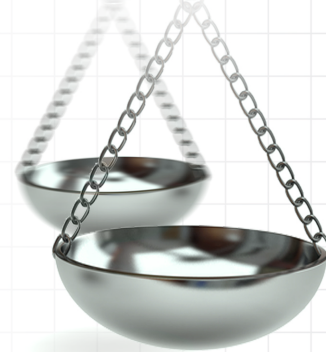




Cost-effectiveness of different strategies for treatment relapsing-remitting multiple sclerosis

Journal of **Comparative Effectiveness Research**

Aim: To compare the cost-effectiveness of different disease-modifying therapies' strategies for treatment of relapsing-remitting multiple sclerosis. **Methods:** A Markov model was developed to assess the cost-effectiveness and incremental cost-effectiveness ratios for different strategies of using disease-modifying therapies from a US third-party payer perspective. All costs were converted to 2014 US\$. **Results:** Over 20 years, the total costs per patient were estimated at US\$161,136.60 for Strategy 1 (symptom management [SM] alone), US\$551,650.66 for Strategy 2 (SM and IFN- β -1a), US\$703,463.60 for Strategy 3 (SM and natalizumab) and US\$670,985.24 for Strategy 4 (SM and alemtuzumab). The accumulated quality-adjusted life years were 10.49, 10.66, 10.69 and 10.71 for each of the four Strategies 1–4, respectively. The resulting incremental cost-effectiveness ratios were 2,297,141.53 comparing Strategy 2 to Strategy 1, and -1,623,918.00 comparing Strategy 4 to Strategy 3. **Conclusion:** Strategy 1 was the cost-effective strategy for treatment of relapsing-remitting multiple sclerosis when compared with other strategies.

Keywords: cost-effectiveness • economic • evaluation • multiple sclerosis • pharmacoeconomic • relapsing-remitting multiple sclerosis • TreeAge

Multiple sclerosis (MS) is a chronic neuro-degenerative disease of the CNS [1–3]. This disease affects the transmission of the neurological signals in the body due to demyelination of neurons [1–3]. There are four disease courses or subtypes including relapsing-remitting multiple sclerosis (RRMS), secondary progressive MS, primary progressive MS and progressive-relapsing MS [4].

The most common subtype of MS is RRMS. Around 85% of MS patients are initially diagnosed with RRMS and the remaining are diagnosed with the progressive forms of the disease [5]. RRMS is characterized by worsening of neurological functions unpredictable attacks (also called exacerbations or relapses), which followed by relative recovery periods (also called remissions) [5]. During the periods of remission, there is partially or completely improvement in the symptoms of RRMS with no apparent disease progression. Most of the MS patients who are ini-

tially diagnosed with RRMS will finally change to secondary progressive MS (steady MS disease progression with or without acute attacks) [6,7].

There is no cure for MS disease. However, there are disease-modifying therapies (DMTs) used with the aims to modify the MS course and reduce or slow progression of the disease. By 31 December 2014, the USA (the US FDA) had approved 12 DMTs for treatment of relapsing forms of MS [8,9].

A previous study assessed trends in prices of DMTs marketed in the USA and concluded that DMT prices increased faster than the US Consumer Price Index [10]. DMTs are the major component in the management of MS disease, but their prices increased over time, which raised concerns regarding their cost-effectiveness [8–9,11]. Previous studies assessed the costs of MS and compared the cost-effectiveness of MS DMTs [12,13]. However, we did not identify

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any study in the scientific literature comparing the cost-effectiveness of MS DMTs based on switchable treatments. Also, we did not find any recent studies comparing recent DMTs with symptom management (SM) alone.

Objectives

The objective of this study was to compare the cost-effectiveness of different strategies for the treatment of patients with RRMS. The cost-effectiveness comparisons include four strategies. The strategies were SM alone, SM in combination with one of the following: IFN- β -1a, natalizumab (after switching from IFN- β -1a) and alemtuzumab (after using IFN- β -1a, then switching to natalizumab) (Figure 1). The sequential treatments reflect the clinical practice and are used as the clinically recommended strategy for treatment of RRMS patients. In addition, these strategies represent common treatment alternatives for patients with RRMS and correspond with the indications approved by the FDA for the drugs evaluated. According to the FDA-approved labels, natalizumab is indicated to treat patients with RRMS after treatment failure with a previous DMT; while alemtuzumab is indicated for use in patients with RRMS when two or

more DMTs have failed. The DMT failure in this study was defined as increasing in the RRMS disease progression that measured by the expanded disability status scale (EDSS). The DMT switching was at specific EDSS points and it is explained in the method section of this paper.

Data & methods

This cost-effectiveness study was performed from a US third-party payer perspective with a time horizon of 20 years to capture all relevant long-term costs and outcomes of DMTs.

The comparators included in the study were:

- IFN- β -1a (Biogen) as a first-line DMT;
- Natalizumab as a second-line DMT (previous DMT failed);
- Alemtuzumab as a third-line DMT (two former DMTs failed).

Patients were considered to use SM in all treatment strategies (Figure 1). This study compared the incremental cost-effectiveness ratios (ICERs) of the following treatment strategies:

