in the analysis as the quality of life gains associated with delayed progression would still be considered in full. For these reasons, separate cost-effectiveness scenarios are presented from the perspectives of the US health-care payer and the CMS.

Cost-Effectiveness Analysis Scenarios and Probabilistic Sensitivity Analysis

It is conventional practice in health economic evaluation to compare the costs and effects of health interventions incrementally, whereby interventions are ranked in order of effectiveness, and cost-effectiveness ratios are calculated for nondominated treatment options. Nevertheless, correlations between the efficacies of the range of IFNβs and GA are unknown and have not been fully evaluated within clinical trials; if one therapy is effective, it is possible that the other therapies are also effective. Consequently, undertaking a full incremental analysis could lead to one or more treatment options becoming dominated as a result of differences in study populations or heterogeneities due to trial design or reporting, rather than superior efficacy. Given the absence of evidence and the broad uncertainty surrounding correlations between efficacies, a standard incremental analysis is unlikely to be helpful for policymakers. Instead, the costs and outcomes associated with each treatment option were compared marginally against the best supportive care option.

The evidence base for the effectiveness and cost-effectiveness of disease-modifying treatments in MS is characterized by substantial uncertainty. First, the evidence used to inform the parameter values in the model is subject to uncertainty. There is further uncertainty regarding usual clinical practice in the United States, particularly concerning the appropriate disability cutoff for therapy cessation. A final form of uncertainty in the evidence base regards the comparability of the efficacy estimates for the different treatments. While an intention-to-treat (ITT) estimate of effectiveness has been published for the majority of the DMTs,

the published estimate of effectiveness for 6 MIU IFNβ-1a is based on an analysis of data only for those patients who completed 2 years in the trial at which point it was stopped.

Cost-effectiveness was analyzed for four key scenarios:

1. Scenario 1: Evidence of effectiveness based exclusively upon placebo-controlled evidence.
2. Scenario 2: Using a mixed treatment comparison model that incorporates evidence from placebo-controlled trials and head-to-head trials of IFNβ.
3. Scenario 3: Treatment discontinuation upon progression to EDSS 7.0.
4. Scenario 4: Analysis undertaken from the perspective of the CMS, whereby costs are based on the empirical disease management costs, which exclude costs associated with nursing home care.

Probabilistic sensitivity analysis was undertaken to characterize the impact of parameter uncertainty surrounding the cost-effectiveness of each of the DMTs. The results of this analysis are presented using Cost-Effectiveness Acceptability Curves (CEACs). These curves describe the probability that each treatment option has a cost-effectiveness ratio that is better than a range of willingness-to-pay thresholds as compared to best supportive care. In other words, the CEACs describe the probability that we would prefer a given treatment option over best supportive care according to how much we are willing to pay for each additional QALY gained. CEACs are presented for each of the four key cost-effectiveness scenarios.

Results

Central Estimates of Cost-Effectiveness

Table 3 presents the central estimates of cost-effectiveness for the DMTs as compared to best supportive care for each of the four key scenarios.

