

Assessment of safety and effectiveness of oral multiple sclerosis medication

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ABSTRACT

الأهداف: قياس مدى فعالية وأمان علاجات المرض الحديثة (فينجوليمود، دايميثيل فيومريت و تيريفلونوميد) في مستشفى محلي في مدينة الرياض، المملكة العربية السعودية.

المنهجية: هذي دراسة بأثر رجعي حيث تم الحصول على الموافقة من مجلس المراجعة المؤسسية في ديسمبر 2015. تم جمع المتغيرات الديموغرافية (العمر، الجنس، ظهور المرض و مدة أخذ الدواء)، المتغيرات السريرية (الأثار الجانبية للدواء و نتائج الأشعة)، بالإضافة الى عدد الانتكاسات بالسنة.

النتائج: تم استرجاع و تحليل سبعة و خمسون ملف مريض من الصيدلية. تم دراسة بيانات ثمان مرضى كانوا على تيريفلونوميد، خمس مرضى على دايميثيل فيومريت و أربعة و أربعون مريض كانوا على فينجوليمود. متوسط أعمار المرضى كان 32.5 سنة، الإناث يمثلون 63% من عينة الدراسة. معدل الانتكاسة السنوية كان 0.24، 0.34، و 0.5 لكل مريض في السنة للمرضى الذين على فينجوليمود، دايميثيل فيومريت و تيريفلونوميد على التوالي. أكثر الأعراض الجانبية شيوعا لمرضى فينجوليمود كانت انخفاض اللمفاويات (91.4%)، قلة العدلات (23%)، بطء القلب (16%).

الخلاصة: من نتائج الدراسة، تم التحقق من فعالية الأدوية للمرضى مع الأثار الجانبية المصاحبة لها. و مع ذلك لا يمكن تعميم نتائج هذي الدراسة على كل المجتمع السعودي.

Objectives: To assess the effectiveness and safety profile of the new disease modifying drugs (fingolimod, teriflunomide, and dimethyl fumarate) at a local hospital in Riyadh, Saudi Arabia.

Methods: This is a retrospective cohort, where institutional review board approval was granted in December 2015. The study was conducted at King Abdulaziz Medical City Research Center, Riyadh, Saudi Arabia. Demographic variables (age, gender, disease onset, and duration on medication), clinical variables (medication side effects and radiological findings), in addition to relapse frequency per year was collected.

Results: Fifty-seven patients' records were retrieved from the pharmacy and included in the analysis. Eight

patients were on teriflunomide, 5 patients on dimethyl fumarate and 44 patients on fingolimod were enrolled. The patients' average age was 32.5 years with female gender representing 63% the study population. Annual relapse rates were 0.24, 0.34, and 0.5 per patient per year for those taking fingolimod, dimethyl fumarate, and teriflunomide, correspondingly, lymphopenia (91.4%), neutropenia (23%), and bradycardia (16%) were the most reported side effects for fingolimod therapy.

Conclusion: The study results were able to capture the effectiveness rate for the targeted treatment in the studied population, with the frequency of incidence of side effects. However, as these results cannot be generalized for the entire Saudi population.

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Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease affecting the central nervous system (CNS) whose etiology is not clearly understood.¹ Multiple sclerosis can be divided into 3 classes.² The first class, relapsing-remitting MS (RRMS), is defined by a clear relapse followed by complete or a partial recovery, and it accounts for 85-90% of MS cases.³ The second type, primary progress MS (PPMS), is characterized by progressive disability without recovery and accounts for 10% of MS cases.⁴ The third type, secondary progressive

MS (SPMS), can be identified by an initial relapse remission followed by continuous worsening without remission or minor improvement.² It was estimated that over half of RRMS patients develop SPMS.⁵