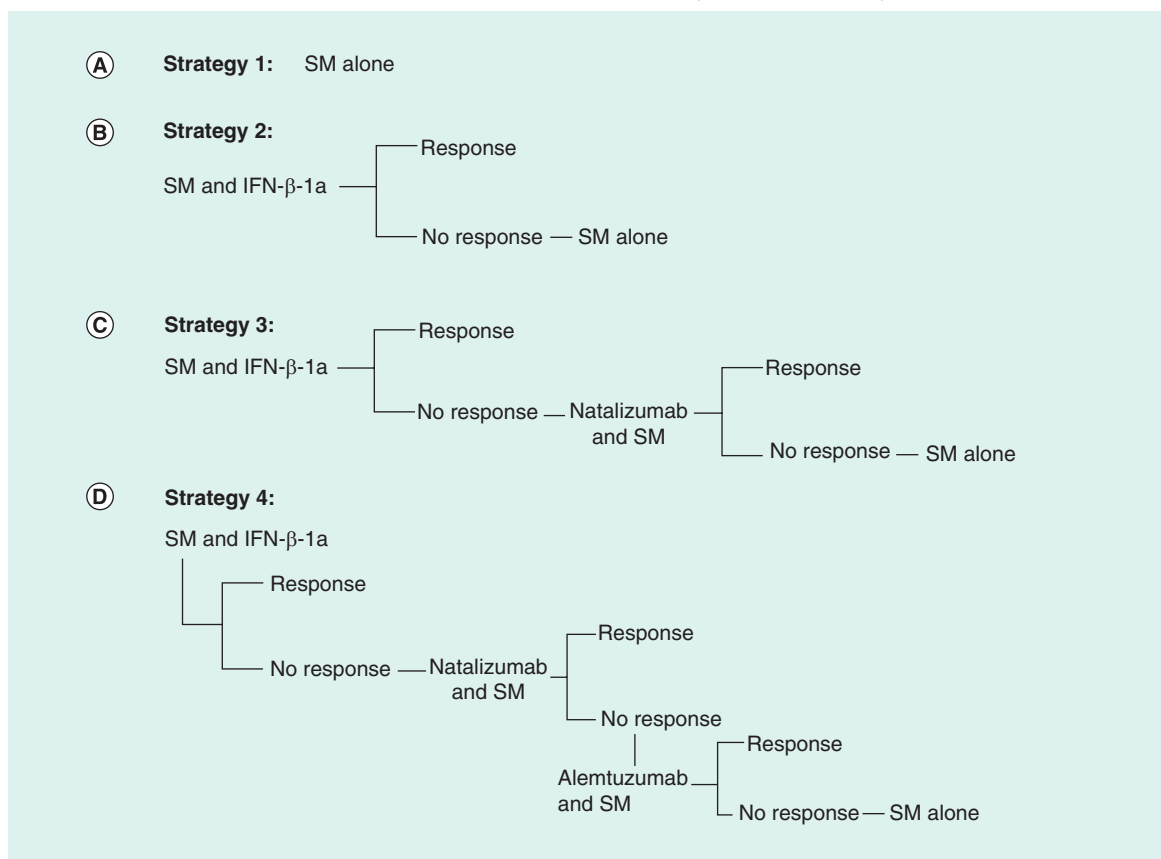


Figure 1. Four treatment strategies for relapsing-remitting multiple sclerosis disease.

SM: Symptom management.

Table 1. Study parameters and ranges in one-way sensitivity analysis.

Study parameters	Base case	Range of one-way sensitivity analysis	Study (year)	Ref.
Annual probability of disease progression (symptom management):				
– EDSS 0.0–2.5 to EDSS 3.0–5.5	0.066972		Scalfari <i>et al.</i> (2010)	[20]
– EDSS 3.0–5.5 to EDSS 6.0–7.5	0.082993		Scalfari <i>et al.</i> (2010)	[20]
– EDSS 6.0–7.5 to EDSS 8.0–9.5	0.066972		Scalfari <i>et al.</i> (2010)	[20]
Annual probability of relapse (symptom management)	0.400		Hoyert and Xu (2012)	[21]
Annual probability of progressing to death:				
– EDSS 0.0–2.5	0.020022		Hoyert and Xu (2012)	[21]
– EDSS 3.0–5.5	0.027815		Hoyert and Xu (2012)	[21]
– EDSS 6.0–7.5	0.036816		Hoyert and Xu (2012)	[21]
– EDSS 8.0–9.5	0.052192		Hoyert and Xu (2012)	[21]
Annual percent reduction in probability of relapse:				
– IFN- β -1a	27%		Filippini <i>et al.</i> (2003) , Khan <i>et al.</i> (2002)	[22,23]
– Natalizumab	68%		Polman <i>et al.</i> (2006), Kerbrat <i>et al.</i> (2011), Dalton <i>et al.</i> (2004)	[24–26]
– Alemtuzumab	49%		Hartung <i>et al.</i> (2015), CAMMS223 Trial Investigators <i>et al.</i> (2008), Cohen <i>et al.</i> (2012), Coles <i>et al.</i> (2012)	[27–30]
Annual percent reduction in probability of disease progression:				
– IFN- β -1a	30%		Filippini <i>et al.</i> (2003), Khan <i>et al.</i> (2002)	[22,23]
– Natalizumab	21%		Polman <i>et al.</i> (2006)	[24]
– Alemtuzumab	21%		Hartung <i>et al.</i> (2015)	[27]
Utilities:				
– EDSS 0.0–2.5	0.899	0.674–1	Prosser <i>et al.</i> (2003)	[19]
– EDSS 3.0–5.5	0.821	0.616–1	Prosser <i>et al.</i> (2003)	[19]
– EDSS 6.0–7.5	0.769	0.577–0.961	Prosser <i>et al.</i> (2003)	[19]
– EDSS 8.0–9.5	0.491	0.368–0.614	Prosser <i>et al.</i> (2003)	[19]
Utility decrement associated with relapse	0.094	0.071–0.118	Kobelt <i>et al.</i> (2006)	[15]
Annual costs (2014), US\$:				
– WAC for IFN- β -1a	62,036	46,527.00–74,443.20	RedBook	[14]
– WAC for natalizumab	60,827	45,620.25–72,992.40	RedBook	[14]
– WAC for alemtuzumab	98,750 (1st year) 59,250	74,062.50–118,500.00	RedBook	[14]

EDSS: Expanded disability status scale; WAC: Wholesale acquisition cost.

