

# Cost-effectiveness of oral agents in relapsing-remitting multiple sclerosis compared to interferon-based therapy in Saudi Arabia

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**BACKGROUND:** Promising clinical and humanistic outcomes are associated with the use of new oral agents in the treatment of relapsing-remitting multiple sclerosis (RRMS). This is the first cost-effectiveness study comparing these medications in Saudi Arabia.

**OBJECTIVES:** We aimed to compare the cost-effectiveness of fingolimod, teriflunomide, dimethyl fumarate, and interferon (IFN)- $\beta$ 1a products (Avonex and Rebif) as first-line therapies in the treatment of patients with RRMS from a Saudi payer perspective.

**DESIGN:** Cohort Simulation Model (Markov Model).

**SETTING:** Tertiary care hospital.

**METHODS:** A hypothetical cohort of 1000 RRMS Saudi patients was assumed to enter a Markov model with a time horizon of 20 years and an annual cycle length. The model was developed based on an expanded disability status scale (EDSS) to evaluate the cost-effectiveness of the five disease-modifying drugs (DMDs) from a healthcare system perspective. Data on EDSS progression and relapse rates were obtained from the literature; cost data were obtained from King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. Results were expressed as incremental cost-effectiveness ratios (ICERs) and net monetary benefits (NMB) in Saudi Riyals and converted to equivalent \$US. The base-case willingness-to-pay (WTP) threshold was assumed to be \$100 000 (SAR375 000). One-way sensitivity analysis and probabilistic sensitivity analysis were conducted to test the robustness of the model.

**MAIN OUTCOME MEASURES:** ICERs and NMB.

**RESULTS:** The base-case analysis results showed Rebif as the optimal therapy at a WTP threshold of \$100 000. Avonex had the lowest ICER value of \$337 282/QALY when compared to Rebif. One-way sensitivity analysis demonstrated that the results were sensitive to utility weights of health state three and four and the cost of Rebif.

**CONCLUSION:** None of the DMDs were found to be cost-effective in the treatment of RRMS at a WTP threshold of \$100 000 in this analysis. The DMDs would only be cost-effective at a WTP above \$300 000.

**LIMITATIONS:** The current analysis did not reflect the Saudi population preference in valuation of health states and did not consider the societal perspective in terms of cost.

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**M**ultiple sclerosis (MS) is a chronic demyelinating disorder of the central nervous system (CNS) that is classified as an immune-mediated inflammatory disease.<sup>1</sup> It is the most common

chronic disabling disease affecting the CNS of young adults in many countries.<sup>2</sup> Women are affected two or three times as often as men.<sup>2</sup> Before 2010, injectable interferon-betas (IFN- $\beta$ ) and glatiramer acetate were

the only available treatment options for relapsing-remitting MS (RRMS) patients. These drugs reduce the frequency of relapses by about one third but are less effective in slowing disability progression compared to newer agents.<sup>3</sup> Although the efficacy of parenteral drugs (subcutaneously or intramuscularly) is well established, non-adherence to these agents for long-term use might contribute to treatment failure. Multiple sclerosis patients also face other barriers to optimal adherence to IFN products. Multiple therapy-related factors such as adverse events (e.g., flu-like symptoms, injection site reactions), efficacy concerns or injection-related factors can result in non-adherence.<sup>4</sup> Many reports about adherence to disease-modifying drugs (DMDs) have indicated that most of the patients discontinue injectable DMD therapy within the first 3-8 years of treatment.<sup>4</sup> For example, a recent study showed that 25% of patients withdrew treatment within the first two years.<sup>5</sup> The occurrence of side effects was the most common reason for patients discontinuation of treatment at this early stage.<sup>5</sup> Thus, using oral agents could be a potential solution for solving medication-related adherence problems associated with injectable DMDs. However, the cost of these new oral agents is much higher than conventional treatments. It is important to note that the medical care required for MS patients and the substantial pharmacy cost imposes an enormous economic burden on policy-makers and caregivers. On average, patients with MS visit their physicians 8 times annually, which is approximately 3 times as often as an individual without the disease.<sup>6</sup> The majority of studies have reported that costs of DMDs occupies a large part of total medical expenditure (64%-91%) in the treatment of MS.<sup>7</sup> Since the introduction of fingolimod in 2010, sales of DMDs have increased sharply in Saudi Arabia and neurologists at King Faisal Specialist Hospital and Research Centre (KFSHRC) started switching patients to oral DMDs. The cost of oral DMDs has increased from SAR 6 million in 2010 to SAR 20 million in 2015.

The Saudi population is dominated by a young generation with only 3% of the population being above the age of 65 and 54% below 18 years of age.<sup>2,8</sup> Unfortunately, recent evidence suggests that there is a moderate to high prevalence of MS in the country, which is approximately 40 to 60 cases per 100000 individuals.<sup>2</sup> Sadly, the mean (SD) age at onset is 25 (5) years, the age at which individuals are planning for their career and lives.<sup>2,8</sup> For these reasons, this study is needed to assess the long-term cost-effectiveness of DMDs in the treatment of RRMS that affects young adults, especially in the absence of head-to-head ran-

domized controlled trials (RCTs) and the lack of population-based observational studies in Saudi Arabia. This study also attempts to evaluate costs associated with each intervention, especially in the current economic downturn. Moreover, this analysis might provide insights on which a treatment option is appropriate for each patient. It might also help in updating treatment guidelines so that guidelines are not based solely on evidence from RCTs, but also from the standpoint of an economic appraisal. To our knowledge, this is the first cost-effectiveness study conducted in Saudi Arabia that utilizes real-world cost data to compare the three new oral agents (fingolimod, teriflunomide, dimethyl fumarate (DMF) and IFN- $\beta$ 1a formulations) in the treatment of RRMS.

