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Cost-Effectiveness of Dimethyl Fumarate Versus Teriflunomide in Patients With Relapsing-Remitting Multiple Sclerosis (RRMS) in Iran

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ABSTRACT

Background and Aims: Multiple sclerosis (MS) is an autoimmune disorder that damages the myelin sheath on nerve fibers in the central nervous system, leading to axonal damage and neuron death. This study aimed to assess the cost-effectiveness of dimethyl fumarate compared with teriflunomide as first-line oral medications for patients with Relapsing-Remitting Multiple Sclerosis (RRMS) in southern Iran in 2022.

Methods: This cost-effectiveness study utilized a Markov model with a lifetime horizon and included 246 randomly selected patients from the MS Center of Shiraz University of Medical Sciences. The study adopted a societal perspective, accounting for all direct medical, direct non-medical and indirect costs. Direct medical cost includes visits, buying medications, the MRI cost, testing, hospitalization, and physiotherapy. Direct non-medical included costs related to patient travel, accommodation in other cities, food costs, and home nursing care, identified through patient interviews and indirect costs include lost income. Outcomes were measured in terms of Quality Adjusted Life Years (QALY) and average relapse rates. One-way and probabilistic sensitivity analyses were conducted using TreeAge and Excel 2016 software for modeling and data analysis.

Results: The study found that dimethyl fumarate was more cost-effective than teriflunomide, with lower costs (\$35,253 vs. \$44,340) and higher QALYs (5.30 vs. 5.24) in Iran. Dimethyl fumarate also had lower relapse rates. Sensitivity analyses, including a tornado diagram, supported these findings. Dimethyl fumarate was identified as the best treatment strategy in 66% of simulations, making it the preferred option across different payment scenarios. Overall, using dimethyl fumarate was shown to be a cost-effective treatment compared to teriflunomide.

Abbreviations: DMC, direct medical costs; DMT, disease-modifying therapies; DNMC, direct non-medical costs; EDSS, expanded disability status scale; GDP, gross domestic product; IC, indirect costs; MS, multiple sclerosis; PPP, purchasing power parity; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life years; RRMS, relapsing remitting multiple sclerosis; TTO, time trade-off method; WTP, willingness to pay.

Dr. Maryam Poursadeghfard and Yasin Farjah, had equal participation as the first author, and we would like to consider both as co-first authors.

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Conclusion: The results showed that dimethyl fumarate has a lower cost and is more effective than teriflunomide. Given its favorable cost-effectiveness profile—characterized by both lower costs and greater effectiveness compared with teriflunomide—dimethyl fumarate represents a more economically and clinically advantageous option, supporting its consideration as a first-line oral therapy for relapsing-remitting multiple sclerosis in settings where resource allocation is a key concern.

1 | Introduction

Multiple sclerosis (MS) is a debilitating autoimmune neurological disorder in which the myelin sheath covering nerve fibers in the central nervous system (brain, optic nerves, and spinal cord) is damaged. This damage leads to secondary axonal damage and neuronal death. It causes sensory, motor, and cognitive dysfunction that may be progressive, transient, or permanent [1, 2].

The cause of MS disorders is still unknown, but several factors, such as genetic factors, environmental factors, and infections, are proposed as the cause of this disease [3, 4]. MS usually occurs at a young age and affects women about three times more than men [5]. Recently, it has been observed that the number of patients older than 40 years is also increasing. In this study, a special subgroup of multiple sclerosis patients with an onset age of over 40 years was examined for the so-called “Late-onset relapsing-remitting multiple sclerosis” [6].

The number of people suffering from MS worldwide in 2025 is estimated at 1.89 million people [7]. The prevalence and occurrence of MS vary in different regions of the world. Thus, the prevalence of MS is higher in Europe and the United States than in Asia [8]. In the United States, the prevalence of MS is 309.2 individuals per 100,000 people [9]. This rate in the Persian Gulf region is 39.31 per 100,000 people [10]. According to a study conducted in 2019, the incidence and prevalence of MS in Iran were estimated at 3.4 and 29.3 individuals per 100,000 people, respectively, varying across different provinces of the country [11].

The results show that the annual healthcare cost for each patient with MS increased during the years 2011 to 2015. Therefore, the annual purchase cost of medications in 2011 compared to 2015 increased from \$26,772 to \$43,606 [12]. Also, the direct medical and nonmedical costs associated with MS increased from \$16,614 in 2006 to \$72,744 in 2017 per patient per year [13].

A recent study in the United States estimated the economic burden to be 85.4 billion dollars. This includes 63.3 billion in direct medical costs (DMC), 22.1 billion in direct non-medical costs (DNMC), and indirect costs (IC). The price was \$65,612 per patient annually [14].