In 2010, the U.S Food and Drug Administration (FDA) approved Fingolimod as the first oral therapy for managing RRMS.⁶ It acts by decreasing the ability of lymphocytes to emerge from the lymph node via activation of sphingosine-1 phosphate S1P receptor, leading to a decrease in the number of lymphocytes in the CNS and in disease activity.⁷ Fingolimod was studied in 3 large phase 3 trials. In the FREEDOMS and FREEDOMS II trials, it was compared using 2 doses, 0.5mg and 1.25 mg, versus a placebo, and in the TRANSFORMS trial, it was also compared using the same 2 doses but versus interferon beta-1a 30 µg weekly.^{8,9}

In September 2012, the FDA approved the second oral medication to treat RRMS, Teriflunomide.¹⁰ It reversibly obstructs pyrimidine synthesis by inhibiting dihydroorotate dehydrogenase enzymes in the mitochondria, ultimately leading to a decrease in the proliferation of B and T cells.¹¹ Three large randomized trials were conducted on Teriflunomide involving 2 doses, 7 mg or 14 mg, versus placebo in the TEMSO and TOWER trials, while the doses were set versus interferon beta-1a 44 µg 3 times weekly in the TENERE trial.¹²

The third medication, dimethyl fumarate (BG-12), was approved by the US FDA in March 2013.¹³ It has anti-inflammatory and cytoprotective properties via activation of the nuclear 1 factor (erythroid-derived2)-like 2 (Nrf2) pathway.¹⁴ Dimethyl fumarate was studied in 2 phase 3 trials with 240 mg either twice or 3 times daily versus placebo in the DEFINE and CONFIRM trials.¹⁴

Scant literature focuses on MS in the Kingdom of Saudi Arabia (KSA).^{15,16} An early work by Yaqub et al¹⁷ reported an increase incidence of MS in the Kingdom. In 2015, the Saudi Arabian National Multiple Sclerosis Registry (NMSR) was initiated with the goal of exploring the epidemiology and clinical symptoms of MS in the KSA.¹⁵ The prevalence of MS among Saudis is an estimated 40 cases per 100,000, which is considered low compared with other parts of the world (namely, more than 100/100,000 in Europe).^{17,18} Saudi females

have a higher prevalence of MS compared to males (2:1 ratio).¹⁵

A study focusing on treating MS in KSA is needed, as most of the previous literature explored the epidemiological view of MS. The main and first objective of this study involved assessing the effectiveness and safety profile of the new disease modifying drugs (fingolimod, teriflunomide, and dimethyl fumarate) at a local hospital in Riyadh, KSA. The second objective sought to explore the monitoring frequency for each medication and their discontinuation rate. The third objective aimed at evaluating the previous treatment before the new disease modifying drugs and the reasons for their discontinuation.

Methods. A retrospective cohort design was applied to explore the effectiveness and safety profile of fingolimod, teriflunomide, and dimethyl fumarate for patients with RRMS. The data collection started in 2016. International Review Board approval from the King Abdullah International Medical Research Center (KAIMRC) was received in December 2015. The study was conducted at King Abdulaziz Medical City-CR (KAMC-CR), which is a tertiary hospital in Riyadh, Saudi Arabia. Fingolimod, teriflunomide, and dimethyl fumarate are available based on patients and physician preferences.

The first objective involved assessing the effectiveness and safety profile of the latest MS modifying drugs. The drugs include fingolimod, teriflunomide, and dimethyl fumarate. The study sample retrieved from the pharmacy computer system and reviewed retrospectively. All patients who received at least one dose of the targeted therapy according to the pharmacy records were reviewed for eligibility. The inclusion criteria were the diagnosis of RRMS and the presence of at least one dose of fingolimod, teriflunomide, or dimethyl fumarate. The exclusion criteria were incomplete medical records (patients came for a second opinion or did not follow-up).

