ORIGINAL RESEARCH ARTICLE

Cost Effectiveness of Fingolimod, Teriflunomide, Dimethyl Fumarate and Intramuscular Interferon-β_{1a} in Relapsing-Remitting Multiple Sclerosis

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Abstract

Objective The aim of the study was to compare the cost effectiveness of fingolimod, teriflunomide, dimethyl fumarate, and intramuscular (IM) interferon (IFN)-β_{1a} as first-line therapies in the treatment of patients with relapsing-remitting multiple sclerosis (RRMS).

Methods A Markov model was developed to evaluate the cost effectiveness of disease-modifying drugs (DMDs) from a US societal perspective. The time horizon in the base case was 5 years. The primary outcome was incremental net monetary benefit (INMB), and the secondary outcome was incremental cost-effectiveness ratio (ICER). The base case INMB willingness-to-pay (WTP) threshold was assumed to be US$150,000 per quality-adjusted life year (QALY), and the costs were in 2012 US dollars. One-way sensitivity analyses and probabilistic sensitivity analysis were conducted to test the robustness of the model results.

Results Dimethyl fumarate dominated all other therapies over the range of WTPs, from US$0 to US$180,000. Compared with IM IFN-β_{1a}, at a WTP of US$150,000, INMBs were estimated at US$36,567, US$49,780, and US$80,611 for fingolimod, teriflunomide, and dimethyl fumarate, respectively. The ICER of fingolimod versus teriflunomide was US$3,201,672. One-way sensitivity analyses demonstrated the model results were sensitive to the acquisition costs of DMDs and the time horizon, but in most scenarios, cost-effectiveness rankings remained stable. Probabilistic sensitivity analysis showed that for more than 90 % of the simulations, dimethyl fumarate was the optimal therapy across all WTP values.

Conclusion The three oral therapies were favored in the cost-effectiveness analysis. Of the four DMDs, dimethyl fumarate was a dominant therapy to manage RRMS. Apart from dimethyl fumarate, teriflunomide was the most cost-effective therapy compared with IM IFN-β_{1a}, with an ICER of US$7,115.

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Key Points

This is the first cost-effectiveness analysis in relapsing-remitting multiple sclerosis to (1) make comprehensive comparisons between the three new oral disease-modifying drugs and the established therapy intramuscular (IM) interferon (IFN)-β_{1a}, (2) incorporate second-line therapy in the model, and (3) present results in terms of incremental net monetary benefit (INMB)

Dimethyl fumarate dominated all other therapies over the range of willingness-to-pay (WTP) values, from US$0 to US$180,000. Compared with IM IFN-β_{1a}, at a WTP of US$150,000, INMBs were estimated at US$36,567, US$49,780, and US$80,611 for fingolimod, teriflunomide, and dimethyl fumarate, respectively. The three oral therapies were favored in the cost-effectiveness analysis

After dimethyl fumarate, teriflunomide was the most cost-effective therapy compared with IM IFN-β_{1a}, with an incremental cost-effectiveness ratio of US$7,115. When the monthly cost is below US$5,132, fingolimod is cost effective compared with IM IFN-β_{1a}. However, fingolimod is not cost effective compared with teriflunomide

1 Introduction

Before the introduction of oral fingolimod (Gilenya™, Novartis, East Hanover, NJ, USA), over half of the patients with relapsing-remitting multiple sclerosis (RRMS) who were treated with disease-modifying drugs (DMDs) were using injected interferons (IFNs) [1], and intramuscular (IM) IFN-β_{1a} (Avonex®, Biogen Idec, Weston, MA, USA) had the largest market share in 2010 [2]. However, IM IFN-β_{1a} and other traditional DMDs require long-term parenteral administration, which imposes a burden on patients and may have a significant impact on medication adherence. Over the past few years, three new oral DMDs, namely fingolimod, teriflunomide (Aubagio®, Sanofi Aventis, Cambridge, MA, USA), and dimethyl fumarate (Tecfidera®, Biogen Idec, Weston, MA, USA), were approved by the FDA in 2010, 2012, and 2013, respectively. Fingolimod was the first oral therapy approved, and the Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANS-FORMS) showed that fingolimod appeared to be more effective than IM IFN-β_{1a} in reducing the frequency of relapses [3]. The large-scale phase III clinical trials the Teriflunomide Multiple Sclerosis Oral (TEMSO) trial and the Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS (DEFINE) trial also demonstrated that teriflunomide and dimethyl fumarate, respectively, significantly reduced annualized relapse rates, slowed disability progression, and reduced the number of lesions on magnetic resonance imaging [4, 5]. Although these new oral therapies were thought to contribute to the growth of the total costs of multiple sclerosis (MS), so far there is no comprehensive evidence on either the cost effectiveness of the new oral DMDs compared with the established treatment IM IFN-β_{1a}, or incremental cost effectiveness among the oral therapies. For these reasons, this paper compares the cost effectiveness of fingolimod, teriflunomide, dimethyl fumarate, and IM IFN-β_{1a} as first-line therapies in the treatment of patients diagnosed with RRMS.