Studies show that the economic burden of MS in Iran was about 199 million PPP dollars in 2019 [15], and the amount of these costs per patient increased from \$7000 in 2011 to \$18,000 in 2019 [16]. Also, most studies show that one of the main reasons for the increase in the costs of patients with MS is the cost of purchasing medicine. It is one of the largest cost components in the treatment portfolio of patients with MS.

Currently, there is no definitive cure for MS. However, various medications are used to control this disease and adapt the patient to the conditions better. Nowadays, the use of oral

medications is welcomed by patients and doctors due to their availability and ease of use. The first oral medication for MS is fingolimod (Gilenia), approved in 2010 [17]. After that, other oral medications, including teriflunomide (Tebazid) and dimethyl fumarate (Tafedra), were also developed. Teriflunomide is a once-daily medication that has side effects, including increased liver enzymes, hair loss, and diarrhea. Patients should also be educated about the teratogenic risk of the medication and screened for tuberculosis before starting treatment [18]. Additionally, dimethyl fumarate (Tafedra) is a twice-daily medication that has side effects including flushing, gastrointestinal complications, lymphopenia, and the risk of Progressive Multifocal Leukoencephalopathy (PML). Patients should receive necessary education regarding the importance of monitoring blood lymphocyte counts and interventions to reduce lymphopenia and gastrointestinal side effects, such as taking medication with food or aspirin [19].

Given the variability in drug costs and effectiveness across patients, and the absence of research on the cost-effectiveness of the two drugs dimethyl fumarate and teriflunomide in Iran, this study sought to assess the cost-effectiveness of dimethyl fumarate and teriflunomide in patients with relapsing-remitting multiple sclerosis (RRMS) in Fars Province in 2022. Thus, a more complete and newer evaluation of the prospect of RRMS treatment can be provided to healthcare decision-makers to prescribe a better medication and provide the correct use of limited resources.

2 | Methods

2.1 | Overview and Model Structure

This study is a cost-effectiveness analysis, a complete economic evaluation of health care programs in patients using two medications, dimethyl fumarate (twice a day) and teriflunomide (once a day). This study was conducted in reference to the MS Association of Shiraz University of Medical Sciences in the year 2022. The sample size was determined to be 123 in each group of patients. These patients were selected and included in the study using a random sampling method. The inclusion criteria of the study were the use of the mentioned medications for at least 1 year and willingness to participate in the study.

Markov model analysis was used in this study due to the persistent and recurring nature of the disease. The characteristics of this model have previously been published by the Canadian Agency for Drugs and Technologies in Health (CADTH) [20] and the Norwegian Institute of Public Health (NIPH) [21]. This basic model has been used in previous studies in Iran [22, 23]. The analysis is based on a Markov model that simulates the progression of a group of RRMS patients from one health state to higher health states, as defined by the EDSS scale (from 0 to 10). This scale determines the degree of disability and

assesses disease progression. Each health state is associated with specific costs and clinical outcomes. The health states in the model are mutually exclusive; in other words, each patient in a hypothetical group can only be in a particular health state at a particular point in time. The schematic representation of the Markov model related to the disease is shown in Figure 1. During the study, the lifetime horizon served as the fixed time horizon, and Markov cycles occurred annually. Each annual cycle in this model involves patients remaining in their current state or transitioning to alternative states. Also, all patients can face relapse or death [24, 25]. Patients remain in RRMS status until they reach an EDSS of 3–5.5. After transitioning to EDSS 6 or higher, patients are classified as secondary progressive MS (SPMS), and given that dimethyl fumarate and teriflunomide medications are not used for SPMS patients, disease-modifying drugs are discontinued for them [26]. The probability of transition to different conditions, annual relapse rate, and mortality probabilities at each EDSS level were all determined by reference to previous studies, as shown in Table 1 [27–30]. Significantly, some clinical trial data are initially presented as rates. Subsequently, they are converted to transmission probabilities using the following formula before inclusion in the model [32].

