Original Article

Achievement of No Evidence of Disease Activity-3 with Oral Disease-Modifying Treatment in Patients with Relapsing–Remitting Multiple Sclerosis

Foziah Jabbar Gossab Alshamrani, Azra Zafar, Rahmah Majed Alsawad[1], Zakia Yasawy, Rizwana Shahid, Saima Nazish, Erum Shariff, Nehad Mahmoud Soltan

Department of Neurology, College of Medicine, Imam Abdulrahman bin Faisal University, Dammam, King Fahd Hospital of the University, Al Khobar, Saudi Arabia, [1]College of Medicine, Dar Aluloom University, Riyadh, Saudi Arabia

Abstract

Background: There is scant data regarding the use of oral disease-modifying treatments (oDMT) in patients with relapsing–remitting multiple sclerosis (PwRRMS) from Saudi Arabia.

Objective: This study aimed to identify the response rate to oDMT in PwRRMS compared to interferon (IFN) in terms of achieving no evidence of disease activity-3 (NEDA-3).

Methods: This retrospective study was conducted at a tertiary care hospital in Saudi Arabia and included all adult PwRRMS over a 2-year period who were on oDMTs or IFN for <1 year. The achievement of overall NEDA-3 and its components (namely, relapse, disability progression, and focal MRI activity) were assessed for each treatment.

Results: A total of 231 patients were included for the analysis of NEDA-3 status, of which 78 (33.8%) were on oDMTs (namely, dimethyl fumarate, teriflunomide, and fingolimod). NEDA-3 status was achieved in 51.3% (OR: 1.86, 95% CI: 1.28–2.71) of patients on oDMTs and in 32% of patients on IFN (OR: 0.72, 95% CI: 0.58–0.89) ($P < 0.001$). Compared to the IFN group, the oDMT group had significantly lower rates of clinical relapse ($P < 0.001$), disability progression ($P = 0.004$), and new focal MRI activity ($P = 0.01$). Patients on dimethyl-fumarate had higher odds of achieving NEDA-3 (OR: 2.18, 95% CI = 1.09–4.34; $P = 0.02$) compared with those on fingolimod (OR: 2.15, 95% CI = 0.70–6.58; $P = 0.16$) and teriflunomide (OR: 1.53, 95% CI = 0.81–2.91; $P = 0.18$).

Conclusion: More than half of the patients with relapsing–remitting multiple sclerosis on oral DMTs achieved NEDA-3 status in this study. Significant differences were observed in NEDA-3 status parameters and achievement between patients on oral DMTs and interferon, with the likeliness being highest among patients treated with dimethyl-fumarate.

Keywords: Disease modifying treatment, interferon, prognosis, oral, relapsing–remitting multiple sclerosis, Saudi Arabia

Address for correspondence: Dr. Foziah Jabbar Gossab Alshamrani, Department of Neurology, College of Medicine, Imam Abdulrahman bin Faisal University, Dammam, King Fahd Hospital of the University, Al Khobar, Saudi Arabia.
E-mail: fshamrani@iau.edu.sa

Submitted: 12-Mar-2024 **Revised:** 11-Jul-2024 **Accepted:** 04-Aug-2024 **Published:** 12-Oct-2024

Access this article online	
Quick Response Code:	Website: https://journals.lww.com/sjmm
	DOI: 10.4103/sjmms.sjmms_148_24

How to cite this article: Alshamrani FJ, Zafar A, Alsawad RM, Yasawy Z, Shahid R, Nazish S, *et al*. Achievement of no evidence of disease activity-3 with oral disease-modifying treatment in patients with relapsing–remitting multiple sclerosis. Saudi J Med Med Sci 2024;12:299-305.

INTRODUCTION

Multiple sclerosis (MS) is the most frequent cause of acquired functional disability in the younger population.[1] In Saudi Arabia, the prevalence of MS has been estimated to be 30–40.4/100,000; however, the actual prevalence could be higher, as MS remains underdiagnosed.[2,3] Relapsing MS (RMS) is the most frequent clinical variant of MS, observed in 60%–90% of the patients with MS in Saudi Arabia.[3-6]

Disease-modifying treatments (DMT) have shown promising results in reducing the relapse rate and subclinical focal inflammatory cerebral activity, as evidenced by a reduction in disease burden on MRI, the appearance of new or enlarging T2-lesions and gadolinium (Gd)-enhancing lesions, and disability progression in patients with relapsing–remitting MS (PwRRMS).[7,8] No evidence of disease activity-3 (NEDA-3), a composite marker comprising the absence of clinical relapse, disability progression, and active disease on MRI, is often considered a treat-to-target strategy of DMT for PwRMSS.[9] It has been reported that patients achieving NEDA-3 status within 2 years of starting DMT have an 80%–90% positive predictive value for remaining free of longer-term functional disability.[10] Further, in one assessment of NEDA-3 status in patients with MS on moderately efficacious (interferon [IFN], glatiramer acetate, teriflunomide [TF], and dimethyl-fumarate [DMF]) and highly efficacious (natalizumab, fingolimod and alemtuzumab) DMT, Simonsen *et al*. observed that the NEDA-3 achievement rate at 1 year of diagnosis was 38%.[11] From Saudi Arabia, a single-center study has shown that NEDA-3 status was achieved in 33.6% of PwRRMS, who were mainly on IFN therapy.[12]