Based on the placebo-controlled evidence alone (Scenario 1), the model analysis suggests that the marginal cost-effectiveness of the DMTs is in the range $104,000 to $312,000 per QALY gained. Crucially, the lowest cost-effectiveness estimate is based on a trial which was not analyzed according to the ITT principle and is likely to produce a systematically biased estimate of the cost-effectiveness of this therapy. As demonstrated in Scenario 2, the use of the modified relative relapse rates and relative hazards of progression estimated using the mixed treatment comparisons results in notably different estimates of cost-effectiveness. The cost-effectiveness estimates for IFNβ-1a 6 MIU appear markedly less favorable than those estimated using the placebo-controlled trial data. The marginal cost-effectiveness of IFNβ-1a 6 MIU versus best supportive care is in the range $104,000 to $111,000 per QALY gained when based on the placebo-controlled evidence alone. When information from the head-to-head trials is used to modify the estimated effectiveness of this therapy, the marginal cost-effectiveness of IFNβ-1a 6 MIU is estimated to be in the range $218,000 to $234,000 per QALY gained. The results of the head-to-head analysis of IFNβ-1a 6 MIU are broadly consistent with the UK commercial-in-confidence ITT analysis of IFNβ-1a 6 MIU, whereby the marginal cost-effectiveness ratio appears considerably less economically attractive compared to the estimate produced using the placebo-controlled trial estimates of effectiveness [6–8]. Scenario 3 suggests that cessation of DMT upon progression to EDSS 7.0 may produce more favorable estimates of cost-effectiveness than those presented in Scenario 1; under this scenario, the marginal cost-effectiveness estimates for IFNβ-1a 44 μg and IFNβ-1b 8 MIU in RRMS are below $100,000 per QALY gained. The analysis undertaken from the CMS perspective (Scenario 4) led to a considerable reduction in the absolute costs of all treatment options including best supportive care; this resulted in only slightly less favorable estimates of marginal cost-effectiveness for the DMTs.

Probabilistic Sensitivity Analysis Results

The results of the probabilistic sensitivity analysis are presented as CEACs in Figure 2.

The economic analysis based on the placebo-controlled evidence only (Scenario 1, Fig. 2a) suggests that the probability that any of the therapies has a cost-effectiveness ratio that is better than $60,000 per QALY gained as compared to best supportive care is approximately 0.08 or lower. Figure 2b suggests that when evidence from head-to-head trials is included in the model analysis, the probability that these therapies have cost-effectiveness ratio that is better than $60,000 per QALY gained as compared to best supportive care is approximately 0.04. Figure 2c suggests that stopping treatment upon progression to EDSS 7.0 has a notably favorable impact upon cost-effectiveness; the probability that any of these therapies has a cost-effectiveness ratio that is better than $60,000 per QALY gained as compared to best supportive care is approximately 0.47 or lower. Figure 2d suggests that when the analysis is considered from the perspective of the CMS, the probability that any of these therapies has a

Table 3 Central estimates of cost-effectiveness of disease-modifying therapies versus best supportive care

	Marginal cost per QALY gained versus best supportive care			
Treatment option	Scenario 1: Placebo-controlled evidence, no treatment discontinuation rule, payer perspective	Scenario 2: Mixed treatment comparisons, no treatment discontinuation rule, payer perspective	Scenario 3: Placebo-controlled evidence, stop treatment at EDSS 7.0, payer perspective	Scenario 4: Placebo-controlled evidence, no treatment discontinuation rule, CMS perspective
Physician-administered IFNβ-1a 6 MIU	$111,138	$233,967	$66,082	$120,853
Self-administered IFNβ-1a 6 MIU	$103,762	$218,206	$60,052	$116,987
IFNβ-1a 22 μg	$189,174	$189,174	$120,688	$199,189
IFNβ-1a 44 μg	$128,728	$172,438	$79,002	$141,135
IFNβ-1b 8 MIU for RRMS	$158,466	$91,515	$97,382	$168,793
GA 20 mg	$309,173	$309,173	$202,648	$316,128
IFNβ-1b 8 MIU for RRMS and SPMS	$312,344	$207,394	$122,202	$278,739
Best supportive care	—	—	—	—

CMS, Centers for Medicare and Medicaid Services; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; IFNβ, interferon beta; MIU, million international units; QALY, quality-adjusted life-year; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