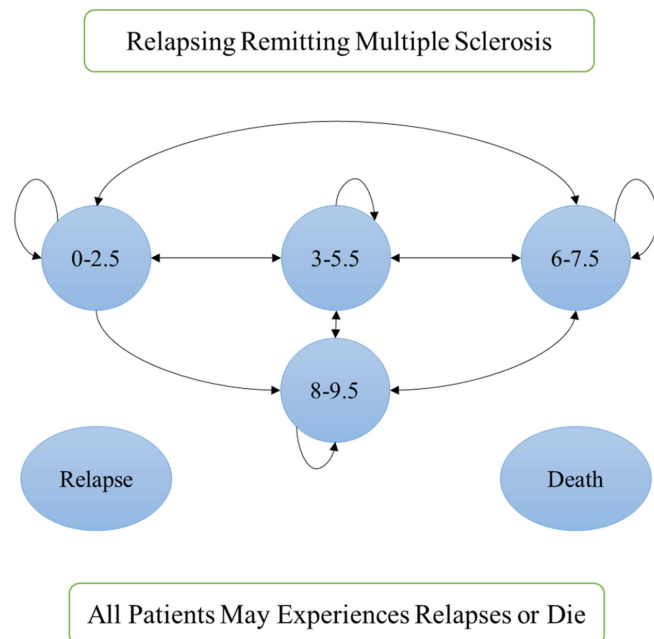


FIGURE 1 | Schematic diagram of the Markov model related to MS [24].

TABLE 1 | Transmission probabilities and annual relapse rate in patients with relapsing-remitting multiple sclerosis.

EDSS From\To	0–2.5	3–5.5	6–7.5	8–9.5	source	Death	Source
0–2.5	82.567	15.93	1.47	0.033	[27–29]	1.343	[30]
3–5.5	10.067	59.73	28.8	1.4		1.718	
6–7.5	0.3	5.5	81.95	12.25		2.685	
8–9.5	0	0.1	4.15	95.75		5.450	
Annualized Relapse Rate			Mean			Source	
Dimethyl fumarate		0.09 [–0.07 to 0.12]				[31]	
Teriflunomide		0.16 [0.13 to 0.20]					

$$P = 1 - \exp(-rt)$$

where p is the wanted transition probability and r is the overall rate over the time of t .

Since the time horizon was more than 1 year, the cost data and consequences of the model were discounted based on the discount rate of 5.8% [33] and 3% [34], respectively.

2.2 | Outcomes

Outcomes in this model include quality adjusted life years (QALYs) and average relapse rates for each health condition and each treatment strategy. To measure the average relapse rate, the total number of relapses of all patients was calculated and divided by the total number of years of medication use to obtain the annual relapse rate of patients. Then, this value was divided by the number of patients using each medication to obtain the average relapse rate of each drug.

Also, the values of utility were extracted using the EQ-5D questionnaire. Health outcomes were evaluated based on QALY [35]. To measure the utility scores, face-to-face interviews or telephone calls with 246 patients with MS in 2022. Interviews were conducted with outpatients referring to hospitals and clinics affiliated with Shiraz University of Medical Sciences.

Importantly, the EQ-5D questionnaire serves as a common tool for evaluating health outcomes. It includes 5 questions that assess 5 aspects of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The respondents' evaluation in each of these dimensions can vary from less than 0 to 1, and a high rating indicates an increase in effectiveness. This questionnaire was presented for the first time in 1990 by the EuroQol group. People with Multiple Sclerosis interested in joining the research were interviewed accordingly. After completing the EQ-5D questionnaire, the 5-digit identifiers of the questionnaire were converted to numerical Utility using the time trade-off (TTO) technique. This conversion considered the specific values for the Iranian setting as identified in the study conducted by Goudarzi et al. [36].

2.3 | Cost

Cost extraction was also done according to a societal perspective. The societal perspective included DMC, DNMC, and IC. DMC related to these medications was retrospectively collected

from March 21, 2021, to March 20, 2022, using a checklist developed by the researchers. The data was prepared from the office of specialist doctors and the MS Association of Fars province. It included expenses such as seeing a doctor, buying medications, the MRI cost, testing, hospitalization, and physiotherapy. The costs for dimethyl fumarate and teriflunomide used in this model reflect the actual acquisition prices for bio-similar and domestically-manufactured formulations available in Iran during the study period (2022). Importantly, the pricing is based on the annual tariff determined by the Ministry of Health and Medical Education [23]. DNMC included costs related to patient travel, accommodation in other cities, food costs, and home nursing care, identified through patient interviews. IC calculation was done based on the human capital approach [37]. Furthermore, all costs were converted to dollars (PPP) using the exchange rate of 64,529 Rials per dollar (PPP) in 2022 [38].

