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Original Article

Assessment of fingolimod versus dimethyl fumarate for the treatment of multiple sclerosis; a 24-month follow-up study

Samane-Sadat Masjedi[1], Masoud Etemadifar[1], Nadia Mohammad Zadeh[2], Mahdieh Afzali[3]

[1]Department of Neurology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran; [2]School of Medicine, Islamic Azad University Tehran Faculty of Medicine, Tehran, Iran; [3]Department of Neurology, School of Medicine, Yas Hospital, Tehran University of Medical Sciences, Tehran, Iran

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Abstract: Background: Oral treatment of multiple sclerosis (MS) using disease-modifying therapies (DMTs) is a challenge worldwide. Fingolimod (FTY) and dimethyl fumarate (DMF) are two approved agents for oral treatment of MS with remarkable efficacy for relapse control and deceleration of disability progression. Therefore, the current study was done to compare disability control, lesions in magnetic resonance imaging (MRI), and adverse effects between the patients treated with FTY and DMF. Methods: This randomized clinical trial (IR.MUI.REC.1396.3.786) was conducted on 60 patients who were randomly divided into two groups of treatment with 0.5 mg daily dose of FTY (n = 30) and 240 mg dose of DMF twice daily (n = 30). Disability of patients was assessed using the expanded disability status scale (EDSS) within 6 weeks, 12, and 24 months following treatment initiation and MRI was performed for all the patients prior to study initiation and within 24 months. Obtained data were compared between two study groups. Results: There was no significant difference between two treatment groups based on EDSS scores, brain lesions in MRI, and newly formed plaques (P>0.05). Skin and gastrointestinal-related complaints were the most common adverse effects of DMF while the increase in liver enzyme level and thrombocytopenia were the most common complications of FTY, respectively (*P*-value = 0.22). Conclusion: According to our findings, within 24-month follow-up, DMF was neither superior nor inferior to FTY comparing MRI lesions, EDSS scores, and adverse effects. Although, further evaluations with larger sample size are recommended.

Keywords: Fingolimod, dimethyl fumarate, multiple sclerosis

Introduction

Multiple sclerosis (MS) is a chronic demyelinating disorder involving central nervous system (CNS). This autoimmune disease affects young adults, especially females and causes axonal injury leading to considerable disabilities [1-6].

Since 1993, injecting agents of disease-modifying therapies (DMTs), such as interferons and glatiramer acetate have been used for treatment of MS [7, 8]. Finding oral DMT agents with acceptable efficacy and negligible side effects has become a great trend worldwide. Therefore, numerous drugs with various efficacy and adverse effects have been introduced to the market, opening new windows for controlling MS symptoms to the neurologists and also causing a great challenge for selection of the best option [9, 10]. Fingolimod (FTY), a sphingosine-1 receptor modulator, with 0.5 mg of the recommended daily dose was the first oral agent for treatment of MS accepted by the United States food and drug administration (FDA) in 2010 [11]. The other DMT agent, dimethyl fumarate (DMF) (prescribed in a dose of 240 mg twice daily), was also approved as an alternative for treatment of MS in 2013 [12, 13]. Three trials in the literature have demonstrated similar efficacy of these agents compared to placebo, for example, annualized relapse rate has been reported between 48-54% and 44-53% following the use of FTY and DMF, respectively [11, 13, 14]. Furthermore, comparison of these oral agents with injecting interferon-beta has revealed considerable

superiority of either FTY or DMF [15, 16]. Tolerability of drugs is another factor significantly influencing its widespread use. FTY consumption is associated with the adverse effects, including nasopharyngitis, diarrhea, fatigue, and headache. Furthermore, eye examinations are required after its consumption because its use is associated with incidence of macular edema. In addition, the first dose of FTY administration should be monitored for 6 hours due to rare reports of cardiac adverse effects [17-19]. Flushing and gastrointestinal -related adverse effects are the most considerable complaints of treatment with this agent with worst presentation in the first weeks of prescription [11, 13].

There are limited studies in the literature comparing these two agents in clinical setting in long-term [9, 20]. Therefore, this study was conducted to compare efficacy of FTY vs. DMF in treatment of MS for 2 years.