2 Materials and Methods

2.1 Model Overview

The cost-effectiveness analysis was conducted from a US societal perspective over a 5-year time horizon. We chose 5-year rather than 10-year or life time as the time horizon because (1) extrapolating a 1- or 2-year randomized controlled trial (RCT) over long time horizons requires more unreliable assumptions on model extrapolations [6] and (2) high discontinuation rates imply that a large proportion of patients will discontinue or develop secondary-progressive multiple sclerosis (SPMS) over time [3–5, 7]. Costs were reported in 2012 US dollars, and both costs and outcomes were discounted at a 3 % annual rate in the base case scenario. The primary outcome was incremental net monetary benefit (INMB), and the secondary outcome was incremental cost-effectiveness ratios (ICERs). INMB was chosen as the primary outcome since, when comparing multiple treatment options, it more clearly delineates treatments with dominance or extended dominance [8, 9]. The willingness-to-pay (WTP) threshold was assumed to be US$150,000 per quality-adjusted life year (QALY), which is three times the 2012 US gross domestic product (GDP) per capita, as recommended by the World Health Organization [10, 11]. The choice of US$150,000 as the WTP threshold rather than the antiquated US$50,000 value in the US context is also supported by the study of Braithwaite et al. [12] and is used in numerous previous studies [13–16].

A Markov model was developed in Microsoft® Excel to simulate the disease progression of patients with RRMS (Fig. 1). The cycle is 1 month. The comparators included oral fingolimod at a daily dose of 0.5 mg, oral teriflunomide 14 mg once daily, oral dimethyl fumarate 120 mg twice a day for the first 7 days and 240 mg twice a day after 7 days, and IM IFN-β_{1a} at a weekly dose of 30 μg [17]. The disease progression was modeled by the Expanded Disability Status Scale (EDSS), which is most widely used in the measurement of MS [18]. Specifically, health

Fig. 1 Markov model for the disease progression of multiple sclerosis. *EDSS* Expanded Disability Status Scale
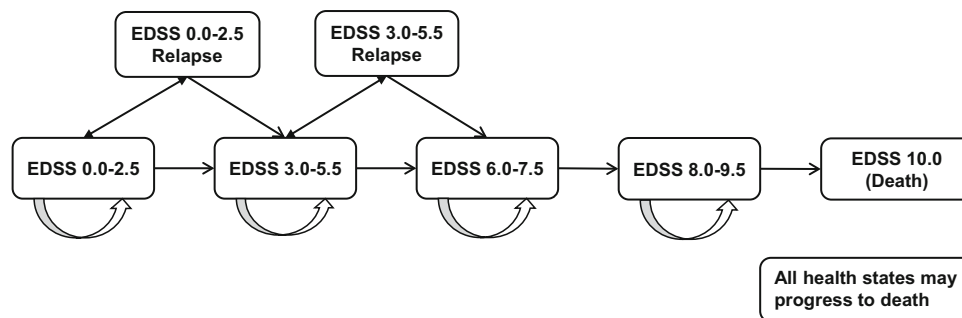
states were divided as EDSS 0.0–2.5 (no or mild disability), EDSS 3.0–5.5 (moderate disability, ambulatory without aid), EDSS 6.0–7.5 (waking aid required), EDSS 8.0–9.5 (restricted to bed), EDSS 10.0 (death) and another two relapse states. Since MS is a progressive disease, patients were assumed to only progress to a more severe health state or a relapse state.

A cohort of 1,000 patients was assumed to enter the model. Consistent with the clinical trials, all patients were initially distributed to EDSS 0.0–2.5 and 3.0–5.5 states and treated with first-line DMDs [3–5]. The EDSS distribution ratio between the two states was estimated from a national cross-sectional survey [19]. In any cycle during the simulation, patients could discontinue the drug and then transition to a second-line treatment, natalizumab, or to the symptom management (SM) arm without active drug therapy. Moreover, patients could also discontinue natalizumab due to insufficient response or adverse events and then switch to SM treatment.

The decision to choose natalizumab as the second-line therapy was based on the fact that (1) natalizumab was specifically indicated for use when previous DMDs failed, as recommended by American Academy of Neurology [20]; (2) a retrospective cohort study found that approximately 10 % of patients who were initially treated with IFN-β or glatiramer acetate (GA) experienced breakthrough disease and either switched to natalizumab or an immunosuppressant (e.g., mitoxantrone) or declined new therapy [21] (however, according to another study, which followed a cohort from 2000 to 2008, only 1 % of the first-line and second-line DMD populations used mitoxantrone [22]); and (3) other first-line drugs are often used as second-line therapies, despite not being indicated after failure of a previous DMD, and they are actually similar in

efficacy; however, there is evidence that switching to natalizumab is more effective than switching to other first-line drugs [23]. Therefore, patients were assumed to receive natalizumab as second-line therapy.