2.4 | Determination of the Incremental Cost-Effectiveness Ratio (ICER)

After obtaining the costs and effectiveness in the previous stages, the ICER was calculated according to the following formula. Then, for the final decision regarding the cost-effectiveness of each of the medications under consideration, the ICER values were compared with the threshold limit [22].

$$ICER = \frac{\text{Costs of Dimethyl fumarate} - \text{Costs of Teriflunomide}}{\text{Outcomes of Dimethyl fumarate} - \text{Outcomes of Teriflunomide}}$$

If the cost of an intervention is lower (higher) and its effectiveness is higher (lower), there is no need to calculate the ICER to make a decision, and the intervention is cost-effective (non-cost-effective). If the costs and effectiveness of an intervention are higher (lower) to make a decision, the calculated ICER should be compared to the willingness to pay threshold. Due to the lack of an explicit threshold limit of willingness to pay (WTP) in Iran, based on the World Health Organization's proposal for developing countries, the willingness to pay per QALY of one to three times per capita GDP was used [39]. In Iran in 2022, the Gross Domestic Product (GDP) was \$18,261 [40], which sets the willingness-to-pay threshold in Iran at one times per capita GDP (\$18,261). Furthermore, for the analysis of the data, Microsoft Excel 2016 and TreeAge Pro 2020 software were utilized.

2.5 | Sensitivity Analysis

Finally, univariate sensitivity analysis and probabilistic sensitivity analysis (PSA) were used to investigate the parameter uncertainty effect on the results. Thus, for univariate sensitivity analysis several important parameters of the study such as (1) the purchase prices of dimethyl fumarate and teriflunomide, (2) The remaining direct costs (except for the cost of purchasing medicine), all indirect costs associated with each EDSS state, and QALYs associated with each EDSS state were changed by

20% for each medication strategy and the findings were shown through a tornado plot. Additionally, the PSA tested the sensitivity of the results using a second-order Monte Carlo simulation with 5000 iterations, allowing simultaneous changes in all the input parameter values using the following distributions: Beta distribution (β) was used to determine the distribution of utility values from 0 to 1, and gamma distribution was used to define the cost distribution. PSA results were shown using cost-effectiveness acceptability curves and incremental cost-effectiveness scatterplots. Cost-effectiveness acceptability curves are useful for decision-makers and healthcare strategists. These charts help assess how cost-effective an intervention is at various willingness-to-pay thresholds, aiding in planning and policy formulation. Also, scatter curves provide additional insights into individual comparisons. These curves represent the proportion of points within the acceptance area that fall below the specified threshold [41].

2.6 | Ethical Considerations

Ethical approval for this study was obtained from the ethics committee of Shiraz University of Medical Sciences with the grant No.28212 and ethical code IR. SUMS. REC.1402.367. Verbal consent was obtained from respondents who completed a questionnaire anonymously, and their response expressed their willingness to participate. Written consent was obtained from participants for the cognitive interviews.

3 | Results

According to the results, most studied patients were women (69.20%) and employed (41.86%). All patients were covered by insurance. Also, the mean age of the patients treated with dimethyl fumarate and teriflunomide was 40.4 ± 6.21 and 36.42 ± 6.31 years, respectively. Table 2 shows the average costs, effectiveness, and average relapse in patients with MS using two medications, dimethyl fumarate and teriflunomide.

According to Table 2, the average amount of DMC and DNMC was in patients using teriflunomide (\$3074.81 and \$545.09, respectively) and dimethyl fumarate (\$2209.51 and \$457.98, respectively). Also, the purchase cost of the original medication, DMC type, was highest in teriflunomide and dimethyl fumarate (\$900.80 for teriflunomide and \$537.35 for dimethyl fumarate). Also, the cost of travel and the lost income of outpatients were the highest types of DNMC and IC in both medications, respectively (\$257.55 and \$209.26 in teriflunomide and \$235.73 and \$228.41 in dimethyl fumarate).

The highest effectiveness score from the EQ. The 5D questionnaire was seen in patients with MS using dimethyl fumarate and with EDSS 2–0.5 (0.727 ± 173). There was a minor difference compared to dimethyl fumarate with EDSS 0–2.5 (0.0 ± 693.157), which scored lower. The lowest average relapse was related to patients using dimethyl fumarate and with EDSS 2–0.5 (0.069 ± 48) (Table 2).

Based on Table 3, the results of the cost-effectiveness analysis using the Markov model indicated that in the dimethyl fumarate arm, the average costs were \$35,316 with a QALY of 5.31. In contrast, in the teriflunomide arm, the average cost

TABLE 2 | The means of costs in patients with RRMS using dimethyl fumarate and teriflunomide.