Effectiveness was measured through relapse rate per year and magnetic resonance imaging (MRI) results. Results from the MRI include new gadolinium enhancing lesions, new T2 weighted lesions, and enlarged T2 weighted lesions. Safety profile was measured through the presence of side effects. Each medication associated with different side effects was reported by various randomized clinical trials or metaanalyses. For fingolimod, the side effects comprise bradycardia (less than 65 beats per minute), hepatotoxicity (alanine

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transaminase greater than upper limit of normal), lymphopenia (less than 1*10⁹ per liter), neutropenia (absolute neutrophil count less than 2*10⁹ per liter), and infections (mainly herpes and upper respiratory tract infection).¹⁹⁻²¹ For Teriflunomide, the side effects include hair thinning, headache, diarrhea, peripheral neuropathy, high systolic blood pressure (more than 160 mm Hg), and neutropenia.²²⁻²⁴ The side effects for dimethyl fumarate consist of proteinuria, pruritus, gastrointestinal symptoms, flushes, and infections.^{3,25-27} The second objective was exploring the frequency of monitoring for each medication, mainly hepatic and blood pressure monitoring and their discontinuation rate. Discontinuation was defined as stopping treatment for any reason.

The third objective covered the previous treatments before the new disease-modifying drugs and the reasons behind their discontinuation. These treatments include interferon beta-1a (subcutaneous SC or intramuscular IM), interferon beta-1b and natalizumab. The reasons for discontinuation were classified into 5 categories: medication intolerance, failure of treatment, side effect, presence of anti-JC-virus (JCV) antibodies associated with natalizumab therapy, and unknown reason.

In addition to the aforementioned variables, age, gender, onset of MS, and duration of therapy were also collected. All the clinical data and variables were collected from either the patient file or the hospital information system and compiled in the data collection sheet. Descriptive data were also conducted, including percentages. Depending of the assumptions, Chi-squared test or Fisher's exact test of independence were employed to explore the relationship between different categories in the dependent variable (type of treatment) and other categorical independent variables. All data analyses were conducted using R:A Language and Environment for Statistical Computing.

Results. Fifty-nine patients' records were retrieved from the pharmacy and reviewed for eligibility. Two patients on fingolimod were excluded because they had

been diagnosed with SPMS; the remaining 57 patients were included (44 on fingolimod, 8 on teriflunomide, and 5 on dimethyl fumarate).

Tables 1 & 2 list the current treatments used, giving their averages and frequencies. The cohort's average age was 32.5 years (±2.31). On average, therapy lasted longest for patients treated with fingolimod (16.59 months) but was shortest for those treated with dimethyl fumarate (7 months). Patients treated with teriflunomide had the longest onset of MS (6.9 years versus the cohort average of 6.2 years). Annual relapse rates were 0.24, 0.34, and 0.5 per patient per year for those taking fingolimod, dimethyl fumarate, and teriflunomide.

Females represented 63% of the study population, and that aligned with each treatment group. More than 70% of the members of each treatment group did not report relapses. Among patients who underwent MRI after starting the therapy, 14.3% of the fingolimod, 50% of the dimethyl fumarate, and 16% of the teriflunomide treatment groups, showed new gadolinium-enhancing lesions. New T2-weighted lesions were seen in 19% of patients on fingolimod as well as in 50% of patients on dimethyl fumarate or teriflunomide. Enlarged T2-weighted lesions were seen in 9.5% of patients on fingolimod and in 33.3% of patients on teriflunomide; no lesions were seen in patients on dimethyl fumarate.

The most frequently reported side effects associated with use of fingolimod were lymphopenia (91.4%), neutropenia (23%), and bradycardia (16%). Of patients who used teriflunomide, 12.5% reported hair thinning, headache, diarrhea, high systolic blood pressure, peripheral neuropathy, and neutropenia. No side effects were documented for patients who used dimethyl fumarate (Table 3). No malignancies were reported in association with any of the treatments used by this cohort of patients.

Table 4 & Table 5 describe previous treatments used as well as the reasons those treatments failed. More than half of patients had taken Interferon Beta-1a, whether subcutaneously (36%) or intramuscularly (21%). A

Table 1 - Description of current treatment (means).