Table 1. Study parameters and ranges in one-way sensitivity analysis (cont.).				
Study parameters	Base case	Range of one-way sensitivity analysis	Study (year)	Ref.
Annual healthcare costs (2014), US\$:				
– Cost of EDSS 0.0–2.5	7742.27	5806.70–9677.84	Kobelt <i>et al.</i> (2006)	[15]
– Cost of EDSS 3.0–5.5	16,227.30	12,170.48–20,284.13	Kobelt <i>et al.</i> (2006)	[15]
– Cost of EDSS 6.0–7.5	40,259.82	30,194.87–50,324.78	Kobelt <i>et al.</i> (2006)	[15]
– Cost of EDSS 8.0–9.5	80,179.74	60,134.80–100,224.67	Kobelt <i>et al.</i> (2006)	[15]
Monthly cost of relapse	5253.84	3940.38–6567.29	Oleen-Burkey <i>et al.</i> (2012)	[16]
EDSS: Expanded disability status scale; WAC: Wholesale acquisition cost.				

- Strategy 1: SM alone (Figure 1A);
- Strategy 2: patients use IFN-β-1a. If there was insufficient response to this DMT, they would continue on SM alone (Figure 1B);
- Strategy 3: patients use IFN-β-1a, but if there was an insufficient response to this DMT (transition of patients to a higher EDSS health state), they switch to use natalizumab. Then, if there was an inadequate response to natalizumab, they will continue on SM alone (Figure 1C);
- Strategy 4: patients use IFN-β-1a, but if there was an insufficient response to this DMT (transition of patients to a higher EDSS health state), they switch to use natalizumab. Then, if there was an insufficient response to natalizumab, they turn to use alemtuzumab. After that, if there was an inadequate response to alemtuzumab, they will continue on SM alone (Figure 1D).

Costs

The wholesale acquisition costs (WACs) were used to calculate the costs of MS DMTs. The WAC is the price for drugs paid by wholesalers to manufacturers. WAC is equal to the average wholesale price (AWP) divided by 1.2. The AWP is the average price where wholesalers sell drugs to pharmacies. AWP per unit for MS DMTs were derived from the RedBook (Truven Health Analytics, Inc.) [14].

Healthcare costs data (ambulatory care, hospital inpatient care, services, tests, adaptations and costs of informal care) were obtained from a study conducted in 2004 by Kobelt *et al.* assessing the cost of MS disease by stratified EDSS health states [15]. Kobelt *et al.* were chosen as a reference for healthcare costs data because the reported costs corresponded to each health state in our model [15]. The costs of MS relapses were extracted from a study conducted in 2009 by Oleen-

Burkey *et al.* that reported the impact of MS relapses on economic costs and health-related quality of life for RRMS patients in the USA [16]. Quality-adjusted life years (QALYs) capture the cost of productivity and other indirect costs [17]. Therefore, the costs of productivity losses and other indirect costs were not included in this study.

All costs were inflated to 2014 US\$ by using the US Consumer Price Index, US city average, medical care items [15,16]. According to the Panel on cost–effectiveness in health and medicine recommendations, costs were discounted using an annual discount rate of 3% [18]. Cost–effectiveness and the ICERs were estimated.

Health outcomes

The utilities for the EDSS health states were derived from a previous study that assessed community preferences for treatments and health states in RRMS patients by using the standard gamble method (Table 1) [19]. Outcomes were discounted using the 3% annual discount rate [18].

Willingness-to-pay

The WHO recommended using three-times the gross domestic product per capita as willingness-to-pay (WTP) threshold per QALY [31,32]. Numerous previous cost–effectiveness studies used US\$50,000 as WTP threshold per QALY in the USA [33–35]. However, this threshold is very unlikely consistent with societal preferences in the USA [36]. Therefore, this study considered several WTP thresholds per QALY in the analyses.

Markov model

TreeAge Pro 2015, R2.0 was used to develop a Markov model for simulation of RRMS disease progression in MS patients (Figure 2). Modeling of RRMS disease progression was based on EDSS. The EDSS is a clinician-reported outcome measure, which is most widely used to assess the MS disease progression [37].

The EDSS is measured on an ordinal scale from 0 (means normal neurological functions) to 10 (means death due to MS) [37].

The model is constructed of mutually exclusive and exhaustive health states. The model includes the following health states: EDSS 0.0–2.5 (no or mild disability), EDSS 3.0–5.5 (moderate disability, ambulatory without help), EDSS 6.0–7.5 (walking support required), EDSS 8.0–9.5 (bed restricted), EDSS 10.0 (death due to MS) and two other relapse states (Figure 2). Probabilities of transition from one EDSS health state to another and probabilities of relapses were obtained from

previous studies that reported data corresponded to our model (Table 1) [20–24,27,38].

All adult RRMS patients began the model in the EDSS 0.0–2.5 health state (no or mild disability). The duration of each cycle is 1 year. However, we assumed that patients that have a relapse would remain in the relapse health state for 1 month. And the cost and utility of the relapse states were adjusted accordingly. RRMS patients stay in their health state as long as they did not deteriorate (moved to a higher EDSS health state) or died. MS is a progressive disease, so patients could move to more severe health state (higher EDSS state)