## METHODS

### *Model overview*

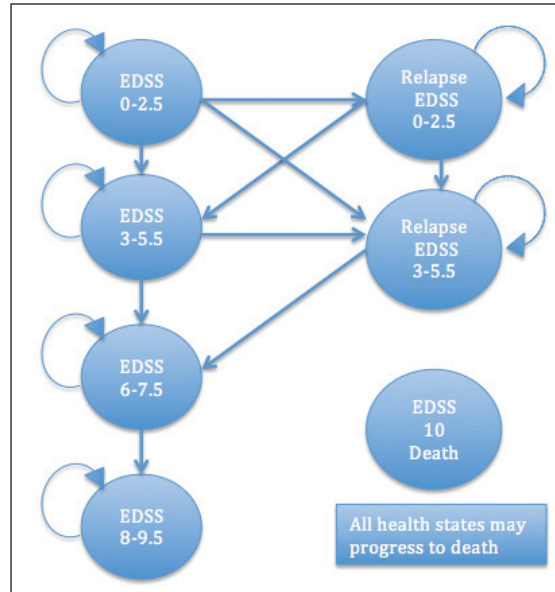
This cost-effectiveness was conducted from a Saudi payer perspective (KFSH&RC). No out-of-pocket costs were incurred by the patients and hence were not included in the assessment, since patients at KFSHRC receive full and free coverage including medications without any copays. A hypothetical cohort of 1000 newly diagnosed RRMS Saudi patients with a mean age of 25 years old were assumed to enter the model. A redesigned Markov model based on a previously published decision model was used to estimate the cost per quality-adjusted life year (QALY) for each treatment option.<sup>9</sup> The model was built in TreeAge Pro software to provide incremental cost-effectiveness ratios (ICERs) and net monetary benefits (NMB) values for five treatment options: IFN- $\beta$  1a IM (Avonex, Biogen, Inc.), IFN- $\beta$  1a SC (Rebif, EMD Serono, USA), fingolimod (Gilenya, Novartis Pharmaceuticals UK Ltd.), teriflunomide (Aubagio, Sanofi-Aventis Pharmaceuticals, Inc.) and dimethyl fumarate (Tecfidera, Biogen, Inc.). The model divided a RRMS course into five health states based on expanded disability status scale (EDSS) scores, as well as on the severity of relapses as shown in **Figure 1**.<sup>9</sup> Relapse is defined as a presence of new or worsening neurological symptom for more than 24 hours with the absence of fever and infection.<sup>10</sup> Intensity of the relapse was classified into three categories: mild, moderate and severe.<sup>11</sup> EDSS health states and severity of relapses have been defined in **Tables 1 and 2**. EDSS is the most commonly used method to evaluate patient quality of life in RRMS, as it is a reliable tool to measure patient physical capacity over time. A 20-year time horizon was used to account for the long-term nature

of the disease. The cycle length was set at 1 year, the time in which patients can remain in the same health state, relapse and stay in the same health state, relapse and progress to the next more severe state; advance to the next severe state, or die.<sup>9,12</sup> Relapses were assumed to occur only in the first and second health states (EDSS 0-7), since the severity of the disease was seen to mask signs and symptoms of relapse beyond EDSS score of 7 according to studies and expert clinical opinion.<sup>9</sup> Adherence rates were assumed to be 100% until the patient reached the EDSS score of 7. All patients were assumed to discontinue DMDs after reaching an EDSS score of 7 since the majority of patients at this stage would have develop secondary progressive MS (SPMS) in which DMDs are no longer effective or show a subtherapeutic response. The model was run until all patients progressed to death as a result of MS or as a consequence of any cause of death. Mortality rates for the Saudi population were obtained from the World Health Organization (WHO) report for 2015.<sup>13</sup> QALYs were used as an outcome in which they were derived from utility weights from the study by Prosser et al.<sup>14</sup> Direct medical costs were obtained from the pharmaceutical care division at KFSHRC. Cost and outcomes were discounted at a 3% rate per annum. All costs were reported in Saudi Riyals (SAR) and converted into the equivalent value of 2015 US dollars. A Saudi payer perspective was adopted to estimate the cost-effectiveness of oral agents versus interferon-based therapy at willingness-to-pay (WTP) of \$100000 (SAR375 500). The current model did not include second-line therapy due to lack of quality-of-life (QOL) data on second-line options used in the treatment of RRMS. All base-case estimates and sensitivity analysis (SA) inputs have been presented in **Table 3**. NMB was reported as a secondary outcome to offer an approach on resource allocation and budget maximization. NMB is a simple technique in which the costs saved by adopting a certain health program can be reported and compared to other alternative programs. It is calculated by first assuming a WTP threshold, then converting health benefits (QALYs) into the common metric of dollars. The cost associated with each treatment strategy is then subtracted, resulting in the net benefit of each strategy expressed in the monetary units.