Patients in EDSS 0.0–2.5 and 3.0–5.5 states would likely transition to a temporary state of relapse and stay for a cycle (1 month). Following a relapse, patients could transition back to the previous state or progress to a next more severe health state. According to a recent natural history study of SPMS, for patients initially diagnosed with RRMS, 80.0 % reached SPMS at or before EDSS 6.0 and 99.5 % at or before EDSS 8.0 [24]. That is to say, for those transitioned to EDSS 6.0, at least 80 % of the patients would have already reached SPMS, and so would almost all of the patients who progressed to EDSS 8.0. Therefore, it was assumed that patients in EDSS 6.0–7.5 and EDSS 8.0–9.5 had developed SPMS and thus were not associated with further relapses. Since these DMDs are indicated for relapse forms of MS, patients transitioned to EDSS 6.0–7.5 and EDSS 8.0–9.5 would stop DMD treatment and then be treated with SM.

The model design in this paper was consistent with previous cost-effectiveness studies comparing DMDs in that the same health states were classified and the same disease progression path was defined [2, 25–27]. The health states were decided in a way that the transition points (EDSS 3.0, 6.0, 8.0, and 10) reflected key disability levels in the natural history of MS and are critical in defining clinical course [7, 28–30]. In our model, we also allowed the patients to switch to second-line DMD treatment when they discontinued the first-line therapy, to better reflect clinical practice [20, 31]. In addition, we had each author verify the model equations and computations independently to ensure the internal validity [32].

Table 1 Baseline characteristics of the patients

Variable	FREEDOMS [33]		TRANSFORMS [3]		TEMSO [4]	DEFINE [5]
	Placebo	FIN	FIN	IM IFN-β₁ₐ	TER	DF
Demographic characteristics						
Age, years						
Mean ± SD	37.2 ± 8.6	36.6 ± 8.8	36.7 ± 8.8	36.0 ± 8.3	37.8 ± 8.2	38.1 ± 9.1
Median (range)	37.0 (18–55)	36.0 (18–55)	37 (18–55)	36 (18–55)	–	–
Female sex, %	71.30	69.60	65.40	67.80	71	72
White race, %	–	–	93.70	93.80	96.90	78
Clinical characteristics						
Relapses, No.						
In previous year, mean ± SD	1.4 ± 0.7	1.5 ± 0.8	1.5 ± 1.2	1.5 ± 0.8	1.3 ± 0.7	1.3 ± 0.7
In previous 2 years, mean ± SD	2.2 ± 1.2	2.1 ± 1.1	2.3 ± 2.2	2.3 ± 1.2	2.2 ± 1.0	–
EDSS score, mean ± SD	2.5 ± 1.3	2.3 ± 1.3	2.24 ± 1.33	2.19 ± 1.26	2.67 ± 1.24	2.40 ± 1.29

DF dimethyl fumarate, *EDSS* Expanded Disability Status Scale, *FIN* fingolimod, *IFN* interferon, *IM* intramuscular, *TER* teriflunomide

2.2 Patient Characteristics

The baseline characteristics of the modeled patients were very similar in the phase III clinical trials across the four DMDs (Table 1) [3–5, 33]. Generally, patients were between 18 and 55 years old, had a diagnosis of RRMS, had had at least two relapses during the previous 2 years or at least one relapse during the previous year before randomization, and had an EDSS score of 0–5.5. Based on a national survey study, the initial proportions of patients distributed in EDSS 0.0–2.5 and EDSS 3.0–5.5 were estimated at 41.3 and 58.7 %, respectively [19].

2.3 Transition Probabilities

Transition probabilities for disease progression, relapses, and discontinuation were obtained from the literature and modeled using the DEALE method (Table 2) [3–5, 33–36]. For patients in SM, the EDSS progression probabilities were estimated from the London Ontario natural history study of MS [7]. The London Ontario data were used because, unlike in other studies, the patients in the study did not receive disease-modifying therapies and the database was subjected to a rigorous quality review in 2009 [37]. There were 806 RRMS-onset patients in the database, and the shortest follow-up was 16 years. Since the patients were similar in demographics and clinical characteristics, for patients treated with fingolimod, teriflunomide, dimethyl fumarate, and natalizumab, the hazard ratios of disease progression for DMDs compared with placebo reported in phase III placebo-controlled trials were used to derive the 1-month transition probabilities for each DMD. For the IFN-β_{1a} arm, the hazard ratio from the head-to-head trial TRANSFORMS between fingolimod and IFN-β_{1a} was also used to estimate transition probabilities [3].