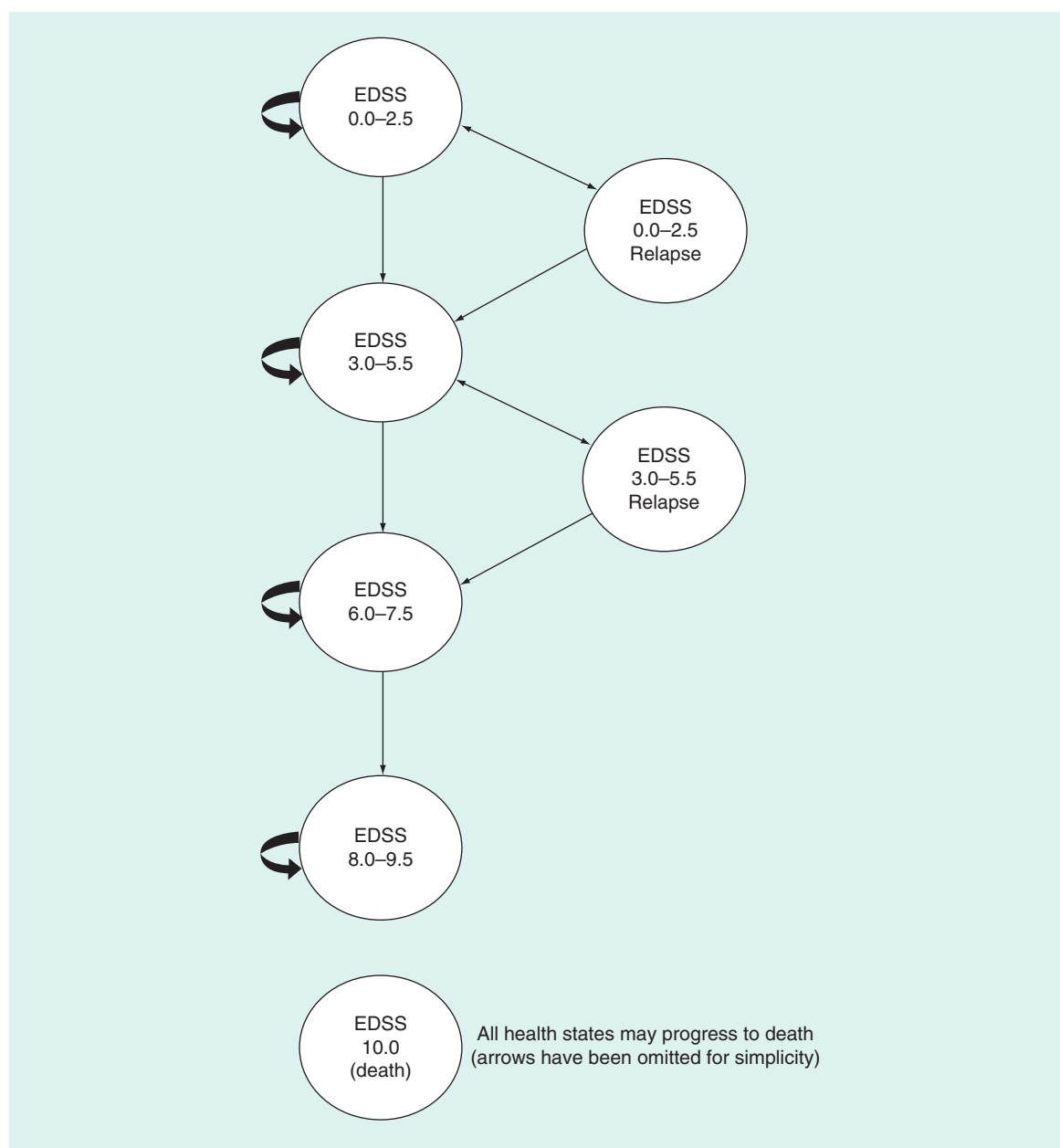


Figure 2. Schematic for the Markov model used in the evaluation.

EDSS: Expanded Disability Status Scale.

