

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.

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

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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 (TRANSFORMS) 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 (TEMSEO) 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.

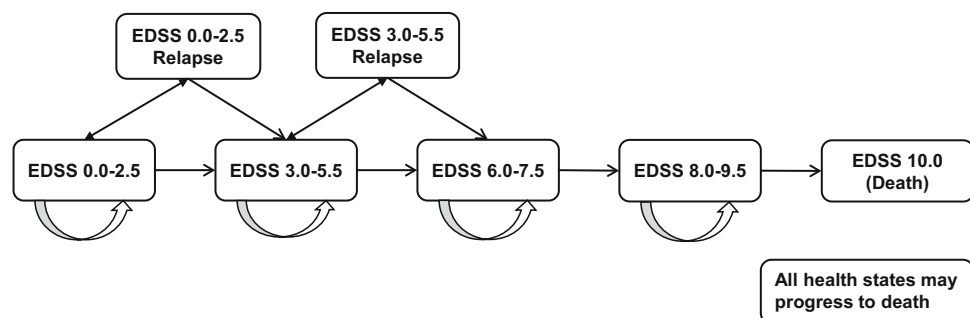
2 Materials and Methods

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 μ g [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 (walking 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]		TEMPO [4]	DEFINE [5]
	Placebo	FIN	FIN	IM IFN β_{1a}	TER	DF
Demographic characteristics						
Age, years						
Mean \pm SD	37.2 \pm 8.6	36.6 \pm 8.8	36.7 \pm 8.8	36.0 \pm 8.3	37.8 \pm 8.2	38.1 \pm 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 \pm SD	1.4 \pm 0.7	1.5 \pm 0.8	1.5 \pm 1.2	1.5 \pm 0.8	1.3 \pm 0.7	1.3 \pm 0.7
In previous 2 years, mean \pm SD	2.2 \pm 1.2	2.1 \pm 1.1	2.3 \pm 2.2	2.3 \pm 1.2	2.2 \pm 1.0	
EDSS score, mean \pm SD	2.5 \pm 1.3	2.3 \pm 1.3	2.24 \pm 1.33	2.19 \pm 1.26	2.67 \pm 1.24	2.40 \pm 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 0–2.5 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- β_{1a}	0.330	0.248	0.413	[3]
HR of disease progression				
FIN vs. SM	0.700	0.525	0.875	[33]
IM IFN- β_{1a} 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- β_{1a}	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- β_{1a}	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- β_{1a}	\$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

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