Methods

Study design

This randomized clinical trial (RCT) study was conducted on 60 newly diagnosed patients with MS using McDonald 2010 criteria [21], referred to MS outpatient clinics affiliated with the Isfahan University of Medical Sciences since March 2016. The 18-55-year-old patients definitely and newly diagnosed with MS who had not received any immunomodulatory therapy except for corticosteroids and had presented their willingness for participation in the study were included. Included patients should have met the criteria for being treated with both agents of Fingolimod and dimethyl fumarate. Previous history of demyelinating diseases, medical history of other autoimmune diseases (i.e., lupus, Sjogrens' syndrome, antiphospholipid syndrome, and Behcets' disease) or chronic/recurrent infections (i.e., syphilis and viral hepatitis B/C), lactation, treatment with viral vaccines in recent 4 months, increased levels of liver enzymes, alanine aminotransferase and aspartate aminotransferase, up to 2.5 folds of normal range, hemoglobin level of less than 8.5 g/dl and platelet count of less than 100000/μl were considered as unmet criteria. Exclusion criteria were reluctance for continuing the study protocol in each of the study stages, failure to refer for follow-up visits, laboratory assessments and/or neuroimaging, presentation of any life-threatening or irrecoverable drug-related adverse effects, and requirement to change the approach of treatment. The study protocol was approved by the Ethic Committee of the Isfahan University of Medical Sciences (IR.MUI.REC.1396.3.786) and also the current study was approved by vice chancellor for Research of the Isfahan University of Medical Sciences (code number: 396786). Thereafter, the study protocol was totally explained for the patients and they were reassured about confidentiality of their personal information. Then, they were requested to present their written consent of participation in this study.

Randomization

Study population was selected through convenience sampling method until achieving the required number of study population. Then, they were randomly divided into groups of treatment with Fingolimod and dimethyl fumarate using random allocation software. Therefore, each of the patients was provided with a number allocating him/her to a study group. The first group was treated with 240 mg of dimethyl fumarate twice daily and the rater group was treated with 0.5 mg daily dose of Fingolimod.

Assessments

Patients' demographic information, including age, gender, occupation, educational level, marital status, habitat, smoking, pregnancy, receiving any alternative treatment, pregnancy and the primary symptom of MS was recorded in the study checklist. The other agents simultaneously used by the patients were recorded as well. Severity of symptoms was assessed based on the expanded disability status scale (EDSS) within 6 weeks, 12, and 24 months following the treatment initiation and the CNS lesions were evaluated through neuroimaging so that, all the patients underwent magnetic resonance imaging (MRI) at the beginning and end of the study. The MRIs were performed with the protocols of T1 phase, T2 phase, and Gadolinium enhancement and the findings were interpreted by a single neuroradiologist to minimize interobserver bias. Number of MS lesions and newly formed MS plaques was reported in interpretations of the MRIs. The patients were visited every 3 months and were evaluated for MS relapse, the onset of new

symptoms associated with relapse, and drug-related adverse effects.

Statistical analysis

Gathered data were entered to statistical package for the social sciences (SPSS) version 20 (Chicago; The United States) and were analyzed. Descriptive data were presented as mean and percentages, Chi-Square and Fisher's Exact tests were used to compare qualitative variables between groups and Mann-Whitney U and one-way analysis of variance (ANOVA) tests were used to compare quantitative variables between groups. *P*-value of less than 0.05 was considered as statistically significant.

Results

Demographic characteristics

In the current study, 67 patients meeting the inclusion criteria were enrolled. Among them, 34 patients were randomly assigned to FTY treatment group and remaining 33 patients were treated with DMF. In the FTY group, two patients left the study because of non-adherence to the treatment protocol and 2 others presented severe relapses requiring injecting treatments. Three members of DMF group presented their unwillingness for continuing the follow-up visits and were excluded from the study. Thus, 60 patients definitely diagnosed with MS were assessed. The patients were randomly divided into two 30-member groups. One of the groups underwent dimethyl fumarate regimen treatment and the rater was treated with Fingolimod.