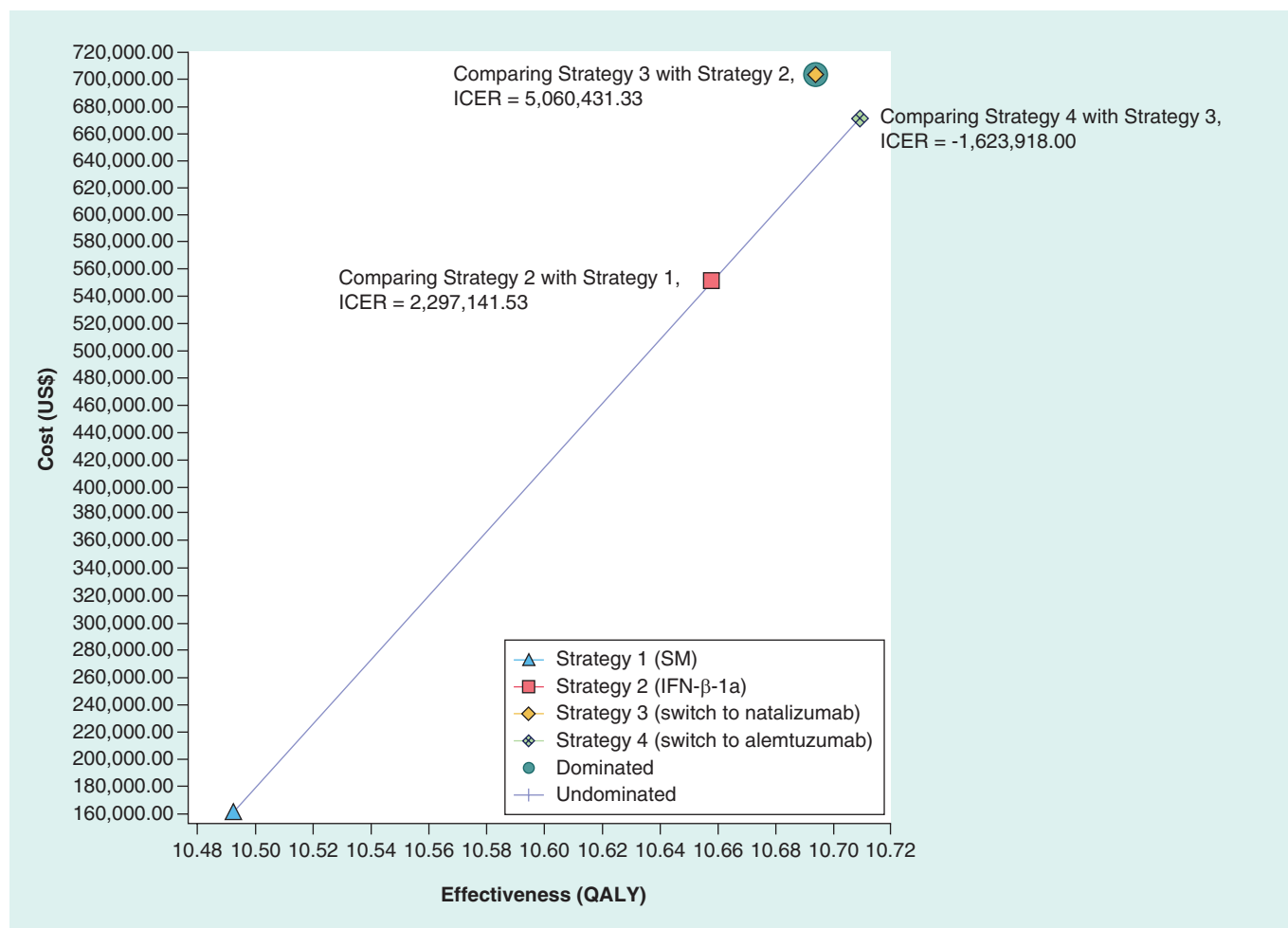


Figure 3. Cost-effectiveness curve.

ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life year; SM: Symptom management.

or a relapse state. Patients who experience relapse could return to the previous health state or deteriorate and move to a higher EDSS state (Figure 2). The probabilities of transition between health states were obtained from the literature [21]. To ensure the internal validity of the model, each author verified the model independently.

Sensitivity analyses

Deterministic one-way sensitivity analyses ($\pm 25\%$ unless indicated otherwise) were conducted to assess the possible effect of an individual parameter's uncertainty (DMT acquisition costs, EDSS health state costs and time horizon) on the base-case analysis results. The upper and lower limits of the sensitivity analyses range ($\pm 25\%$) were differed markedly from the base-case parameter inputs and comparable to their corresponding confidence intervals (CI = 95%). In the deterministic one-way sensitivity analyses, the upper limits for DMT acquisition costs were 20% more than WAC for DMTs under the assumption that the AWP (WAC is 80% of the AWP) is the maximum price paid for DMTs in the US market.

In addition, Tornado diagrams were plotted to show the impact of individual parameter on the expected value (most sensitive parameter at the top of the diagram and least sensitive parameter at the bottom of the diagram).

Probabilistic sensitivity analysis (second-order Monte Carlo simulation, 1000-times) was conducted to assess the possible combined uncertainty of the parameters (healthcare costs for EDSS health states, DMT acquisition costs and utilities) on the overall confidence in the base-case results. The distribution was assumed to be a gamma distribution for healthcare costs of EDSS health states and DMT acquisition costs [39]. The distribution was assumed to be a beta distribution (between 0 and 1) for utilities [39].

Results

Base-case scenario

Over 20 years, the total costs per patient were estimated at US\$161,136.60 for Strategy 1 (SM alone), US\$551,650.66 for Strategy 2 (SM and IFN-β-1a), US\$703,463.60 for Strategy 3 (SM and natalizumab)

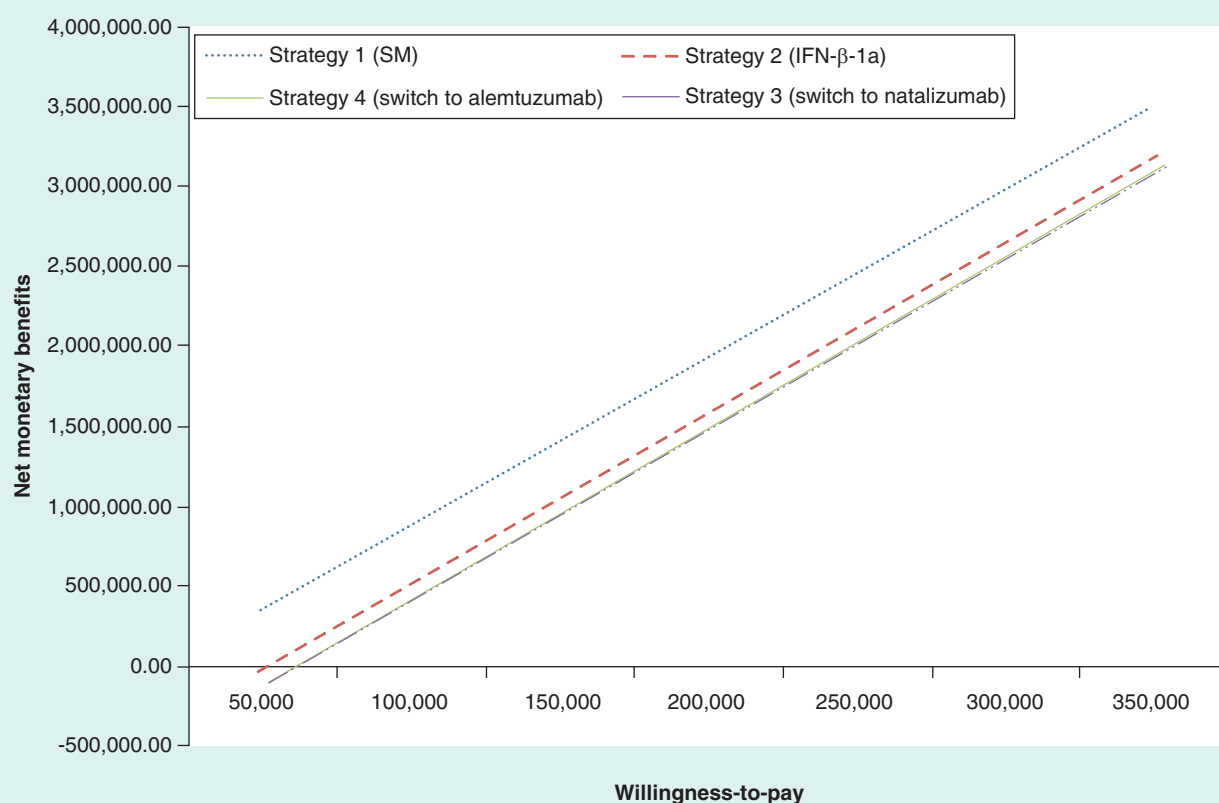


Figure 4. Net monetary benefits of the strategies for treating relapsing-remitting multiple sclerosis.