The transition probabilities of relapses for patients in SM were obtained from the placebo group in the FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS) trial [33]. Hazard ratios of relapses between DMDs (teriflunomide, dimethyl fumarate, and natalizumab) and placebo were used to derive the transition probabilities to relapse state for the DMDs. For patients treated with fingolimod and IFN-β_{1a}, relapse probabilities were estimated by using the data in the TRANSFORMS trial [3]. All discontinuation rates were extracted from the corresponding phase III clinical trials. After discontinuation of the first-line therapy, the assignment ratio between natalizumab and SM was assumed to be equal in the base case scenario, and extreme cases were tested in sensitivity analyses. Since the mortality rate due to MS is very low, survival probabilities were based on the mortality rates of the general population [38]. The age-specific mortality rates were estimated from the life expectancy data in national vital statistics reports using the DEALE method [35, 36, 39].

2.4 Utilities

Since utilities were not available in the pivotal RCTs, we reviewed the literature and identified the best available evidence to support the utility estimates. The utilities for each health state from EDSS 0.0 to EDSS 9.5 and the disutility for IFN-β_{1a} were obtained from the Prosser et al. [40] quality-of-life study. The study used the standard-gamble method to measure patient and community preferences for treatments and health states in patients with RRMS. The Prosser et al. [41] study was used because standard-gamble was thought to be the gold standard in preference elicitation since it is the only method that estimates Von-Neumann–Morgenstern utility (preference measured under uncertainty) [41]. Also, since this study was performed from a societal perspective, use of community preferences was more appropriate as it reflected the society's preference on the resource allocation [42]. Disutility for relapses was based on the Kobelt et al. study [19]. For the effects of fingolimod and natalizumab, though there was evidence that fingolimod and natalizumab could improve the quality of life of MS patients significantly [43–45], no study on utility impacts was available. Therefore, to be conservative, the disutility for fingolimod and natalizumab was assumed to be 0 in the base case scenario. Changes in assumed base case utility were explored in sensitivity analyses. For teriflunomide, one study has demonstrated that there was no disutility associated with administration of teriflunomide, so the impact of teriflunomide on utility was assumed to be 0 in the base case analysis [46]. Dimethyl fumarate has been reported to have significant improvements in physical and mental aspects of health and functioning, where the change in EQ-5D value was 0.01 [47, 48]. The base case utilities and the effects of DMDs on utilities are shown in Table 2.

2.5 Costs

Costs in the model were mainly obtained from the cost-of-illness study by Kobelt et al. [19] and inflated to 2012 dollars (Table 2). We applied the results from the Kobelt et al. [19] study because the costs were reported on the basis of stratified EDSS score, which corresponded to each health state in our model. The costs included costs of hospital inpatient care, ambulatory care, tests, drugs (DMDs and other drugs), services, adaptations and costs of informal care. The productivity losses were not included, because the costs associated with productivity were captured in the QALYs [49]. All drug costs were obtained

Table 2 Parameters and range in one-way sensitivity analysis

Parameters	Base case	One-way SA range[a]		Sources
Monthly probability of disease progression (SM)				
EDSS 0.0–2.5	0.005760	N/A		[7]
EDSS 3.0–5.5	0.007194			[7]
EDSS 6.0–7.5	0.005760			[7]
Monthly probability of progressing to death				
EDSS 0.0–2.5	0.001684	N/A		[39]
EDSS 3.0–5.5	0.002348			[39]
EDSS 6.0–7.5	0.003121			[39]
EDSS 8.0–9.5	0.004457			[39]
Annual relapse rate for SM	0.400	N/A		[39]
Annual relapse rate for FIN	0.160	0.120	0.200	[3]
Annual relapse rate for IM IFN-β₁ₐ	0.330	0.248	0.413	[3]
HR of disease progression				
FIN vs. SM	0.700	0.525	0.875	[33]
IM IFN-β₁ₐ vs. FIN	1.353	1.015	1.692	[3]
TER vs. SM	0.700	0.525	0.875	[4]
DF vs. SM	0.620	0.465	0.775	[5]
NAT vs. SM	0.580	N/A		[34]
HR of annual relapse rate				
TER vs. SM	0.720	0.540	0.900	[4]
DF vs. SM	0.510	0.383	0.638	[5]
NAT vs. SM	0.410	N/A		[34]
Annual discontinuation rate for FIN	0.103	0.077	0.128	[3]
Annual discontinuation rate for IM IFN-β₁ₐ	0.118	0.089	0.148	[3]
Discontinuation rate for TER, 2 year	0.265	0.199	0.332	[4]
Discontinuation rate for DF, 2 year	0.310	0.233	0.388	[5]
Discontinuation rate for NAT, 2 year	0.083	N/A		[34]
Assignment ratio between NAT and SM	0.5:0.5	0:1	1:0	
Utilities estimates				
Utility EDSS 0.0–0–2.5	0.899	0.674	1	[40]
Utility EDSS 3.0–0–5.5	0.821	0.616	1	[40]
Utility EDSS 6.0–0–7.5	0.769	0.577	0.961	[40]
Utility EDSS 8.0–0–9.5	0.491	0.368	0.614	[40]
Disutility for relapse	−0.094	−0.071	−0.118	[19]
Disutility for IM IFN-β₁ₐ	−0.115	−0.086	−0.144	[40]
Impact of FIN on utility	0	−0.03	0.03	[43, 44]
Impact of TER on utility	0	−0.03	0.03	[46]
Impact of DF on utility	0.01	−0.03	0.03	[47, 48]
Impact of NAT on utility	0	N/A		[45]
Monthly costs, 2012 US dollars				
WAC for FIN	$4,164	$3,123	$5,204	[50]
WAC for IM IFN-β₁ₐ	$3,835	$2,876	$4,794	[50]
WAC for NAT	$3,320	$2,490	$4,150	[50]
WAC for TER	$3,704	$2,778	$4,630	[50]
WAC for DF	$3,346	$2,509	$4,182	[50]
Cost of EDSS 0.0–2.5	$615	$1,298	$2,163	[19]
Cost of EDSS 3.0–5.5	$1,289	$2,768	$4,614	[19]
Cost of EDSS 6.0–7.5	$3,198	$4,047	$6,744	[19]
Cost of EDSS 8.0–9.5	$6,369	$8,093	$13,489	[19]
Cost of relapse	$5,008	$3,756	$6,259	[51]
Discount rate	0.03	0	0.05	
Time horizon	5 years	2 years	10 years	