Costs	Dimethyl fumarate		Teriflunomide	
	USD	Percentage	USD	Percentage
Direct medical costs				
Physicians' visits	196.73	8.91	367.19	11.94
Main medicines	537.35	24.32	900.80	29.29
Supplementary medicines	340.09	15.39	526.23	17.14
Laboratory tests	142.58	6.45	301.45	9.80
MRIs	390.64	17.68	334.29	10.87
Physiotherapy & other services costs	308.00	13.94	283.43	9.21
Hospitalization & surgeries	294.12	13.31	361.38	11.75
Total	2209.51	70.84	3074.77	75.86
Direct non-medical costs				
Transportation	235.72	51.47	257.55	47.25
Accommodation	127.22	27.78	196.54	36.06
Meals	95.04	20.75	90.98	16.69
Total	457.98	14.68	545.07	13.44
Indirect costs				
Income lost due to outpatient visits	228.41	50.57	209.26	48.26
Income lost due to hospitalization	149.14	33.02	133.36	30.75
Patient's family costs	74.09	16.41	91.00	20.99
Total	451.64	14.48	433.62	10.69
Total costs	3119.13	100.00	4053.46	100.00
Total costs base each health state	Mean	SD	Mean	SD
EDSS 0.0–2.5	2875.12	367.83	3726.92	535.52
EDSS 3.0–5.5	3668.46	357.63	4820.56	288.92
Utility scores				
EDSS 0.0–2.5	0.727	0.173	0.693	0.157
EDSS 3.0–5.5	0.361	0.106	0.345	0.118
Relapse rates				
EDSS 0.0–2.5	0.69	0.48	1.31	1.11
EDSS 3.0–5.5	1.37	0.79	1.92	1.56

was \$44,340 with a QALY of 5.24. Therefore, given that dimethyl fumarate has a lower cost and is more effective, it is the cost-effective option and the dominant choice, as shown in Table 3.

3.1 | One-Way Sensitivity Analysis

According to the Tornado diagram in Figure 2, the results showed that ICER was the most sensitive to the related costs of teriflunomide in patients with a disability level of 0–2.5 and the least sensitive to the QALY of both medications. This indicates that changes in the costs of teriflunomide and dimethyl fumarate have the greatest impact on the ICER. In contrast, QALY of teriflunomide and dimethyl fumarate show relatively less influence, suggesting more stable outcomes against QALY fluctuations. Additionally, the changes in the input parameters had little effect on the result, and the ICER rate remained negative.

3.2 | Probabilistic Sensitivity Analysis (PSA)

The results of uncertainty measurement using cost-effectiveness acceptability curves and incremental cost-effectiveness scatterplots are presented as follows.

The acceptability curve reveals that at Iran's WTP threshold of \$18,261 per QALY, dimethyl fumarate has a 66% probability of being cost-effective. As the WTP threshold increases, the probability of dimethyl fumarate's cost-effectiveness rises accordingly, demonstrating its economic efficiency across different payment scenarios (Figure 3).

The results of the acceptability curve also showed that in 66% of the cases, dimethyl fumarate was placed in the acceptance area and below the threshold and defeated teriflunomide, and therefore, it is considered a more cost-effective strategy. (Figure 4).

While PSA confirmed the lower cost of dimethyl fumarate in 100% of simulations ($p < 0.01$), the incremental effectiveness showed uncertainty. At Iran's WTP threshold (\$18,261/QALY),

TABLE 3 | The base-case analysis results (the lifetime analysis).

	Strategy	cost (PPP\$)	QALY	Incremental Cost	Incremental QALY	ICUR (Incremental cost per QALY Gained) PPP\$
Cost-utility analysis	teriflunomide	44,340	5.24	—	—	—
	dimethyl fumarate	35,253	5.30	−9087	0.06	Strongly dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, Quality Adjusted Life Year