SM: Symptom management.

and US\$668,806.50 for Strategy 4 (SM and alemtuzumab). The accumulated QALYs were 10.49, 10.66, 10.69 and 10.71 for each of the four strategies 1–4, respectively.

Strategy 4 had higher effect (10.71 vs 10.69) and lower cost (US\$670,985.24 vs US\$703,463.60) than Strategy 3, thus Strategy 3 was dominated by Strategy 4. Strategy 2 was extendedly dominated by Strategy 1 and Strategy 4 (Figure 3). Ruling out strategies through dominance or extended dominance; the com-

parison of Strategy 4 and Strategy 1 results in an ICER of 2,317,493.82. As long as the WTP was greater than US\$100,000, the net monetary benefits of Strategies 2–4 would be greater than zero (Figure 4).

Compared with Strategy 1, the ICER was 2,297,141.53 for Strategy 2. In addition, comparing Strategy 4 to Strategy 3 results in ICERs of -1,623,918.00. Therefore, Strategy 1 (SM alone) was the cost-effective strategy for treatment of RRMS when compared with other strategies (Table 2).

Table 2. Results for the base-case scenario.

Strategy	Cost (US\$)	Incremental cost (US\$)	Effect	Incremental effect	ICER
Strategy 1 (SM alone)	161,136.60	–	10.49	–	–
Strategy 2 (IFN-β-1a)	551,650.66	390,514.06	10.66	0.17	2,297,141.53
Strategy 3 (switch to natalizumab)	703,463.60	151,812.94	10.69	0.03	5,060,431.33
Strategy 4 (switch to alemtuzumab)	670,985.24	-32,478.36	10.71	0.02	-1,623,918.00

In this table, each strategy compared with the strategy mentioned above it (i.e., Strategy 2 compared with Strategy 1, Strategy 3 compared with Strategy 2 and Strategy 4 compared with Strategy 3).
 Strategy 1 (SM alone) was the cost-effective strategies for the treatment of relapsing-remitting multiple sclerosis when compared with other strategies at willingness-to-pay = US\$50,000/quality-adjusted life year.
 ICER: Incremental cost-effectiveness ratio; SM: Symptom management.

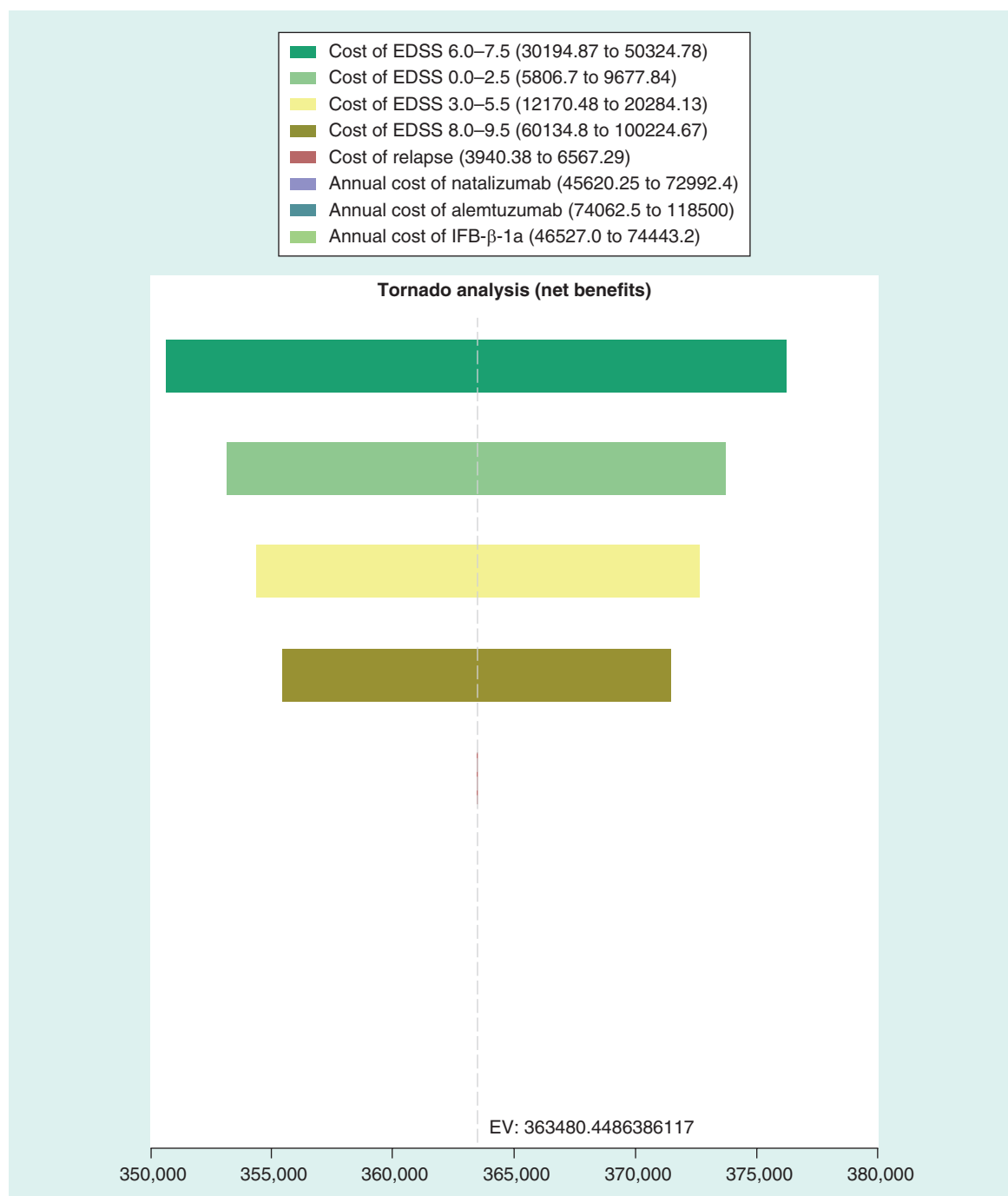


Figure 5. Sensitivity analysis (willingness-to-pay = US\$50,000).