Factor	Treatments			Total
	Fingolimod	Dimethyl fumarate	Teriflunomide	
Age (years)	31.64 (29.17 - 34.09)	29.80 (20.39 - 39.23)	39.37 (30.87 - 47.87)	32.56 (30.25 - 34.86)
Duration of therapy (months)	16.59 (13.38 - 19.79)	7.00 (0.25 - 13.74)	12.00 (6.96 - 17.03)	15.10 (12.43 - 17.77)
Onset of MS (years)	6.14 (4.98 - 7.30)	5.70 (0.47 - 11.87)	6.98 (3.33 - 10.64)	6.22 (5.17 - 7.26)
Annual relapse rate (rate/patient/year)	0.24	0.34	0.50	0.28

Values are presented as mean (95% confidence intervals)

Table 2 - Description of current treatment (frequencies).

Factors	Treatments			Total	P-value
	Fingolimod	Dimethyl Fumarate	Teriflunomide		
<i>Gender</i>					
Male	17 (29.8)	1 (1.8)	3 (5.3)	21 (36.8)	0.89
Female	27 (47.4)	4 (7.0)	5 (8.8)	36 (63.2)	
<i>Reported side effects*</i>					
No	10 (17.5)	5 (8.8)	3 (5.3)	18 (31.6)	0.001
Yes	34 (59.7)	0 (0.0)	5 (8.8)	39 (68.4)	
<i>Reported relapse</i>					
No	31 (54.4)	4 (7.0)	5 (8.8)	40 (70.2)	0.88
Yes	13 (22.8)	1 (1.8)	3 (5.26)	17 (29.8)	
<i>MRI monitoring</i>					
No	23 (40.4)	3 (5.3)	2 (3.5)	28 (49.1)	0.38
Yes	21 (36.8)	2 (3.5)	6 (10.5)	29 (50.9)	
<i>New gadolinium enhancing lesion[†]</i>					
No	18 (31.6)	1 (1.8)	5 (8.8)	24 (42.1)	0.28
Yes	3 (5.3)	1 (1.8)	1 (1.8)	5 (8.8)	
<i>New T2 weighted lesion</i>					
No	17 (29.8)	1 (1.8)	3 (5.3)	21 (36.8)	0.19
Yes	4 (7.0)	1 (1.8)	3 (5.3)	8 (14.0)	
<i>Enlarged T2 weighted lesion</i>					
No	19 (33.3)	2 (3.5)	4 (7.0)	25 (43.9)	0.24
Yes	2 (3.5)	0 (0.0)	2 (3.5)	4 (7.0)	
<i>Treatment discontinuation</i>					
No	42 (73.7)	5 (8.8)	6 (10.5)	53 (93.0)	0.12
Yes	2 (3.5)	0 (0.00)	2 (3.5)	4 (7.0)	

*type of side effect varied for each medication, [†]results for patients that had MRI monitoring in the hospital medical records

Table 3 - Side effect explored in each current treatment.

Detected side effect	Number of patients (%)
<i>Fingolimod</i>	
Lymphopenia	32 (91.0)
Neutropenia	8 (23.0)
Bradycardia	7 (16.0)
Infection	6 (13.0)
Hepatotoxicity	2 (5.6)
<i>Dimethyl Fumarate</i>	
Proteinuria	0
Gastrointestinal	0
Flushes	0
Pruitus	0
Infection	0
<i>Teriflunomide</i>	
Hair thinning	1 (12.5)
Headache	1 (12.5)
Diarrhea	1 (12.5)
Neutropenia	1 (12.5)
High systolic blood pressure	1 (12.5)
Infection	0
Hepatotoxicity	0

third of patients reported that previous treatments had failed, and 28% of patients who had changed their mode of treatment because of an inability to tolerate previous treatments. A total of 4 patients had discontinued their medications after contracting an infection; 3 of them had been treated using fingolimod.