Demographic information of the participants was recorded. Two groups presented no statistical differences regarding age (P = 0.26), gender (P = 1), marital status (P = 1), occupation (P = 0.65), pregnancy (P = 0.051), receiving alternative therapies (P = 0.67), and onset MS symptoms (P = 0.42). While, the two groups were statistically different in terms of educational level (P = 0.01), habitat (P = 0.01), and smoking (P<0.001). Detailed information is presented in **Table 1**.

Clinical information

EDSS scores of the patients were compared within 6 weeks, a year, and 2 years following treatment initiation. Comparison of Fingolimod vs. dimethyl fumarate represented no significant differences (P = 0.06). Number of lesions in the MRI findings was compared as well. No significant difference was detected between two groups in the first imaging (P = 0.11) while comparison of the second imaging findings showed a significant decrease in number of lesions in dimethyl fumarate-treated group (P = 0.04). Comparison of two groups regarding new lesions in the MRI showed no significant difference (P = 0.53) (**Table 2**). Relapse presentation, remedy-related adverse effects, and symptoms at relapse were not statistically different while comparing the Fingolimod-treated patients with those treated with the rater agent (P>0.05) (**Table 3**).

Discussion

Establishing a long-term efficient treatment approach with negligible side effects through the use of DMTs is a great challenge for MS control regarding its relapse rate and incidence or progression of disabilities. Recently, numerous oral agents have been introduced making selection of the best agent more challenging. On the other hand, there is limited information about efficacy of these agents through comparative assessments. Therefore, in this study, two common oral DMT regimens of MS were compared in long- term (2 years) [22].

In the current study, similar relapse rate of 10% was observed in both groups either treated with Fingolimod or DMF within 2 years of treatment. All the participants presented the improved EDSS scores regardless of their treatment approach but comparison of FTY with DMF based on the EDSS scores demonstrated no significant difference in any of assessment intervals. Our findings are somewhat greater than the study by Hersh et al., who presented 8.5 and 8.3% of annualized relapse rate for FTY and DMF, respectively [23]. They continued to follow up their patients for another year and presented similar outcomes to the previous one. In addition, DMF intolerability was remarkably higher leading to discontinuation of the treatment [24]. Vollmer et al., also conducted a two-year cohort study on a large number of patients and presented 8.9 and 12.9% of clinical relapse among the patients treated with FTY and DMF, respectively [7, 9].

On the other hand, neuroimaging findings revealed the lesions detected in the MRI and

Table 1. Demographic information of study participants based on their group

Parameters		Fingolimod	Dimethyl fumarate	*P*-value
Age	20-25	3 (5%)	3 (5%)	0.26
	26-30	6 (10%)	12 (20%)	
	31-35	6 (10%)	5 (8.3%)	
	36-40	4 (6.7%)	7 (11.7%)	
	41-45	6 (10%)	1 (1.7%)	
	46-50	3 (5%)	1 (1.7%)	
	51-55	2 (3.3%)	1 (1.7%)	
Gender	Female	22 (36.7)	22 (36.7%)	1
	Male	8 (13.3%)	8 (13.3%)	
Marital status	Single	10 (16.7%)	10 (16.7%)	1
	Married	20 (33.3%)	20 (33.3%)	
Educational level	Primary school	0	1 (1.7%)	0.01
	High school	4 (6.7%)	0	
	Diploma	14 (23.3%)	7 (11.7%)	
	University education	12 (20%)	22 (36.7%)	
Occupation	Employee/worker	7 (11.7%)	12 (20%)	0.65
	Jobless/housewife	15 (25%)	10 (16.7%)	
	Self-employed	8 (13.3%)	8 (13.3%)	
Smoking	Negative	27 (45%)	19 (31.7%)	0.01
	Positive	3 (5%)	11 (18.3%)	
Pregnancy	Positive	13 (21.7%)	5 (8.3%)	0.051
	Negative	9 (15%)	17 (28.3%)	
Alternative therapy	Negative	26 (43.3%)	28 (46.7%)	0.67
	Positive	4 (6.7%)	2 (3.3%)	
The primary presentation of multiple sclerosis	Ataxia	1 (3.4%)	0	0.42
	Diplopia	4 (13.4%)	1 (0.4%)	
	Optic neuritis	5 (16.6%)	8 (26.6%)	
	Hemiparesia	7 (23.4%)	2 (3.4%)	
	Paresthesia	5 (13.4%)	8 (26.6%)	
	Dysartheria	0	2 (6.6%)	
	Paraparesia	2 (6.6%)	2 (6.6%)	
	Hemiparesia and paresthesia	0	1 (3.4%)	
	Ataxia and diplopia	2 (6.6%)	3 (10%)	
	Diplopia and paresthesia	3 (10%)	2 (6.6%)	
	Paresthesia and paraparesia	1 (3.4%)	1 (3.4%)	