*Transition probabilities and efficacy data*

Transition probabilities within RRMS health states were derived from Canadian Agency for Drugs and Technologies in Health (CADTH) report based on a long-term observational study performed in Canada.<sup>15,16</sup> The transition probabilities were calculated based on

the efficacy of each treatment option on disability progression and annualized relapse rates. The relative risk (RR) of sustained disability and the relapse rate of the natural history of the disease was multiplied by the RR



**Figure 1.** Schematic representation of modified Markov model.

**Table 1.** Description of Markov model health states.<sup>9</sup>

Health state	Description
Health state 1 (EDSS 0 to 2.5)	No or few limitations in mobility
Health state 2 (EDSS 3 to 5.5)	Moderate limitations in mobility
Health state 3 (EDSS 6 to 7.5)	Walking aid or wheelchair required
Health state 4 (EDSS 8 to 9.5)	Restricted to bed
Health state 5 Death (EDSS 10)	Death due to MS

**Table 2.** Types of relapse.<sup>11</sup>

Severity of relapse	Description
Mild	Symptomatic management by home meds and regular physician office visits
Moderate	Management requires the use of the emergency room (ER), or an observational unit, or administration of acute treatments requiring formal intervention, such as intravenous (IV) methylprednisolone given in an outpatient or home setting.
Severe	Management requires hospital admission.

**Table 3.** Base case estimates and ranges for parameters in one-way sensitivity analysis.

Parameter	Base-case	One-way SA range	Source
Annual probability of disease progression (natural history of the disease)			
EDSS 0	0.144	0.1296-0.1584	CADTH <sup>9</sup>
EDSS 1	0.075	0.0675-0.0825	CADTH <sup>9</sup>
EDSS 2	0.152	0.1368-0.1672	CADTH <sup>9</sup>
EDSS 3	0.272	0.2448-0.2992	CADTH <sup>9</sup>
EDSS 4	0.45	0.405-0.495	CADTH <sup>9</sup>
EDSS 5	0.485	0.4365-0.5335	CADTH <sup>9</sup>
EDSS 6	0.283	NA	
EDSS 7	0.342	NA	
EDSS 8	0.105	NA	
EDSS 9	0.167	NA	
Relative risk of sustained disability progression of DMDs			
Avonex	0.868	0.668-1.091	CADTH <sup>9</sup>
Rebif	0.836	0.613-1.083	CADTH <sup>9</sup>
Fingolimod	0.763	0.521-1.036	CADTH <sup>9</sup>
Teriflunomide	0.803	0.499-1.150	CADTH <sup>9</sup>
DMF	0.734	0.528-0.974	CADTH <sup>9</sup>
Relative Risk of Relapse rate of DMDs			
Avonex	0.864	0.766-0.974	CADTH <sup>9</sup>
Rebif	0.678	0.599-0.758	CADTH <sup>9</sup>
Fingolimod	0.443	0.375-0.525	CADTH <sup>9</sup>
Teriflunomide	0.743	0.592-0.924	CADTH <sup>9</sup>
DMF	0.506	0.437-0.590	CADTH <sup>9</sup>
Utility weight of each health state			
EDSS 0-2.5	0.954	0.936-0.971	Prosser <sup>14</sup>
EDSS 3-5.5	0.870	0.823-0.917	Prosser <sup>14</sup>
EDSS 6-7.5	0.769	0.68-0.858	Prosser <sup>14</sup>
EDSS 8-9.5	0.491	0.372-0.607	Prosser <sup>14</sup>
EDSS 10 (Death)	0.000	0.000	Prosser <sup>14</sup>
Disutility of mild/ moderate relapse	-0.091	-0.063 to -0.0119	Prosser <sup>14</sup>
Disutility of severe relapse	-0.302	-0.366 to -0.238	Prosser <sup>14</sup>
Annual cost of DMDs per patient (\$US, 2015)			
Avonex	27,444	15,087-27,444	KFSH&RC, SFDA
Rebif	5,184	5,184-15,264	KFSH&RC, SFDA

**Table 3 (cont).** Base case estimates and ranges for parameters in one-way sensitivity analysis.

Parameter	Base-case	One-way SA range	Source
Fingolimod	32,132	32,132-32,967	KFSH&RC, SFDA
Teriflunomide	24,980	12,480-24,980	KFSH&RC, SFDA
DMF	38,842	19,535-38,842	KFSH&RC, SFDA
Average annual cost of each health state per patient (\$US, 2015)			
Cost of EDSS 0-2.5	1,123	NA	Calculated
Cost of EDSS 3-5.5	13,708	NA	Calculated
Cost of EDSS 6-7.7	19,406	NA	Calculated
Cost of EDSS 8-9.5	20,101	NA	Calculated
Average cost per patient per event (\$US, 2015)			
Cost of mild relapse	150	NA	KFSH&RC
Cost of moderate relapse	500	NA	KFSH&RC
Cost of sever relapse	3283	NA	KFSH&RC
Discount rate	0.03 (3%)	NA	-
Time horizon	20 years	NA	-