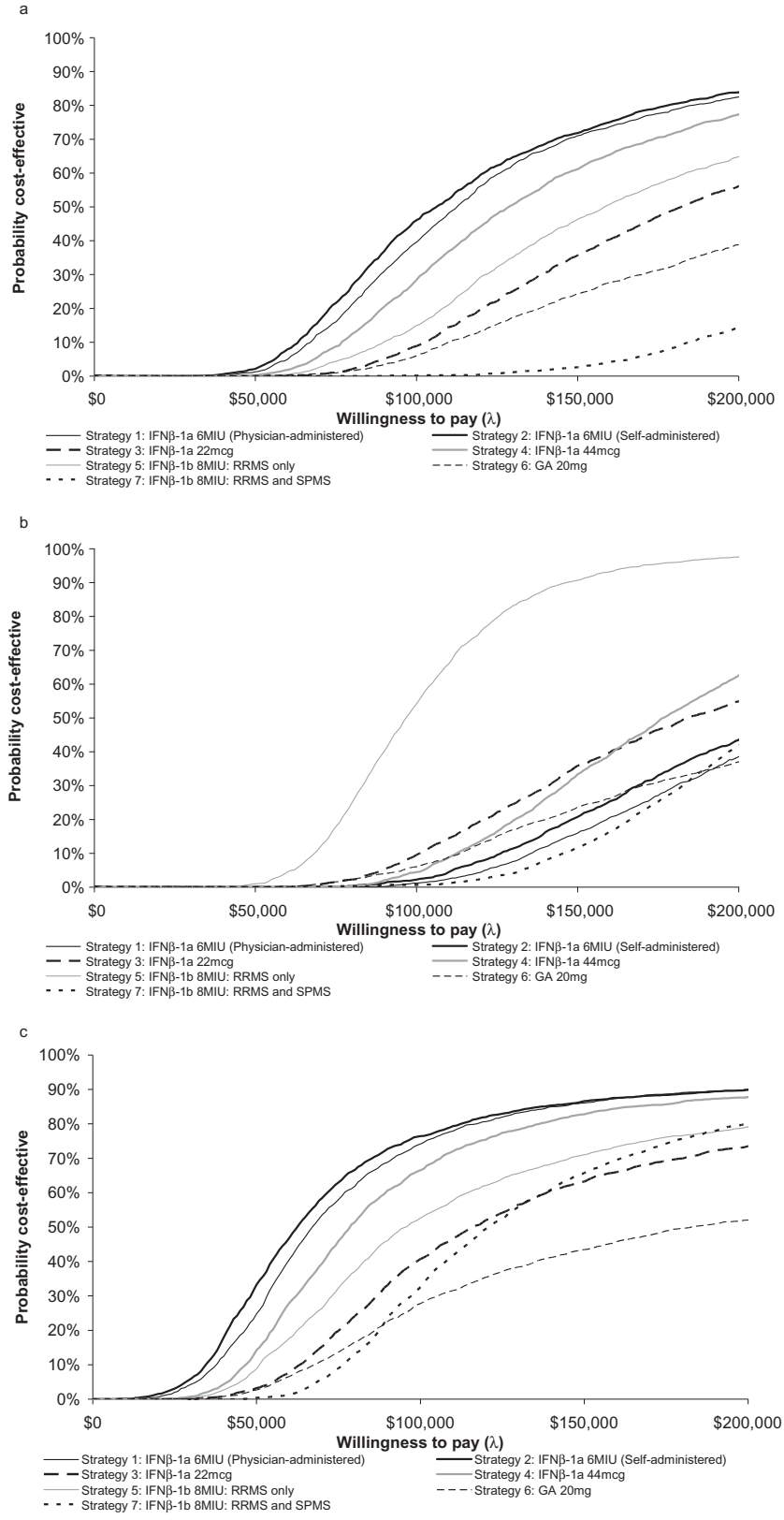

Figure 2 Cost-effectiveness acceptability curves for disease-modifying therapies versus best supportive care. (a) Scenario 1: Placebo-controlled evidence, no stopping rule, health-care payer perspective; (b) Scenario 2: Mixed treatment comparisons, no stopping rule, health-care payer perspective; (c) Scenario 3: Placebo-controlled evidence, stop treatment at Expanded Disability Status Scale 7.0, health-care payer perspective; (d) Scenario 4: Placebo-controlled evidence, no stopping rule, Centers for Medicare and Medicaid Services perspective. GA, glatiramer acetate; IFNβ, interferon beta; MIU, million international units; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