EDSS: Expanded disability status scale.

Deterministic one-way sensitivity analyses

SM was the optimal strategy, and there was no effect of individual parameters' uncertainty (DMT acquisition costs and EDSS health state costs) on the base-case analysis results. The results of the base-case analysis were relatively sensitive to changes in the cost of the EDSS 6.0–7.5 health state and the cost for EDSS 0.0–2.5 (Figure 5). The results of the base-case analysis

were not sensitive to the extension of the study time horizon. In addition, the base-case analyses results were relatively stable to changes in all other parameters.

Probabilistic sensitivity analyses

Over a range of different WTPs, Strategy 2 was the optimal treatment strategy with 59.7% acceptability (Figure 6). Both Strategy 1 and Strategy 4 had a less

than 22% chance of being the optimal strategy treatment for RRMS. However, the probability for Strategy 4 being preferred was constantly higher than that for Strategy 3. Finally, Strategy 3 had a negligible probability of being the optimal treatment strategy.

Discussion

The results of this study indicate that all the ICERs for the different treatment strategies evaluated were above the \$100,000 WTP threshold per QALY, and only Strategy 1 (SM) was cost effective. Strategy 3 (SM and natalizumab) was dominated by Strategy 4 (SM and alemtuzumab) as the latter was more effective and less costly. Strategy 2 (SM and IFN- β -1a) was extendedly dominated by Strategy 1 and Strategy 4 (Figure 3). Strategy 4 had an ICER that exceeded US\$2.3 million in comparison with Strategy 1, well above the WTP typically considered as cost effective in the USA.

Over 20 years, the total costs per patient for Strategy 4 (US\$670,985.24) were lower than that for Strategy 3 (\$703,463.60; Table 2). The dose of alemtuzumab (Strategy 4) was intravenous infusion given to RRMS patients on five consecutive days in the first year of alemtuzumab use, followed by intravenous

infusion on three consecutive days 1 year later. Then, alemtuzumab was not given to the RRMS patients. Therefore, the total cost of Strategy 4 was lower than that Strategy 3.

Compared with Strategy 1, the ICER was 2,297,141.53 for Strategy 2. In addition, comparing Strategy 3 to Strategy 2 and Strategy 4 to Strategy 3 results in ICERs of 5,060,431.33 and -1,623,918.00, respectively. The negative ICER given by comparing Strategy 4 to Strategy 3 means that Strategy 4 was cost saving compared with Strategy 3 (Strategy 4 has lower cost and higher effect compared with Strategy 3). Strategy 1 (SM alone) was the most cost-effective strategy for treatment of RRMS when compared with other strategies (Table 2).

Previous studies assessed the ICER of individual DMTs (e.g., IFN- β -1a and natalizumab [33–34,40]). However, these studies did not assess the ICER of sequential treatments that reflect the clinical practice and used as the clinically recommended strategy for treatment of RRMS patients. Our study found that the ICERs for the assessed strategies of sequential treatment were significantly higher than the ICER of the individual DMTs described in previous studies.