EDSS: Expanded Disability Status Scale, SA: sensitivity analysis, DMDs: Disease-modifying Drugs, Avonex: Interferon  $\beta$ -1a intramuscular (IM), Rebif: Interferon  $\beta$ -1a Subcutaneous (SC), DMF: Dimethyl Fumarate, KFSH&RC: King Faisal Specialist Hospital and Research Centre, SFDA: Saudi Food and Drug Authority

of the sustained disability and relapse rate of each treatment option path to obtain the transition probability for each health state and sub-state. This study assumed that mild/moderate relapses accounted for 77% and kept patients in the same state calculating the state reward as disutility for mild relapses, while severe relapses (23%) were assumed to transit the patient to the next severe state calculating the state rewards in disutility for severe relapses.<sup>9</sup> The probability of relapses was estimated for each treatment option using the same technique. Patients who discontinued treatment progress according to the rates for disability progression of the natural history of the disease but retain benefits received. Since the mortality rate due to MS is very low, survival probabilities were based on the mortality rates of the general population in Saudi Arabia. The age-specific mortality rates for females who are at a higher risk of developing MS were used in the model. Death rates were derived from life expectancy table data reported by WHO for the Saudi population in 2015 (latest).<sup>13</sup>

#### Utilities: QALYs

Health benefits were measured in the form of QALYs, a preference-based measure that combines both mortality and morbidity of life-years gained from adopting

a certain intervention or using a specific treatment. Since utility weights were not available in randomized control trials (RCTs), the literature was reviewed and identified for the best source of information that serves the current model design. Utility weights for each health state and disutilities of relapses were obtained from the Prosser study.<sup>14</sup> Prosser et al used the standard gamble method to measure patients and community preferences in valuing health states and benefits offered by each treatment. Utility scores obtained from the Prosser study were gathered via a 30-minute computer interview administered to a convenience sample from San Diego, USA.<sup>14</sup> QALYs were discounted at 3 % per year.

#### Cost

Since this study adopted a payer perspective (KFSHRC), only direct medical costs were included in the analysis. All costs were presented in local currency (Saudi Riyals) and converted into equivalent US dollars. Cost data were gathered for more than 400 real MS patients identified through the Venus billing system by CPT code 99215 for neuroimmunology clinic visits in 2015. The reason behind choosing that period was the novelty and availability of cost data, since the financial department started implementing

the Venus Billing System that used CPT codes for medical interventions in 2010. Costs were gathered in two steps: first, costs of DMDs and other medications used for symptoms management were collected from the Integrated Clinical Information System (ICIS) via pharmacy portal (PharmNet), Cerner Millennium, Cerner Corporation. Other medical costs were then derived from the financial department including physician office visits, ER visits, hospitalization, laboratory and imaging tests, walking aids and other specialist care. Pharmacy items were not identified according to the CPT coding system, while medical interventions were identified via the CPT coding system. Hospital cost was used to measure the cost of medications, while contract price was used to measure the cost of medical interventions and was multiplied by the quantity of service provided to estimate hospital charges when there were missing values. The base case analysis included the average cost per person per year in relation to EDSS scores in which it was estimated per patient consumption of DMDs and medical services based on previously published studies.<sup>17-19</sup> Cost was measured in value equivalent to 2015 Saudi Riyals (SAR) and 3% discount rate was applied to account for inflation rate of 3.2% as reported by latest global medical trend rates report.<sup>20</sup>

*Sensitivity analysis*

The Markov model estimated the cost-effectiveness of oral DMDs versus IFNs using data from different sources; therefore, an extensive sensitivity analysis was conducted to test for uncertainties of the base-case analysis results. Uncertainty in parameter estimates, especially transition probabilities and the efficacy of treatments on relapse and disease progression rates were explored using deterministic and probabilistic sensitivity analysis (PSA). A one-way SA was performed as a

form of deterministic SA to test the robustness of the pairwise comparison of the three new oral DMDs and Avonex versus Rebif and the robustness of the optimal therapy selection by using NMB as an outcome, which was used to offer results on the best approach for resource allocation. The ranges for parameters were obtained from different sources as shown in **Table 3**, the lower and upper bounds of the utility weights for each health state were used to test the uncertainty of the population preference. The lower and upper bound for the relative risks of disability progression and relapse rates across all DMDs were also tested for uncertainty of treatment efficacy in real-life. Since this study has adopted a payer perspective, cost was a key element that was studied from different aspects. SFDA sets the regulations for drug registration and pricing in Saudi Arabia, hence the public price was set as the maximum cost for DMDs when it exceeded the hospital cost, while the hospital cost was set as the upper range when the public price was lower than the hospital cost. A probabilistic sensitivity analysis based on a second-order Monte Carlo simulation (1000 times) was also performed to test the robustness of the base-case scenario results. The distribution of each parameter was obtained from the CADTH report to test for the uncertainty of each variable used in the model.<sup>9</sup> Transition probabilities and utility values were characterized by a beta distribution, disutilities of relapses were characterized by log-normal distributions, and relapse rates were assumed to follow Dirichlet distributions to fit the model inputs, while costs were assumed to be normally distributed.<sup>9</sup> The elements for each distribution function were obtained from a report published by the Centre for Bayesian Statistics in Health Economics of the University of Sheffield, School of Health and Related Research (SchHARR).<sup>13</sup>