Discussion. This study included 57 patients who had been diagnosed with RRMS. This sample size was similar to those of previous studies focusing on treatment of multiple sclerosis (MS), whether in Saudi Arabia or internationally.^{28,29} Algahtani et al²⁸ conducted a cross-sectional study in Jeddah, Saudi Arabia, in which they evaluated various treatments for RRMS among a sample size of 32 patients. In Switzerland, Naegelin et al²⁹ evaluated different types of MS therapy among 25 patients. These relatively small sample sizes can be attributed to 2 factors: the studies' having focused on a single site rather than multiple sites and MS's remaining a low prevalence disease.³⁰

The effectiveness and safety profiles of fingolimod, teriflunomide, and dimethyl fumarate was assessed.

Table 4 - Previous Treatment.

Factor	Treatments			Total	P-value
	Fingolimod	Dimethyl Fumarate	Teriflunomide		
<i>Utilized treatment</i>					
No	7 (12.3)	2 (3.5)	1 (1.8)	10 (17.5)	0.38
Yes	37 (64.9)	3 (5.3)	7 (12.3)	47 (82.5)	
<i>Interferon beta-1a subcutaneously</i>					
No	28 (49.1)	3 (5.3)	5 (8.8)	36 (63.2)	0.99
Yes	16 (28.1)	2 (3.5)	3 (5.3)	21 (36.8)	
<i>Interferon beta-1a intramuscular</i>					
No	34 (59.7)	5 (8.8)	6 (10.5)	45 (79.0)	0.71
Yes	10 (17.5)	0	2 (3.5)	12 (21.1)	
<i>Interferon beta-1b subcutaneously</i>					
No	40 (70.2)	5 (8.8)	8 (14.0)	53 (93.0)	0.99
Yes	4 (7.0)	0	0	4 (7.0)	
<i>Natalizumab intravenous</i>					
No	40 (70.2)	5 (8.8)	7 (12.3)	52 (91.2)	0.99
Yes	4 (7.0)	0	1 (1.8)	5 (8.8)	
<i>Mycophenolate per os</i>					
No	43 (75.4)	5 (8.8)	8 (14.0)	56 (98.3)	0.99
Yes	1 (1.8)	0	0	1 (1.8)	
<i>Teriflunomide per os</i>					
No	42 (73.7)	5 (8.8)	7 (12.3)	55 (96.5)	0.99
Yes	2 (3.5)	0	0	2 (3.5)	
<i>Fingolimod per os</i>					
No	44 (77.2)	4 (7.0)	7 (12.3)	55 (96.5)	0.99
Yes	0	1 (1.8)	1 (1.8)	2 (3.5)	

Table 5 - Treatment history and the reason of treatment changed.

Factor	Treatments			Total	P-value
	Fingolimod	Dimethyl Fumarate	Teriflunomide		
<i>Treatment failure</i>					
No	26 (45.6)	5 (8.8)	7 (12.3)	38 (66.7)	0.10
Yes	18 (31.2)	0	1 (1.8)	19 (33.3)	
<i>Intolerant</i>					
No	33 (57.9)	3 (5.3)	5 (8.8)	41 (71.9)	0.59
Yes	11 (19.3)	2 (3.5)	3 (5.3)	16 (28.1)	
<i>Side effect</i>					
No	43 (75.4)	4 (7.0)	7 (12.3)	54 (94.7)	0.12
Yes	1 (1.8)	1 (1.8)	1 (1.8)	3 (5.3)	
<i>John Cunningham virus antibodies positive*</i>					
No	41 (71.9)	5 (8.8)	7 (12.3)	53 (93.0)	0.65
Yes	3 (5.3)	0	1 (1.8)	4 (7.0)	
<i>Unknown reason</i>					
No	40 (70.2)	5 (8.8)	7 (12.3)	41 (71.9)	0.99
Yes	4 (7.1)	0	1 (1.8)	5 (8.8)	