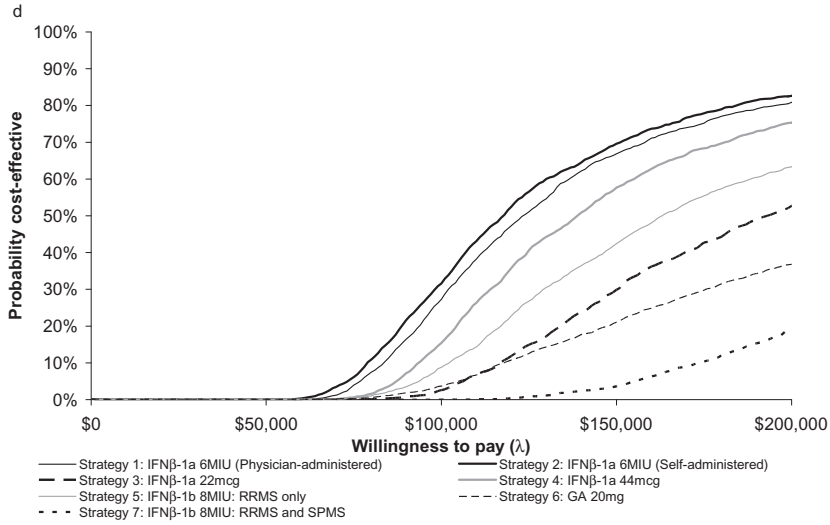

Figure 2 Continued.

cost-effectiveness ratio that is better than $60,000 per QALY gained is close to zero.

Discussion

At the time of their introduction, IFNβ and GA were considered to be extremely expensive. Nevertheless, in the intervening years, several more therapies have been launched with similar or even higher costs. As a result of the associated cost pressures, healthcare systems are increasingly interested in assessing whether treatments represent good value for money. The MRDD and the new prescription drug benefit increased CMS' exposure to such cost pressures.

Arguably, the most important finding is that in the US healthcare system, the DMTs could generate health benefits at a cost that could be considered cost-effective by certain decision-makers. The marginal cost-effectiveness estimates for IFNβ-1a 44 μg and IFNβ-1b 8 MIU are below $100,000 per QALY gained when treatment is stopped at EDSS 7.0. Interestingly, extending treatment beyond this point significantly increases the total cost of care while producing very little additional health gain. A second important finding is that when the evidence from the head-to-head comparisons of the different treatments is synthesized together with the placebo-controlled trial data, the estimated efficacy for IFNβ-1a 6 MIU is substantially reduced, thus having a markedly unfavorable impact upon its cost-effectiveness profile.

There remains substantial uncertainty surrounding the clinical effectiveness and cost-effectiveness of the treatments considered in this analysis. The pivotal trials for these therapies were relatively small in terms of the number of subjects, and adopted remarkably short follow-up periods for a chronic condition. In addition, the measurement properties of the outcome measure are increasingly considered to be inadequate [31]. The absence of high-quality data on the costs or quality of life associated with MS, held in a form that can be linked to the effectiveness evidence base, results in further uncertainty. We consulted long-term observational studies of the DMTs to attempt to validate the long-term predictions of the model [32]. However, where available, such studies were consistently subject to numerous important methodological and statistical limitations, which may result in confounding of outcomes [32]. Only one long-term study was identified which prospectively evaluated EDSS outcomes beyond 10 years of follow-up [33]. This suggested that GA results in long-term improvements in EDSS progression based on indirect comparisons against longitudinal natural history studies. EDSS outcomes were presented for patients remaining on GA at 10 years and patients who were followed up but had since withdrawn from therapy. However, patients who discontinued treatment were not well represented in the sample, and the group of patients still on treatment may be subject to a selection bias when compared to natural history data. A tentative analysis indicated that our model is more pessimistic, suggesting a typically faster rate of disease progression than that reported by Ford et al. [33]. This result is to be expected, as the statistical analysis of both the trial and the observational study assumes that MS disability may improve while our model explicitly does not. As Ford et al. [33] do not report the distribution of EDSS at baseline, this finding is difficult to confirm. Had better long-term data been available, we would have used this to inform treatment efficacy parameters rather than external model validation.