DF dimethyl fumarate, *EDSS* Expanded Disability Status Scale, *FIN* fingolimod, *HR* hazard ratio, *IFN* interferon, *IM* intramuscular, *NAT* natalizumab, *SA* sensitivity analysis, *SM* symptom management, *TER* teriflunomide, *WAC* wholesale average cost

[a] ±25 % unless indicated

from the Federal Supply Schedule drug prices [50]. Costs of relapses were estimated from a cross-sectional, web-based survey that investigated the impacts of relapses on costs and quality of life for patients with RRMS in the USA [51].

2.6 Sensitivity Analysis

One-way sensitivity analyses were conducted to test the robustness of the pairwise comparisons of three oral therapies versus IM IFN-β_{1a} and the robustness of the optimal therapy selection by using INMB as the outcome. The base case inputs of the parameters were varied by 25 % in both positive and negative directions, unless indicated otherwise (Table 2). We varied the parameters by 25 % so that the upper and lower bound of the sensitivity analysis range differed markedly from the base case inputs. The 25 % variation ranges of the parameters were also comparable to their corresponding 95 % confidence intervals where available. Key parameters that may affect the disease progression, utilities and costs were included in the analysis. In addition, a threshold analysis was conducted if a

parameter variation resulted in a major change in conclusion [49]. Tornado diagrams were plotted in the order from most sensitive parameter to least sensitive. Moreover, sensitivity to time horizon was specifically tested by varying the time horizon from 2 to 30 years under both discounted and non-discounted scenarios.

The robustness of the base case results was also tested by probabilistic sensitivity analysis based on a second order Monte Carlo simulation (1,000 times). Choice of the distribution for the model inputs was based on the recommendations and reflected how the confidence interval of each parameter was estimated [52]. The distributions of hazard ratios and annual relapse rates were assumed to be log-normal [53]. Utilities were assumed to follow a beta distribution which is confined between 0 and 1 [53]. Health care costs for each health state and drug acquisition costs were assumed to follow a gamma distribution [53]. The result of the probabilistic sensitivity analysis was reported as the probability of each drug maximizing the net monetary benefits (NMBs) over the range of WTPs [54]. That is the probability of each drug being the optimal therapy.

Table 3 Results for the base case scenario (WTP = US$150,000)

DMDs	Cost	QALY	NMB	INMB vs. IM IFN-β_{1a}	ICER vs. IM IFN-β_{1a}	ICER: FIN vs. TER
IM IFN-β_{1a}	$223,606	3.34	$276,745	–	–	–
TER	$226,085	3.68	$326,525	$49,780	$7,115	–
FIN	$239,947	3.69	$313,312	$36,567	$46,328	$3,201,672
DF	$200,145	3.72	$357,356	$80,611	Dominant	–

DF dimethyl fumarate, *DMDs* disease-modifying drugs, *FIN* fingolimod, *ICER* incremental cost-effectiveness ratio, *IFN* interferon, *IM* intramuscular, *INMB* incremental net monetary benefit, *NMB* net monetary benefit, *QALY* quality-adjusted life year, *TER* teriflunomide, *WTP* willingness to pay