**Table 4.** Results from the base-case analysis: DMDs vs. Rebif (WTP=\$100 000), 1\$US=3.75 SAR.

DMDs	Cost	QALY	ICER (\$/QALY) vs. Rebif	NMB	INMB vs. Rebif
Interferon β1a (Rebif 44 mcg)	\$298 892 SAR1,120,530	9.78	-	\$679,440 SAR 2,547,190	-
Teriflunomide	\$360,631 SAR1,351,990	9.72	Dominated	\$611,857 SAR2,293,820	\$ -67,583 SAR -253,365
Interferon β1a (Avonex 30 mcg)	\$374,502 SAR1,655,307	10.01	\$337,282 SAR1,264,450	\$626,247 SAR2,348,130	\$ -53,193 SAR -199,418
Fingolimod	\$391,603 SAR1,468,100	10.05	\$347,338 SAR1,302,150	\$613,420 SAR2,299,680	\$ -66,020 SAR -247,506
Dimethyl Fumarate (DMF)	\$426,030 SAR1,609,040	10.02	\$531,329 SAR1,991,930	\$576,230 SAR2,160,260	\$ -103,210 SAR -386,929

QALY: quality-adjusted life years, ICER: Incremental cost-effectiveness ratio, INMB: incremental net monetary benefit, NMB: net monetary benefit.

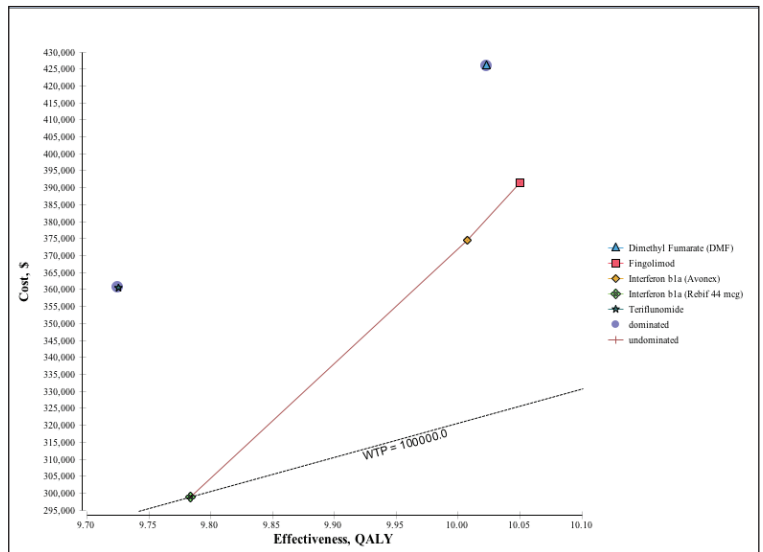
**RESULTS**

*Base-case analysis*

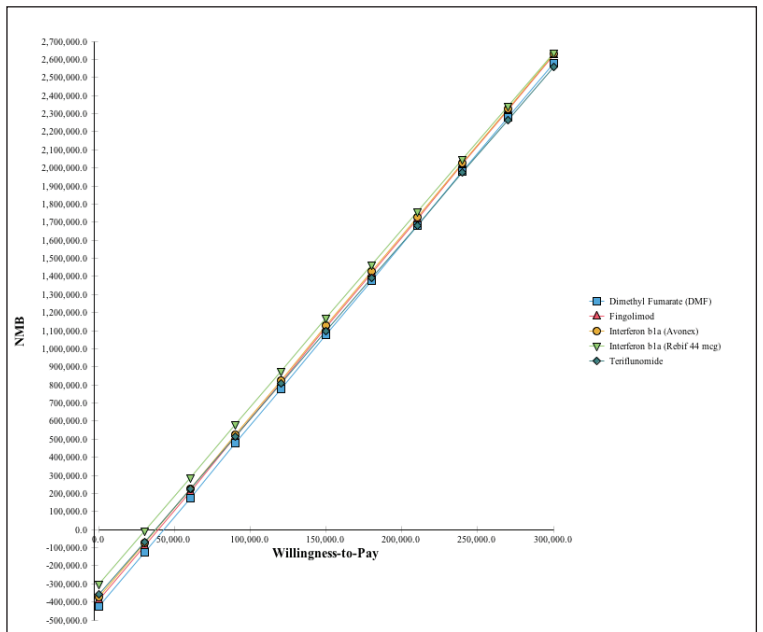
Over 20 years, the total costs per patient ranged from \$300 000 to \$430 000. The accumulated QALYs were 9.72, 9.78, 10.01, 10.02 and 10.05 for teriflunomide, Rebif, Avonex, DMF and fingolimod, respectively. Assuming a WTP of US\$100 000 Rebif was the optimal therapy in the treatment of RRMS from the KFSHRC pharmacy division perspective. Avonex reported the lowest ICER value of \$337 282/QALY compared to Rebif as a common comparator. Fingolimod was the only oral DMD that might be considered a cost-effective option (ICER=\$347 338/QALY) when a WTP higher than \$300 000 is considered. Teriflunomide and DMF were dominated by other options considering their high ICER values. In other words, they offered lower benefits than other agents with a higher cost. The NMB of Rebif was the highest at WTP of \$100 000 considering the low cost of the drug. The NMB of oral DMDs at a WTP of \$100 000 (SAR375 000) was lower than the NMB of Rebif, showing that oral DMDs were a costly option. The results of the base-case analysis are presented in **Table 4, and Figures 2 and 3.**