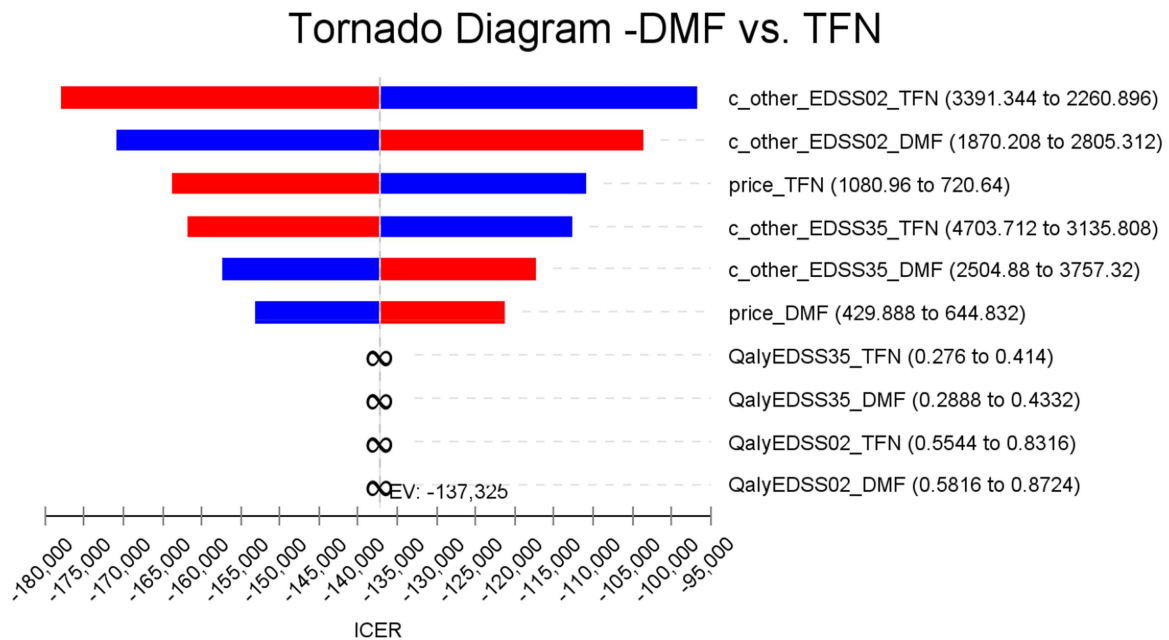


FIGURE 2 | Tornado diagrams of the cost-utility of the studied patients with RRMS under treatment with dimethyl fumarate and teriflunomide.

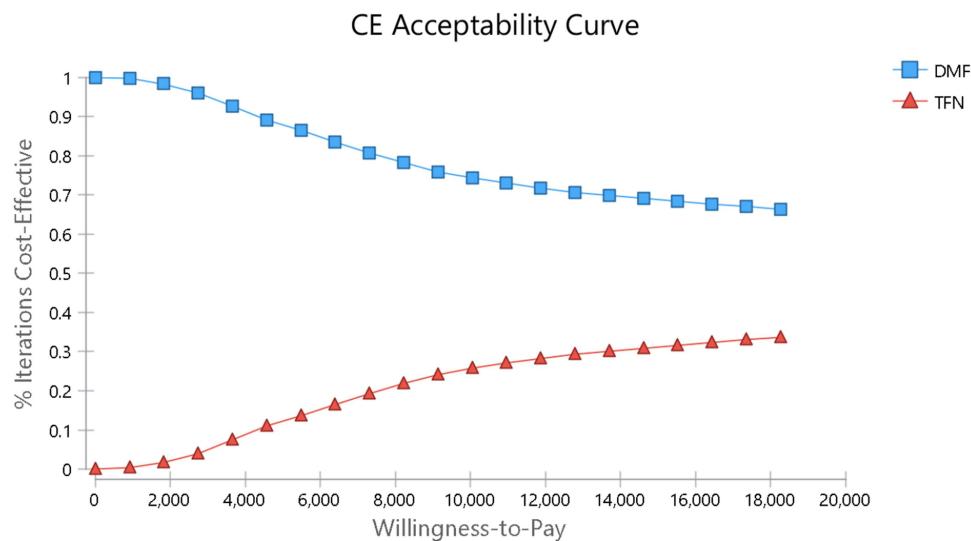


FIGURE 3 | The cost-effectiveness acceptability curves of dimethyl fumarate versus teriflunomide based on the QALY obtained through the Monte Carlo simulation.

dimethyl fumarate had a 66% probability of being cost-effective. However, the 95% CI for ICER (−\$28,761 to \$12,342) indicates scenarios where the modest QALY advantage of dimethyl fumarate (0.06) may not offset cost differences. This suggests that while dimethyl fumarate is economically preferable, its clinical superiority requires further validation.

4 | Discussion

Despite recent advances in medical science, most treatments available for MS currently focus on managing symptoms, slowing disease progression, and reducing inflammatory damage in the CNS. Given the high costs associated with disease-