Fig. 2 Net monetary benefits of the disease-modifying drugs. *IFN* interferon, *IM* intramuscular
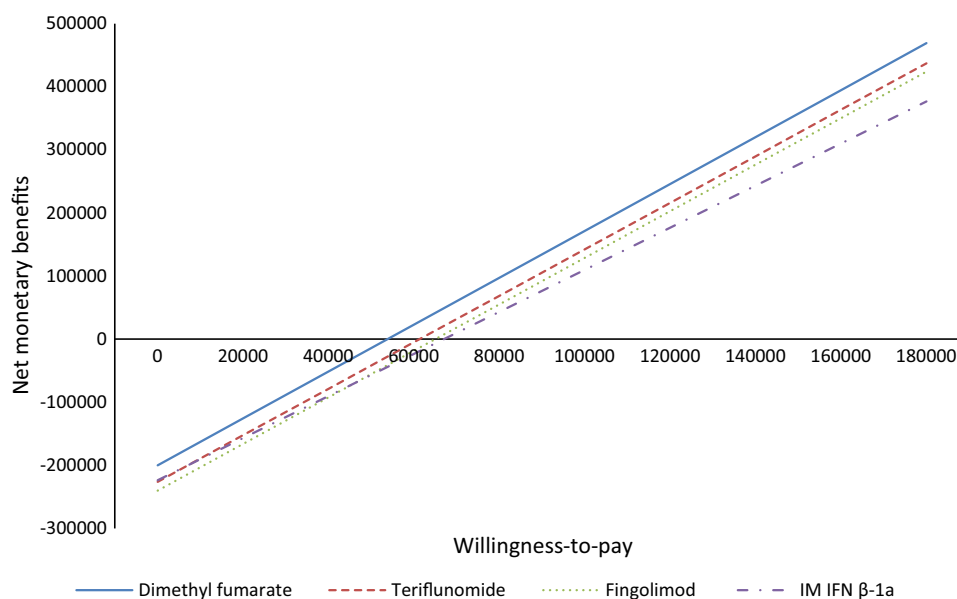
Fig. 3 Results for one-way sensitivity analysis. *DF* dimethyl fumarate, *EDSS* Expanded Disability Status Scale, *FIN* fingolimod, *IFN* interferon, *IM* intramuscular, *NAT* natalizumab, *SM* symptom management, *TER* teriflunomide, *WAC* wholesale average cost, *yr* years

(a) Fingolimod vs. IM IFN β-1a

Monthly WAC for FIN
Monthly WAC for IM IFN β-1a
Time horizon
Impact of FIN on utility
Disutility for IM IFN β-1a
Annual discontinuation rate for IM IFN β-1a
Annual discontinuation rate for FIN
Utility EDSS 6.0-0-7.5
Discount rate
Assignment ratio between NAT and SM

Incremental net monetary benefit

(b) Teriflunomide VS. IM IFN β-1a

Monthly WAC for TER
Monthly WAC for IM IFN β-1a
Time horizon
Impact of TER on utility
Disutility for IM IFN β-1a
Annual discontinuation rate for IM IFN β-1a
Discontinuation rate for TER, 2yr
Assignment ratio between NAT and SM
Utility EDSS 6.0-0-7.5
Discount rate

Incremental net monetary benefit

(c) Dimethyl fumarate VS. IM IFN β-1a

Time horizon
Monthly WAC for IM IFN β-1a
Monthly WAC for DF
Disutility for IM IFN β-1a
Impact of DF on utility
Annual discontinuation rate for IM IFN β-1a
Assignment ratio between NAT and SM
Discontinuation rate for DF, 2yr
Discount rate
Utility EDSS 6.0-0-7.5

Incremental net monetary benefit

3 Results

3.1 Base-Case Scenario

Over 5 years, the total costs per patient were estimated at US$223,606, US$239,947, US$226,085, and US$200,145 for IM IFN-β₁ₐ, fingolimod, teriflunomide, and dimethyl fumarate, respectively (Table 3). The accumulated QALYs were 3.34, 3.69, 3.68, and 3.72 for IM IFN-β₁ₐ, fingolimod, teriflunomide, and dimethyl fumarate, respectively. Assuming a WTP at US$150,000, the NMBs were at US$276,745, US$313,312, US$326,525, and US$357,356 for each of the DMDs above. Having the lowest costs and

highest QALYs, dimethyl fumarate dominated all other drugs.

Compared with IM IFN-β₁ₐ, the INMBs were US$36,567, US$49,780, and US$80,611 for fingolimod, teriflunomide, and dimethyl fumarate, respectively (Table 3). The NMBs of the four DMDs over a range of WTPs are shown in Fig. 2. As long as the WTP was greater than US$100,000, NMBs of all the drugs would be greater than zero. Dimethyl fumarate dominated all other drugs across the range of WTPs.

The ICERs for fingolimod and teriflunomide compared with IM IFN-β₁ₐ were US$46,328 and US$7,115, respectively, so both fingolimod and teriflunomide are cost

effective compared with IM IFN-β_{1a}. In addition, the ICER of fingolimod compared against teriflunomide was US\$3,201,672 (Table 3). Therefore, apart from dimethyl fumarate, teriflunomide was the most cost effective therapy at a WTP threshold of US\$150,000.