*One-way sensitivity analysis*

A tornado diagram was used to test for multiple variables at the same time to compare between oral DMDs and Rebif using NMB as an outcome. The parameters were chosen based on their effect on the results of the base-case analysis. According to the literature, the efficacy of DMDs on relapse rate, the utility weights of each health state and the cost of medications, had the greatest impact on the base-case analysis results. Age, as another variable, was also tested in a one-way sensitivity analysis. Generally, the results for the base-case analysis were somehow stable to the changes in most parameters. Rebif remained the most optimal therapy in the treatment of RRMS in Saudi Arabia even though it was not cost-effective. Based on the tornado diagram, the top three most significant parameters were common in all pairwise comparisons. Utility weights of health state 3, 4 and the cost of DMDs were the most sensitive variables in the one-way sensitivity analyses as shown in **Figures 4, 5, 6 and 7.** For the comparison between Avonex and Rebif, when the cost of Avonex was reduced to \$15 087 (SAR56 576) per year as per the public price set by the SFDA, and the cost of Rebif was increased to \$15 264 (SAR57 240) per year. Avonex thus, became the most cost-effective and the most cost-saving strategy generating an average ICER value of \$120 000/QALY (SAR450 000/QALY) with an NMB



**Figure 2.** Base-case analysis results at willingness-to-pay=\$100 000.



**Figure 3.** Net monetary benefits (NMB) at different willingness-to-pay thresholds.

value of \$700k. Similarly for the comparison between fingolimod and Rebif, the cost of fingolimod was not changed significantly from hospital charge to consumer price. When the annual cost of Rebif exceeded the hospital charge by 194% (from \$5184 to \$15 264) fingolimod generated an average ICER value of \$196 000/QALY (SAR735 000/QALY) and a NMB value of \$690 000, which is comparable to Avonex in terms of savings. When DMF and teriflunomide costs were reduced

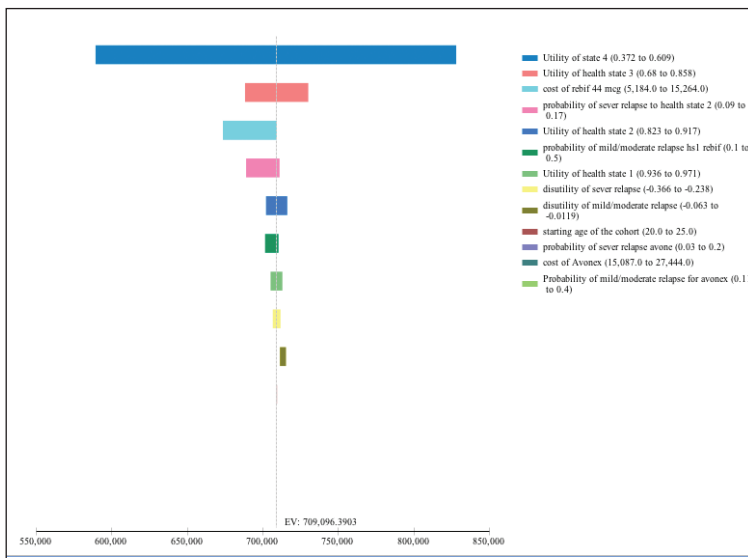


Figure 4. Tornado diagram of one-way sensitivity analysis: Avonex vs. Rebif.

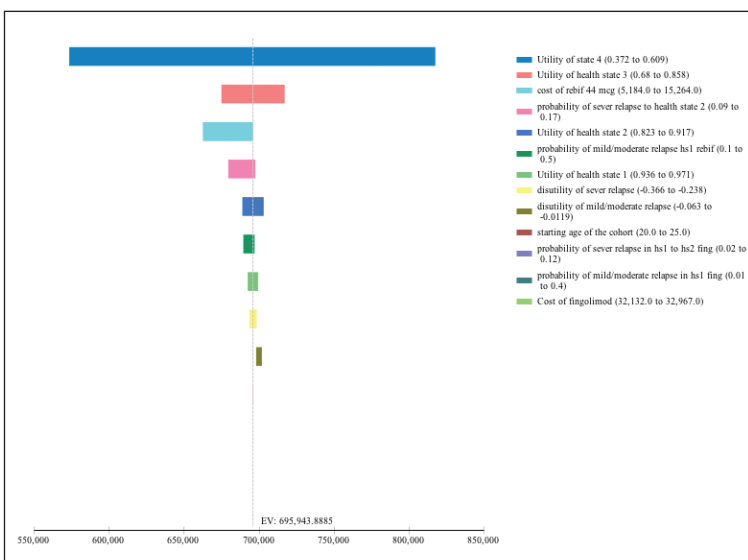


Figure 5. Tornado diagram of one-way sensitivity analysis: Fingolimod vs. Rebif.

in the SA to the consumer price of \$19535 (SAR73256) and \$12480 (SAR46800) per year, respectively, DMF became a cost-effective option since the average ICER value generated was \$152000/QALY (SAR570,000/QALY), which was much lower than the reported value in the base-case analysis but still higher than the proposed WTP threshold. Teriflunomide generated a higher ICER value (\$9243000/QALY) considering its low effectiveness as compared to Rebif even after reducing the cost of teriflunomide per year to the consumer price.