Table 2. Comparison of treatment outcomes of dimethyl fumarate with fingolimod considering EDSS and imaging findings

	Dimethyl fumarate	Fingolimod	*P*-value
Extended disability status scale (mean ± standard deviation)			
Within 6 weeks	2.20±1.24	2.50±1.28	0.65
Within 12 months	1.33±0.54	1.73±0.90	0.26
Within 24 months	1.30±0.70	1.67±0.95	0.38
Magnetic resonance imaging lesions (mean ± standard deviation)			
First MRI	1.33±1.15	2.07±2.013	0.11
Second MRI	1.1±1.5	1.4±1.8	0.64
New lesions	1.2±1.7	1.92±0.73	0.53

also formation of new lesions. Our findings showed no significant differences regarding number of lesions found in the MRI taken within 24 months following the treatments and simi-

Table 3. Relapse associated symptoms and drug related adverse effects

Parameters		Fingolimod	Dimethyl fumarate	*P*-value
Relapse re-experience	Positive	3 (10%)	3 (10%)	1
	Negative	27 (90%)	27 (90%)	
Adverse effects	Skin related presentation	2 (6.6%)	6 (20%)	0.22
	Gastrointestinal presentation	1 (3.4%)	5 (16.6%)	
	Liver function test impairment	4 (13.4%)	3 (10%)	
	Thrombocytopenia	2 (6.6%)	1 (3.4%)	
	Gastrointestinal and skin disorders	1 (3.4%)	2 (6.6%)	
	Negative	20 (66.7%)	13 (43.4%)	
Symptoms at relapse	No relapse	27 (90%)	27 (90%)	1
	Ataxia	1 (3.4%)	0	
	Diplopia	0	1 (3.4%)	
	Hemiparesia	1 (3.4%)	1 (3.4%)	
	Paraparesia	0	1 (3.4%)	
	Diplopia and paresthesia	1 (3.4%)	0	

larly, no statistically significant difference was found in terms of the newly formed plaques. Previous studies have presented similar outcomes regarding number of lesions detected in MRI images [13, 19]. Consistent with our study, Hersh et al., generally presented similar efficacy of FTY vs. DMF for T2 MRI findings but significant increase in the number of lesions detected in Gadolinium enhancement protocol [23]. They also confirmed their statements through another 12-month follow-up of the patients [24].

Similar to the studies in the literature, skin -related complications followed by gastrointestinal-related ones were the most common complaints regarding the use of DMF [25, 26]. Abnormal change in liver enzyme levels and thrombocytopenia were the most common adverse effects presented by patients undergone FTY treatment in our study. In general, rate of adverse effects due to FTY administration was less than DMF with no statistical difference. Although, drug discontinuation was not assessed in the current study, considerable higher rate of DMF discontinuation presented in the previous studies can be attributed to remarkably higher rate of the adverse effects, especially gastrointestinal-related ones [9, 23].

Conclusion

According to our findings, within 24-month of follow-up, DMF was neither superior nor inferior to FTY comparing MRI lesions, EDSS scores, and adverse effects. Nevertheless, further evaluations with larger sample size are recommended.

Disclosure of conflict of interest

None.

Address correspondence to: Mahdieh Afzali, Yas Hospital, Tehran University of Medical Sciences, North Nejatollahi Street, Kharim Khan Avenue, Tehran, Iran. Tel: +98-9127294976; E-mail: m.afzali2219@gmail.com

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