Incremental Cost-Effectiveness, DMF v. TFN

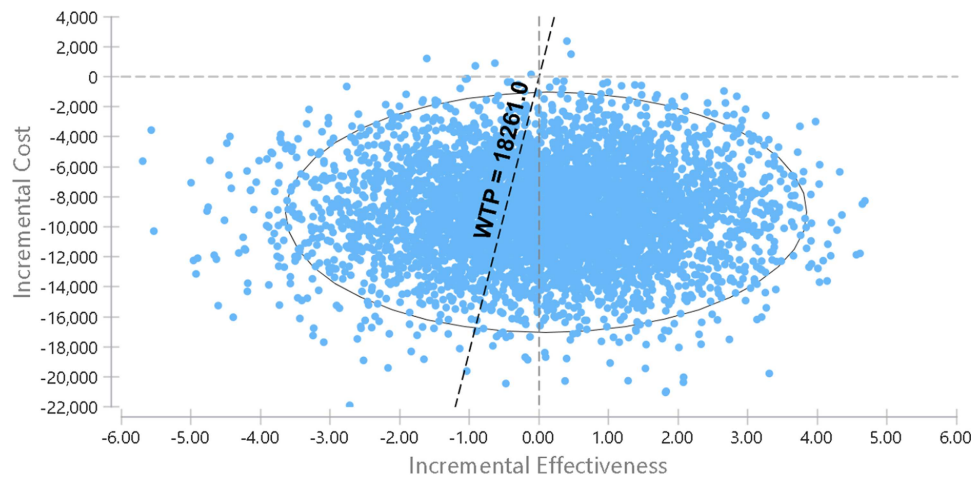


FIGURE 4 | The incremental cost-effectiveness scatter plots of dimethyl fumarate versus teriflunomide based on the QALY.

modifying therapies worldwide, there is an urgent need to reduce the financial burden on families and communities. This requires a coordinated effort to reduce the costs associated with MS treatment and increase access to cost-effective and effective treatment options. Such efforts include promoting research and development initiatives for generic medications, optimizing production methodologies for enhanced practicality and cost-efficiency, supporting optimal utilization of healthcare resources, and formulating appropriate health and economic policies [42]. As a result, identifying the most effective and ultimately cost-effective medications through comprehensive economic evaluations is essential. These evaluations should also provide essential recommendations to healthcare providers regarding the use and prescription of medications. By conducting such studies, healthcare policymakers can effectively reduce out-of-pocket expenses for patients. Notably, economic evaluation studies comparing the cost-effectiveness of dimethyl fumarate versus teriflunomide in patients with MS have not been conducted in Iran so far. Therefore, the main goal of this study was to investigate the cost-effectiveness of dimethyl fumarate compared with teriflunomide in patients with MS.

Based on the findings, the annual treatment cost with teriflunomide is \$4053.46, compared to \$3119.13 for dimethyl fumarate. Therefore, the average cost of a treatment period per patient treated with dimethyl fumarate is lower than that of treatment with teriflunomide. It seems that the reason is that the free price of the teriflunomide molecule itself was about 35% more expensive than that of dimethyl fumarate. In the Iranian clinical setting during the study period, teriflunomide's prescribing guidelines mandated regular liver function tests due to its known risk of hepatotoxicity and its pregnancy category X status. This requirement contributed to higher associated laboratory monitoring costs compared to dimethyl fumarate. Additionally, the clinical management of teriflunomide, including monitoring for potential drug interactions and managing its known side effect profile, may have led to additional healthcare utilization and associated costs. These interactions could contribute to the higher average cost among teriflunomide users compared with dimethyl fumarate. Mantovani et al., Zhang et al., and Soini et al. demonstrated in

their studies that dimethyl fumarate is a cost-effective option compared with other approved medications for treating MS [43–45]. The findings of these studies are consistent with the current study, where the percentage breakdown of costs for dimethyl fumarate includes 70.84% DMC, 14.68% DNMC, and 14.48% IC. Similarly, for teriflunomide, these percentages are 75.86% DMC, 13.44% DNMC, and 10.69% IC. The predominant share of the costs for both medications consists of direct costs, with the largest portion attributed to the purchase of the original medication at 24.32% and 29.29%, respectively.

The findings of the present study indicate that the highest level of utility and the lowest relapse rate for each drug are associated with patients with EDSS 0–2.5. As the level of disability increases, the level of utility decreases, and the relapse rate increases. The observed greater relapse reduction efficacy in lower EDSS patients (0–2.5) versus higher EDSS (3.0–5.5) likely reflects two key factors: (a) Early Intervention Effect: Neuroprotective mechanisms of DMTs may be more effective when initiated earlier in the disease course, as supported by recent evidence showing superior blood–brain barrier penetration and immunomodulation in less advanced MS [46, 47]. (b) Disease Biology: The inflammatory component driving relapses predominates in earlier disease stages (EDSS < 3), while progressive neurodegeneration becomes more prominent at higher EDSS levels, potentially reducing DMTs' relapse prevention efficacy [48]. This may be attributed to the fact that as EDSS scores rise, patients experience greater limitations, which could lead to an increased relapse rate and a lower level of utility [49]. In this respect, the results of this study are in line with those of Rezaee et al., Torgauten et al., Hellgren et al., Borealmalm et al., and Yamout et al. [23, 50–53].