*associated with Natalizumab therapy

The effectiveness was captured by tracking relapse rate per year and by assessing MRI results. Relapse rate per patient per year varied: 0.5 for teriflunomide, 0.34 for dimethyl fumarate, and 0.24 for fingolimod. This study's estimate for fingolimod aligned with the estimates reported by previous clinical trials, such as the TRANSFORMS trial (0.2), FREEDOMS trial (0.18), and FREEDOMS II trial (0.21).^{8,9} The relapse rate recorded for dimethyl fumarate, however, was higher than seen in previous clinical trials, such as the DEFINE trial (0.17) and CONFIRM trial (0.22),¹⁴ as was the rate for teriflunomide compared with the figures seen in the TEMSO trial (0.37), TOWER trial (0.32), and TENERE trial (0.26).¹² Notably, however, the fingolimod group was the largest in this study, perhaps explaining why the estimates for this group more closely aligned with the findings of clinical trials than were the estimates for the 2 other groups.

Effectiveness can also be measured using MRI results, in this case, in descending order of frequency, new T2-weighted lesion, new gadolinium-enhancing lesion, and enlarged T2-weighted lesion. However, these MRI results should be interpreted with caution, as only half of patients underwent MRI monitoring, an alarming finding considering that the International Advisory Committee on Clinical Trials of MS has recommended that MRI scanning be conducted at least annually.² Despite this recommendation, however, MRI frequency, timing, and protocols differ among care centers, both locally and internationally.³¹

The discontinuation rate was explored, which at 7.2% overall was significantly lower than the 29.7% reported by Hua et al.³² The magnitude of this difference might be a function of the average age of study participants, 32 years for the present study versus 60 years for the prior one.³² Moreover, the treatments included in our study were given as many patients' second-line therapy, whereas previous reports focused on discontinuation rates for first-line therapies.³³ In our study population, the fingolimod group reported a 4.5% discontinuation rate, lower than that seen in larger clinical trials, such as the TRANSFORMS trial (5.6%), FREEDOMS trial (7.5%), and FREEDOMS II trial (18%).^{8,9} In the teriflunomide group, 2 patients (25%) discontinued the medication, compared with 10.9% in the TEMSO trial, 16% in the TOWER trial, and 10.9% in the TENERE trial.¹²

Finally, treatment history was investigated. More than 80% of the study sample had used previous treatments, half of which had in turn involved use of Interferon Beta-1a. These results align with international therapeutic practice, for although no clear guidelines

exist for the pharmacological management of MS, many clinicians consider Interferon Beta-1a to be the first-line therapy for RRMS.³⁴ However, more than a third of our population had changed their first-line therapy after it had failed, consistent with previous reports in the literature that treatment failure is a significant burden on patients who have MS.^{35,36} However, as definitions and timings of treatment failure are inconsistent internationally, further research is needed into this issue.³⁶

Study limitations. The average duration of treatment in this study was 15 months. However, even though longer durations are preferred, the study was nonetheless able to capture significant number of relapse rates for each treatment group. Moreover, a 15-months duration of treatment aligns with the ranges seen in larger clinical trials that have studied treatment for MS, which have featured durations ranging from 12 months to 24 months.^{8,9,12,14} Additionally, the main parameters used to gauge effectiveness in this study were relapse rate per year and MRI results; a proposed targeted MS treatment endpoint that relied on evidence of disease activity status was discussed in the literature but could not be measured in this study.³⁷ Further research, however, could apply this new measure to compare various MS treatments.

In conclusion, our results were able to capture the effectiveness rate for the targeted treatment in the studied population, with the frequency of incidence of side effects. However, as these results cannot be generalized for the entire Saudi population, owing to this study's small sample size, clinicians should focus on monitoring patients for both effectiveness and safety.

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