For the probabilistic SA, Monte Carlo simulation results showed that Rebif was the most cost-effective therapy at WTP of \$50 000 with 95% probability. As the WTP threshold was increased, the chance of oral DMDs becoming cost-effective also increased, especially for fingolimod with a maximum probability of 35% (0.35) at WTP thresholds higher than \$100 000 as shown in Figure 8.

## DISCUSSION

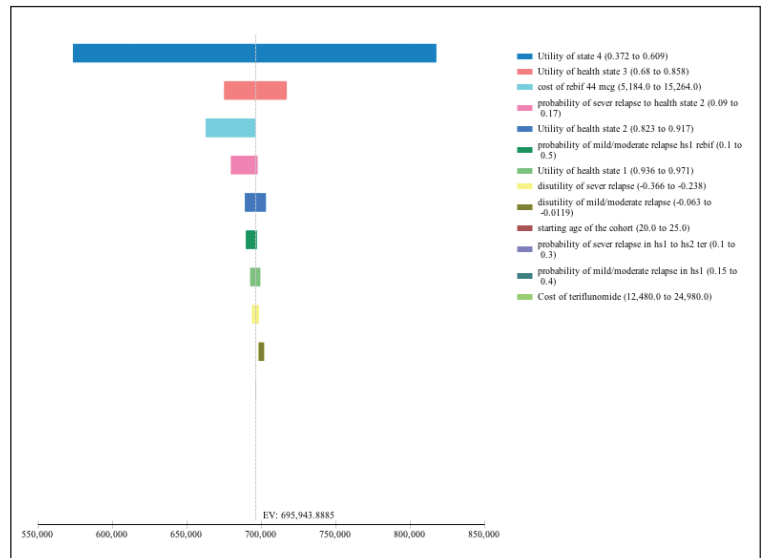
Overall, the results from this study were consistent with previous studies performed on RRMS treatment in the US. Several CE studies have indicated that DMDs in general are of low value in the treatment of RRMS at the traditional WTP threshold of \$50 000 in the US. The current analysis indicated that Rebif would be the optimal therapy in the treatment of RRMS in Saudi Arabia. This may be due to the low annual cost of Rebif compared to other agents used in the model. The base-case analysis results have shown Avonex as the second preferred option compared to Rebif due to the projected low ICER value. Contrary to the recent study done by Zhang and colleagues in 2014,<sup>21</sup> DMF was found to be the least favorable option due to the low benefits offered and high annual cost from a payer perspective. However, when the cost of oral DMDs were changed to the consumer price in the SA, which was lower than the hospital cost, the probability of oral DMDs becoming CE increased, especially for DMF. In the PSA, Rebif remained the most preferred therapy followed by fingolimod as the second option. Based on the literature, only a few studies compared oral DMDs with other treatment strategies. Fingolimod is the only oral DMD that was incorporated in a CE analysis in previous studies. A study by Lee et al compared fingolimod with IFN-β 1a.<sup>23</sup> The study concluded that fingolimod was associated with more benefits (higher QALY gained) versus IFN but at a higher cost, which means that fingolimod was not a CE option unless the cost of fingolimod fell below \$40 000 per year or a WTP higher than \$100 000 was considered by decision-makers. The results of this analysis matched the results displayed by Lee et al.<sup>23</sup> Agashivala and colleagues published another two studies comparing fingolimod and IFN formulations.<sup>24,25</sup> Both studies utilized a short time horizon (2 years) and outcome data from RCTs. These studies concluded that fingolimod was the most CE drug in the treatment of RRMS when initiated in the earliest phase of the disease, as compared to IFNs.<sup>24,25</sup> This can be attributed to the clinical benefits associated with the use of fingolimod in comparison with IFN, which have been proven in RCTs. Fingolimod is more effec-



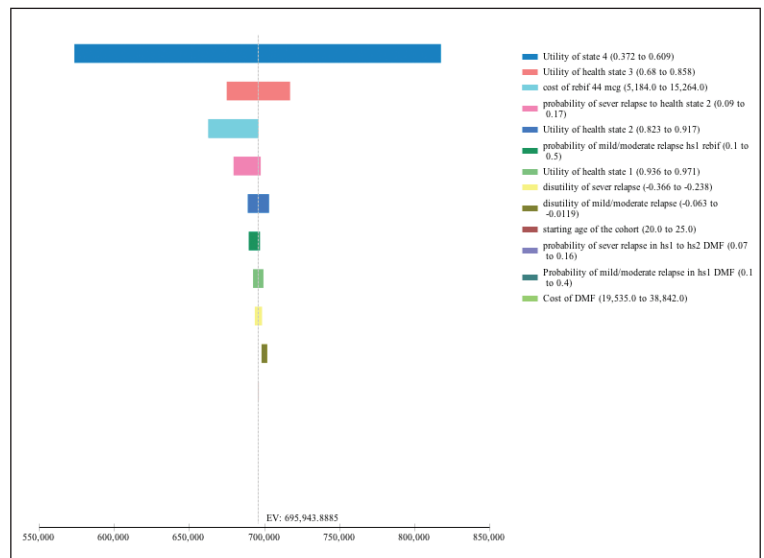
tive in terms of reducing relapse and EDSS progression rates by 52% and 37% versus Avonex, respectively.<sup>22</sup> A recent paper by Zhang and colleagues that was published in 2014 compared the three new oral DMDs versus IM IFN.<sup>21</sup> The Zhang et al study adopted a US societal perspective and used a short time horizon (5 years) for their analysis.<sup>21</sup> DMF was found to be the most CE drug in the treatment of RRMS US patients from a societal perspective.<sup>21</sup> This too can be attributed to the low acquisition cost of DMF in the US as compared to other agents used in the analysis. Moreover, this study assumed that the use of DMF will improve the patient QOL with an overall increase in utility score of 0.01, while other options will not positively impact the utility weights.