3.2 One-Way Sensitivity Analysis

The ten most sensitive parameters are shown in Fig. 3. Generally, the results for base case analysis were stable to the change in most parameters. For the comparison between fingolimod and IM IFN-β_{1a} (Fig. 3a), the monthly costs for fingolimod and IM IFN-β_{1a} were the most sensitive parameters. When the monthly cost for fingolimod exceeded US\$5,132, fingolimod was no longer cost effective. A decrease in the cost of IM IFN-β_{1a} substantially reduced the INMB, but fingolimod still remained cost effective. For the sensitivity analysis of teriflunomide and dimethyl fumarate compared with IM IFN-β_{1a} (Fig. 3b, c), the INMBs were consistently greater than 0. For all of the three oral therapies versus IM IFN-β_{1a}, INMB increased as the time horizon became longer under both discounted and non-discounted cases (Fig. 4), indicating oral therapies are associated with greater benefits for long-term care.

For the sensitivity analysis of therapy selection, dimethyl fumarate remained the optimal therapy in almost all of the cases. The result was only sensitive to the monthly cost for teriflunomide. If the monthly cost for teriflunomide was lower than US\$2,908, teriflunomide would be the most cost-effective therapy.

3.3 Probabilistic Sensitivity Analysis

Figure 5 shows the probability that each drug maximized the NMBs. Over the range of WTPs, the probability that dimethyl fumarate was the highest value therapy always exceeded 90 %. As a result, both teriflunomide and fingolimod had a less than 10 % chance of having the highest value. However, the probability for teriflunomide being preferred was constantly higher than that for fingolimod. Finally, IM IFN-β_{1a} had a negligible probability of being the highest value treatment.

4 Discussion

This paper evaluated the cost effectiveness of three oral therapies, fingolimod, teriflunomide, and dimethyl fumarate, compared with IM IFN-β_{1a} as first-line therapies in the treatment of RRMS patients. A Markov model based on EDSS disability level was developed to simulate disease progression over a 5-year time horizon.

To our knowledge, this is the first paper to compare the cost effectiveness of the new oral DMDs comprehensively and incorporate second-line therapy in the model. Model results favored oral therapies in economic and health benefits compared with IM IFN-β_{1a}. Over a range of time horizons and WTPs, dimethyl fumarate was always the dominant strategy because of high QALY gained and low total costs. Leaving aside the dominance of dimethyl fumarate, given a WTP threshold of