A limitation of the analysis is the use of health utility estimates sourced from patients in Canada rather than the United States. While studies have presented preference-based health utilities for MS patients in the United States, these have not reported health utilities for individual EDSS states across the entire spectrum of disability [34]. We compared the HUI3 utility estimates to Euroqol-5D (EQ-5D) estimates for mild, moderate, and severe MS reported by Kobelt et al. [34]. The HUI3 utilities appear to be consistently lower than those reported by Kobelt et al.: mild MS (HUI3 0.64 vs. EQ-5D 0.82); moderate MS (HUI3 0.36 vs. EQ-5D 0.68); and severe MS (HUI3 0.19 vs. EQ-5D 0.533). It is unclear whether these differences are driven by the use of different HRQoL measurement and valuation instruments, different cross-sections of disability at the point of evaluation or real differences in quality of life between patients in different geographical locations. Reanalysis of our model using the banded utility estimates reported by Kobelt et al. did not dramatically influence the cost-utility results; under Scenario 1, the marginal cost-utility of the DMTs ranged from $115,000 to 315,000 per QALY gained.

An innovative aspect of our study has been the use of Bayesian evidence synthesis methods to obtain comparable estimates of the effectiveness of the DMTs. While the assumptions required to undertake this type of analysis require caution in their inter-

pretation, and the evidence base can be synthesized using a variety of methods, the results of this analysis are consistent with the hypothesis that non–intention-to-treat analyses will overstate the effectiveness and thus the cost-effectiveness of interventions. This, in turn, suggests that the estimated cost-effectiveness of 6 MIU IFNβ-1a presented within Scenario 1 should be approached with caution as the trial was not undertaken according to the ITT principle. Despite having been available for nearly two decades, the evidence base for the effectiveness and cost-effectiveness of DMTs in RRMS and SPMS remains poor. Of particular concern is the lack of an ITT estimate of the efficacy of IFNB-1a 6 MIU obtained from a substantial randomized controlled trial (RCT). Furthermore, the use of a short follow-up duration within all of the trials results in a considerable degree of uncertainty surrounding the long-term effectiveness of these therapies.

There are a number of areas in which further research is warranted.

1. Existing RCTs of IFNβ and GA have used trial durations of between 9 months [14] and 5 years [15]. Further research concerning the impact of the DMTs on disease progression and relapse would be of considerable value. However, direct observational studies of MS are particularly expensive in terms of both financial cost and study follow-up requirements.
2. There is a dearth of evidence concerning the effectiveness of sequences of these therapies. The health economic analysis presented within this study does not include the possibility of switching between therapies. Further research concerning the clinical effectiveness and cost-effectiveness of alternative sequences of DMTs is merited.
3. The Sonya Slifka data set [9,10] is clearly a rich and valuable source of health-care utilization data for individuals with MS. However, the transposition of these resource use data, which are based on a specific ADL scale, onto the EDSS is problematic. The absence of robust cost evidence to inform cost-effectiveness analysis has been noted within previous cost-effectiveness models developed in the United States [29]. Further research on the relationship between the EDSS, health-care utilization, and costs of MS care would be highly informative for further economic evaluations.
4. While the Canadian HUI3 data [27] used within this analysis are highly consistent with other utility sources from other countries, US valuations may differ from those used in this analysis. Further information concerning the relationship between EDSS and health utilities within the US Medicare population may be valuable.

Conclusion

Further research is required to examine the long-term clinical effectiveness and cost-effectiveness of these therapies. There is no definitive guidance in the United States concerning discontinuation of DMTs; this study suggests that the prudent use of a treatment discontinuation rule may improve the cost-effectiveness of DMTs.

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