**Limitations**

The present model has a number of limitations that need to be highlighted. Since it was difficult to incorporate efficacy or quality of life data taken from the Saudi population in the absence of current epidemiological and observational studies, the CADTH report served as an excellent source of information of all DMDs including new agents. Additionally, it also contained a comprehensive list of inputs for the economic model that was used in this study. Ideally, this model should have used efficacy data from the Saudi population to come up with more reliable results that fit the population needs. However, a conservative assumption was made based on the opinions of clinical experts that the course of MS in Saudi Arabia resembles the western type of MS with minor variations in signs and symptoms, considering the difference in age at onset, which is lower in the Saudi population.<sup>8</sup> Secondly, this model assumed 100% adherence across all treatment options, which is obviously higher than rates expected in real-world settings. As reported by several studies, oral DMDs might have higher adherence rates than IFNs, and that might be attributed to the adverse events associated with injectable medications, needle phobia or suboptimal response to IFNs.<sup>4</sup> However, this study chose to use a conservative approach of assuming equal adherence with all treatments regardless of differences in the adverse effect profile. Thirdly, extending the generalizability of a model from one country to another requires more than just changing the currency. Difficulty in linking the cost data with the current health state of each patient was experienced; therefore, the average total cost for each health state was calculated looking at the quantity of DMDs and other medications dispensed, and the recorded number of visits and service utilization from the hospital. The approach used was based on the author's

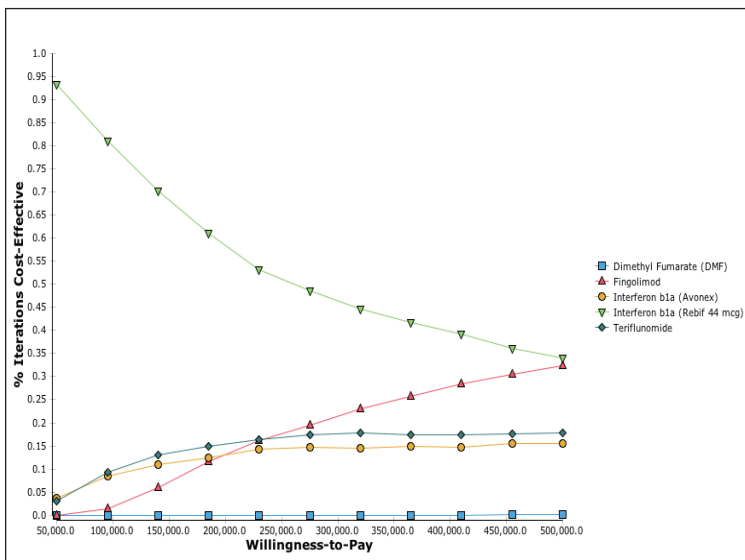


**Figure 6.** Tornado diagram of one-way sensitivity analysis: Teriflunomide vs. Rebif.



**Figure 7.** Tornado diagram of one-way sensitivity analysis: DMF vs. Rebif.

clinical background and an earlier published work.<sup>17-19</sup> Future analysis could focus on the applicability of transferring utility values for health states from one country to another. Although the course of MS and progression of disability is similar worldwide, patient preferences in valuing and measuring their own health state might vary from one country to another, based on cultural differences. This may include a willingness to trade quantity for quality of life, and the differences in the weight communities place on each dimension of the survey instruments used to measure overall health and quality of life.



**Figure 8.** Cost-effectiveness acceptability curve at different willingness-to-pay thresholds.

Therefore, a cross-validation instrument should be considered to eliminate bias and reflect country-specific model inputs in order to generate more reliable and valid results. Another potential solution is to tailor-make a survey instrument that measures patient preferences in valuing different health states based on the economic and social indicators of Saudi Arabia.

## CONCLUSION

This study shows that the DMDs included in the study may not be cost-effective at a WTP threshold of \$100,000 due to their high cost, especially oral agents. Avonex was projected to have the lowest ICER value at \$337,282/QALY (SAR1,264,450), which is not considered

cost-effective at acceptable universal WTP thresholds. Indeed, it was found to be far above the conventional thresholds cited in the US of \$50,000 to \$150,000 per QALY gained. Unless the pharmacy division at KFSHRC were willing to pay more than \$300,000 per extra QALY gain. In that case, all interventions would be considered cost-effective except for DMF. Additionally, there is uncertainty around the model inputs due to variations in community-based preferences in valuing health states measured by utility weights and the efficacy and safety data of DMDs derived from different sources. Therefore, additional research is required based on Saudi population preferences in order to determine the long-term efficacy and health-related outcomes associated with the use of DMDs in the treatment of RRMS in Saudi Arabia.

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## Conflict of interest

Authors, reviewers and investigators have no conflicts of interest to declare. No funding was received for the preparation of this manuscript.

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