Fig. 4 Incremental net monetary benefit vs. intramuscular interferon-β_{1a}
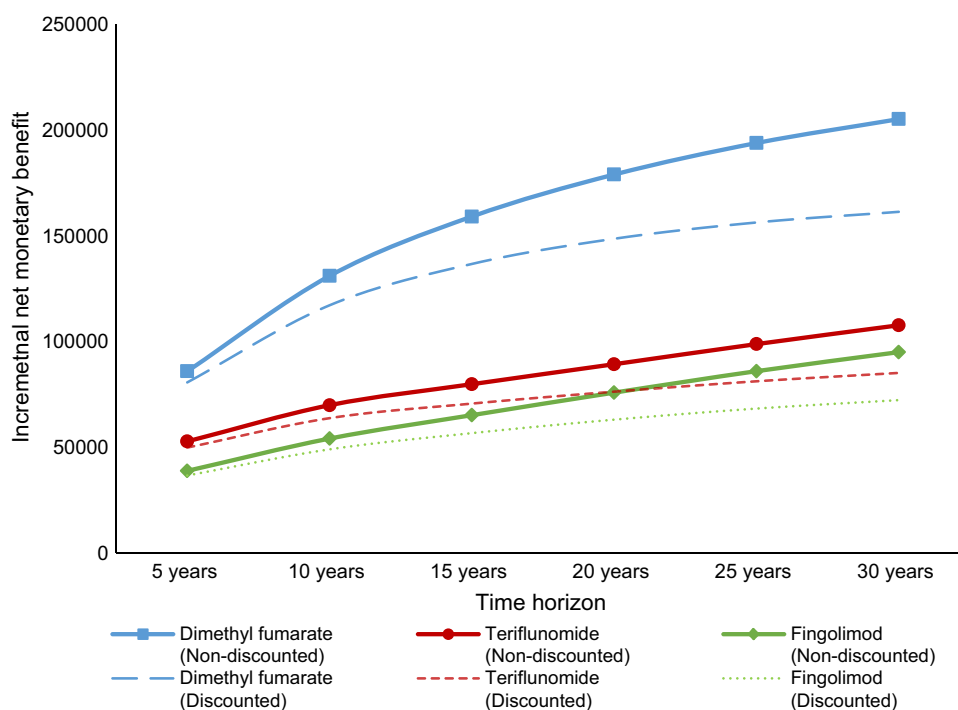
Fig. 5 Probability that each therapy maximizes NMB. *IFN* interferon, *IM* intramuscular, *NMB* net monetary benefit
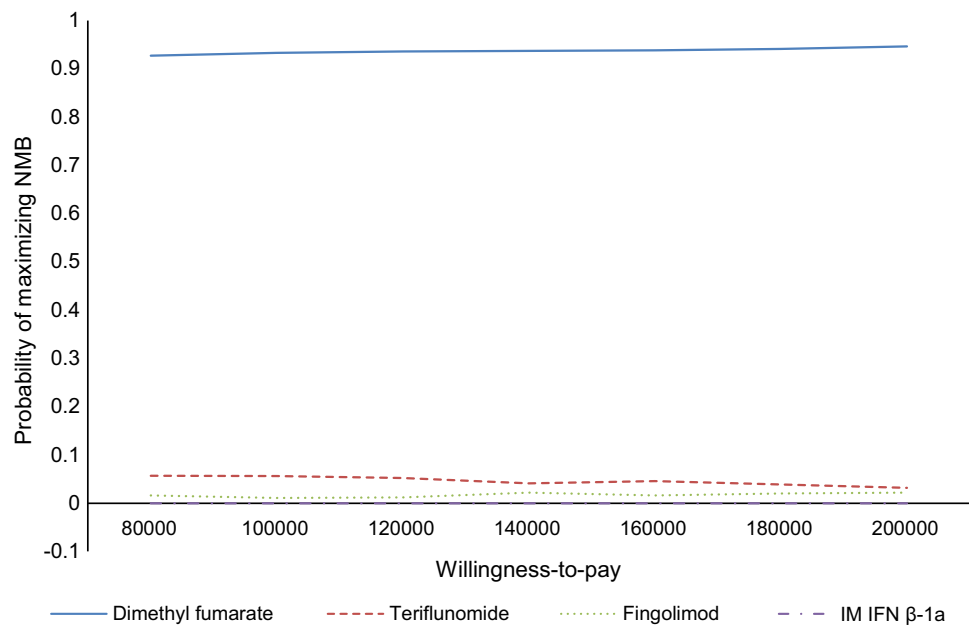
US$150,000, fingolimod and teriflunomide were cost effective compared with IM IFN-β₁ₐ, with ICERs of US$46,328 and US$7,115, respectively. However, fingolimod was not cost effective compared with teriflunomide, and thus teriflunomide was the most cost-effective therapy after dimethyl fumarate. One-way sensitivity analyses indicated that model results were most sensitive to acquisition costs for DMDs and time horizon, yet the results were rarely reversed and the decision-making rankings based on the results were robust in one-way sensitivity analyses. Probabilistic sensitivity analysis also showed dimethyl fumarate was the optimal therapy most of the time, whereas teriflunomide was the second best choice.

In prior studies, fingolimod was the only oral therapy that was evaluated using cost-effectiveness analysis. Lee et al. [2] compared fingolimod with IM IFN-β₁ₐ by building a Markov model on a 10-year time horizon. They estimated the ICER for fingolimod at US$73,975 compared with US$46,328 in this paper. However, given the annual discontinuation rate of about 10 %, a 10-year time horizon would imply that essentially all patients would have discontinued by the end of the simulation. Moreover, since Lee et al. [2] ignored second-line treatments, their results may not be realistic. O'Day et al. [55] compared fingolimod with natalizumab in the treatment of RRMS, with incremental cost per relapse avoided as the outcome. The study found that natalizumab dominated fingolimod since it was less costly and more effective in reducing relapses. Natalizumab was not included as a comparator in this study, because it is recommended for use after alternative therapies failed, while fingolimod has been approved as a first-line therapy.

This study is subject to some limitations. First, all data on the effects of the DMDs, such as hazard ratio of disease progression, annual relapse rates, and discontinuation rates, were taken from the corresponding phase III RCTs. Though RCTs are thought to have strong internal validity, their external validity is often limited. Also, hazard ratios extracted from RCTs that do not compare all of the active comparators are not an ideal data. However, since the oral DMDs have been available in the US market for about 4 years, there is a limited number of RCTs and no high-quality meta-analyses are available. Therefore, the large-scale phase III pivotal clinical trials with each drug compared with placebo constitute the best available evidence we could have at this point. Finally, as mentioned above, given the clinical trial follow-up periods of 1–2 years, extrapolating the time horizon to 5 years required modeling assumptions. For example, we assumed that the drug treatment effects would persist over a 5-year time horizon. However, our model sensitivity analysis demonstrated that the results were stable at a 2-year time horizon.

Second, the disease progression parameters for the SM were estimated from the London Ontario natural history study data, which were collected decades ago [7]. The disease progression of patients today may be different from the progression rate when the data were collected. Also, the data collected in Canada may not be generalizable to the US population. However, other natural study data are either inaccessible or are not proper for this analysis. For example, The Olmsted County study had patients on DMD treatment and the British Columbia study did not report information required for this analysis [56, 57]. Therefore, the London Ontario study is still the best source we could use to estimate the probabilities for the SM arm.

text

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