The results of the Markov model analysis using the societal perspectives and the time horizon of life span showed that dimethyl fumarate had a lower cost (\$35,253 vs. \$44,340) and higher effectiveness (5.30 vs. 5.24 QALY). Therefore, dimethyl fumarate is the dominant option. In the study conducted by Mantovani et al., it was also demonstrated that dimethyl fumarate compared with teriflunomide had lower costs (\$1.01 million vs. \$1.03 million) and higher effectiveness (6.526 vs. 5.953 QALY), which is consistent with this study [43]. Also,

Chevalier et al. showed that dimethyl fumarate had a lower cost (767,474 vs. 768,323 euros) and higher effectiveness (5.271 vs. 5.047 QALYs) than teriflunomide, which is consistent with the results of this study [54]. Additionally, Zhang et al. showed that dimethyl fumarate had a lower cost (\$200,145 vs. \$226,085) and higher effectiveness (3.72 vs. 3.68 QALY) than teriflunomide, which is consistent with the results of this study [44]. However, in the study by Soini et al., it was observed that dimethyl fumarate had higher costs and effectiveness compared with teriflunomide. The calculated ICER for these two drugs was 75,431 euros, which is not consistent with the results obtained in this study [45].

The results of the one-way sensitivity analysis showed that in the cost-effectiveness analysis, the ICER value was negative, and the highest sensitivity was compared with the costs associated with teriflunomide. The fact that in the cost-effectiveness sensitivity analysis, the ICER value remains negative confirms the results of this study. Also, the results of possible sensitivity analysis showed that the dimethyl fumarate regimen was more cost-effective compared with teriflunomide, and in 66% of cases, it is in the acceptance area and below the threshold, and it achieved the best results considering the aforementioned prices. Therefore, the results showed that the sensitivity analysis did not change the status of dimethyl fumarate as the most effective medication regimen. Thus, this study is consistent with the results of the studies of Chevalier et al. and Zhang et al. [44, 54].

The limitations of the current study include self-reporting by patients or their caregivers regarding DNMC and IC, which may be subject to issues such as forgetfulness or inaccurate estimation. An additional limitation is the short duration of the study for a chronic long-term condition; therefore, it is recommended that a more extensive study be undertaken to ascertain how employment status is altered or remains constant.

Furthermore, the findings of this study should be interpreted within the context of the Iranian healthcare system and pharmaceutical market in 2022. The cost advantage of dimethyl fumarate is largely attributable to the greater availability and lower pricing of its biosimilar formulations in Iran, whereas teriflunomide, despite also being available as a biosimilar, carried a higher acquisition cost during the study period. Additionally, the mandated liver function monitoring protocol for teriflunomide under local guidelines contributed to its higher associated costs. Therefore, the generalizability of these results to other countries may be limited, particularly in settings where the relative pricing of these biosimilars differs or where monitoring practices vary. Future studies in diverse economic and clinical contexts are needed to validate these findings.

5 | Conclusion

Based on the results, dimethyl fumarate is more cost-effective compared with teriflunomide. Therefore, according to the sensitivity analysis and the robustness of the results, it is suggested that the treatment method of dimethyl fumarate should be prioritized in patients with MS compared with teriflunomide. Policymakers and health managers should increase insurance coverage and try to reduce the payment for patients.

Author Contributions

Maryam Poursadeghfard: conceptualization, data curation, methodology, supervision, validation, writing – review and editing. **Yasin Farjah:** data curation, methodology, software, writing – original draft. **Mehdi Rezaee:** conceptualization, data curation, supervision, validation, writing – review and editing. **Nastaran Momtahan:** data curation, methodology, software, writing – original draft. **Mohammad Hossein Morowvat:** conceptualization, data curation, supervision, validation, writing – review and editing. **Ahmad Gholami:** conceptualization, data curation, methodology, software, project administration, investigation, supervision, validation, writing – review and editing. **Khosro Keshavarz:** conceptualization, data curation, methodology, software, project administration, investigation, supervision, validation, writing – review and editing. All authors have read and approved the final version of the manuscript corresponding author had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

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Ethics Statement

This study was approved by the ethical committee of Shiraz University of Medical Sciences with the grant No.28212 and ethical code IR. SUMS. REC.1402.367. Verbal consent was obtained from respondents who completed a questionnaire anonymously, and their response expressed their willingness to participate. Written consent was obtained from participants for the cognitive interviews.

Conflicts of Interest

The authors declare no conflicts of interest.

Consent for Publication

All participants completed a consent form, stating that they were well-informed about the Content of questionnaires and that they agreed upon the publication of anonymized data.

Data Availability Statement

The datasets generated and analyzed during the current study are not publicly available because they contain information that could compromise the privacy of research participants, but are available from the corresponding author upon reasonable request.

Transparency Statement

The lead authors, Ahmad Gholami and Khosro Keshavarz, affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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