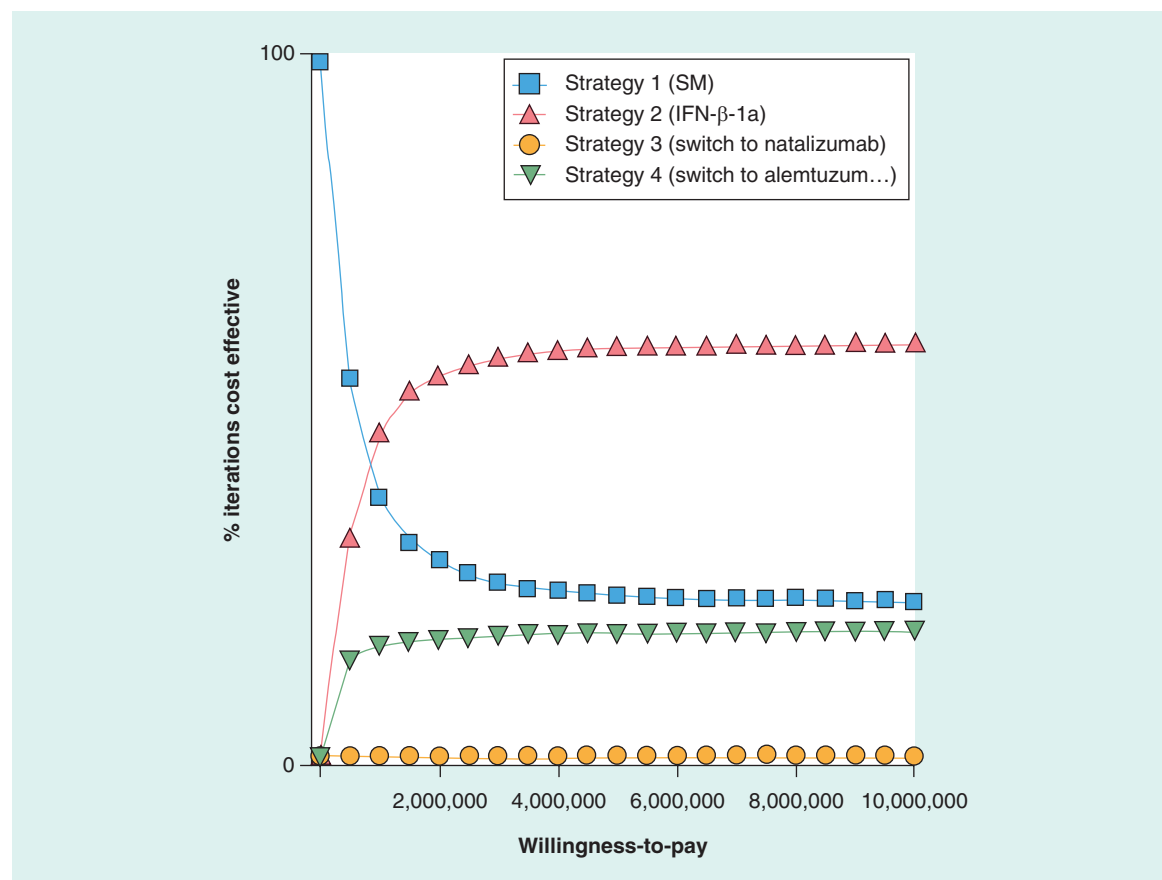


Figure 6. Cost-effectiveness acceptability curve.

SM: Symptom management.

The transition points EDSS 3.0, 6.0, 8.0 and 10 are critical in defining the clinical course of MS disease [20,41–43]. The results of the analysis were consistent with previous cost–effectiveness studies comparing different DMTs for treatment RRMS using the same EDSS health states classification and the same path for MS disease progression [33–34,40,44]. Our model better reflects the clinical practice in which patients can switch from IFN- β -1a to natalizumab as a second-line therapy [45,46].

While the EMA registered fingolimod as second-line DMT in RRMS, fingolimod was registered in the USA by the FDA as a first-line DMT in RRMS. So far natalizumab registered in the USA as second-line DMT. Since our study is from the USA perspective, natalizumab was used as second-line DMT in treatment of RRMS. The American Academy of Neurology recommended using natalizumab when a previous DMT failed [45]. A previous study suggested that switching to natalizumab is more effective than switching among first-line therapies in RRMS patients who failed a first-line therapy [47]. Our study includes RRMS treatment strategies in which patients use a DMT and if there was insufficient response to that DMT, they would continue on SM alone (Figure 1). This is reflecting the real life in which some patients get frustrated and stop the DMT when they see no response. Moreover, switching to another DMT could be expensive. Patients may have no access to the alternative DMT (e.g., the alternative DMT may not be covered by their healthcare plan or even it covered, the out-of-pocket payments is too high and they cannot afford it). Healthcare plans should consider

including the cost-effective treatments in their drug formulary.

Study limitations

This cost–effectiveness study used time horizon of 20 years to capture many relevant long-term costs and outcomes of DMTs. Extrapolating the results from randomized controlled trials over long time horizons requires model assumptions that could affect the final results of the study. Many MS patients would remain alive after the 20-year time horizon, and potential long-term benefits and costs associated with the alternative treatment are not completely captured in the study. However, the sensitivity analysis was done and the results of the base-case analysis were not sensitive to the extension of the study time horizon.

The model uses QALYs for assessing the outcomes in the EDSS health states. However, the negative effects of adverse drug events related to DMTs may not be fully included in the QALY used in the analyses.

The SM is different from RRMS patient to another. However, this study assumed that all RRMS patients used SM in all treatment strategies because the study included cohort RRMS patients. This study excluded several possible RRMS treatment alternatives (e.g., switching between first-line therapies). However, switching to natalizumab is considered more effective than switching among first-line therapies in RRMS patients who failed a first-line therapy [47].

Conclusion

The results of this study indicate that all the ICERs for the different treatment strategies evaluated were above

Executive summary

- Disease-modifying therapies (DMTs) are the major component in the management of multiple sclerosis disease, but their prices increased over time, which raised concerns regarding their cost–effectiveness.
- A Markov model was developed to assess the cost–effectiveness and incremental cost–effectiveness ratios (ICERs) for different strategies of using DMTs from a US third-party payer perspective.
- The cost–effectiveness comparisons include four strategies. The strategies were symptom management (SM) alone, SM in combination with one of the following: IFN- β -1a, natalizumab (after switching from IFN- β -1a) and alemtuzumab (after using IFN- β -1a, then switching to natalizumab).
- Over 20 years, the total costs per patient were estimated at US\$161,136.60 for strategy 1 (SM alone), US\$551,650.66 for Strategy 2 (SM and IFN- β -1a), US\$703,463.60 for Strategy 3 (SM and natalizumab) and US\$670,985.24 for Strategy 4 (SM and alemtuzumab).
- The accumulated quality-adjusted life years were 10.49, 10.66, 10.69 and 10.71 for each of the four strategies 1–4, respectively. The resulting ICERs were 2,297,141.53 comparing Strategy 2 to Strategy 1 and -1,623,918.00, comparing Strategy 4 to Strategy 3.
- All the ICERs for the different treatment strategies evaluated were above the US\$100,000 willingness-to-pay threshold per quality-adjusted life year, and only Strategy 1 (SM) was cost-effective.
- Previous studies assessed the ICER of IFN- β -1a and natalizumab. However, these studies did not assess the ICER of sequential treatments that reflect the clinical practice and used as the clinically recommended strategy for treatment of relapsing-remitting multiple sclerosis patients. Our study found that the ICERs for the assessed strategies of sequential treatment were significantly higher than the ICER of the individual DMTs described in previous studies.

the US\$100,000 WTP threshold per QALY, and only Strategy 1 (SM) was cost effective. Use of the most expensive DMTs resulted in ICERs that exceeded the WTP typically considered as cost-effective in the USA. The results of the study were no sensitive to changes in the parameters used in the base-case model. More studies are needed to assess the cost and effectiveness of using DMTs in MS patients. Future studies should include all first-line DMTs available in the US market. Changes in the DMTs safety profiles may result in changes in the utility and hence changes in the available study results. Cost-effectiveness studies should be updated as new DMTs access the US market. Future changes in the prices of DMTs may lead to different results.

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