Oral DMT (oDMT) are convenient and easy-to-use medication that have similar or superior efficacy to injectable DMT;[13] notably, studies have found that oDMT are preferred to parenterally administered products.[14,15] The first approved oDMTs to treat MS included TF, DMF, and fingolimod,[16] all of which are available and administered to PwRRMS in Saudi Arabia, and their effectiveness has been documented by one study from Riyadh.[17] The current study aimed to assess the achievement of NEDA-3 in PwRRMS taking oDMTs, considering that patients are likely to be more adherent to oDMTs than parenteral treatments. The results of this study would provide evidence regarding the responsiveness to oDMT among Saudis, which was previously lacking.

METHODS

Setting and sampling

This retrospective study was conducted in the Neurology Department at King Fahd Hospital of the University, Al Khobar, Saudi Arabia, from January 2021 until December 2022, after obtaining ethical approval from the Institution Review Board. The hospital runs two separate specialized MS clinics per week, in addition to an infusion unit, with staff skilled in oDMT and IFN management working under the supervision of qualified MS consultants. Data for all PwRRMS were maintained in the hospital's electronic medical record (EMR) system.

Inclusion and exclusion criteria

All adult patients (aged ≥18 years) with a diagnosis of RRMS based on the 2010 McDonald criteria[18] and the 2017 revised criteria[19] who were on oDMTs or IFN for a duration of <1 year were enrolled in the study. Patients taking oDMT or IFN with significant functional disability at baseline, as evidenced by an Expanded Disability Status Scale (EDSS)[20] >5, were excluded.

Data collection methods

The data collection methods were as described previously.[12] The EMR of PwRRMS diagnosis was reviewed for demographic and clinical details. Demographic, clinical, and radiological characteristics of PwRRMS were noted. Clinical features, EDSS, and radiological findings on MRI were noted prior to starting DMT, and at least 1 year after starting oDMTs. Disability progression was documented based on the EDSS scores. Three oDMTs were available at our hospital (TF, DMF, and fingolimod). However, each patient only received any of these and were followed-up with the same medication for a median duration of 36 months.

Definitions

The definitions used for NEDA-3 status[21] and its components, namely, relapse,[18] disability progression,[22] and focal MRI activity,[21] were in accordance with the published literature as follows:

1. Relapse: The appearance of either a new neurological abnormality, or the worsening of a previously stable abnormality lasting for ≥24 h, in the absence of fever or infection within 1 week of symptom onset[18]
2. Disability progression: An increase in the EDSS score of ≥1.5 points between two time points, if the baseline EDSS score was 0.0, ≥1.0 point if the baseline EDSS score was 1.5, and ≥0.5 points if the baseline EDSS score was >5.0[22]

3. Focal MRI activity: Development of new (>3 mm) or enlargement of established T2 lesions, and/or Gd-enhanced T1 lesions. Patients for whom Gd-enhancing lesions were not assessed during the follow-up period were assumed to have no Gd-enhancing lesions if they had no new or enlarged T2 lesions[21]
4. NEDA-3 status: No relapse, no disability progression, and no new/enlarged T2-or Gd-enhancing lesions.[21]

Statistical analysis

Statistical analyses were performed using SPSS version 28 (IBM Co., Armonk, NY, USA). Numerical parametric data are presented as mean and standard deviation (SD) and were analyzed using an independent sample *t*-test. Non-parametric data are presented as median and interquartile range (IQR) and were analyzed using the Mann–Whitney *U* test. Categorical data are presented as frequencies and percentages and were analyzed using the Chi-square test or Fisher's exact test, as appropriate.

Logistic regression analysis was performed to assess the different factors associated with the achievement of NEDA-3 status and to compare parameters between patients receiving oDMTs and IFN. Statistical significance was defined as a two-tailed *P* value <0.05.

RESULTS

The study population comprised 236 PwRRMS. The median (IQR) age was 34 (28–40) years, with a female predominance (68.2%). The median baseline EDSS was 1.5, and did not differ between the two groups ($P = 0.15$). Demographic and clinical characteristics of the patients according to the treatment received is shown in Table 1.

The most frequent clinical manifestations at presentation were related to the pyramidal tract: motor (28%), cerebellar ataxia and dysarthria (26.3%), sensory symptoms (22.9%), and optic neuritis (17.8%). Incontinence, headache, and seizures were reported in 20.3%, 14.7%, and 7% of the patients, respectively. Sensory symptoms, optic neuritis, and incontinence were less frequent in patients prescribed oDMTs than those prescribed IFN [Table 1]. oDMTs were taken by 35.2% of the patients (TF, 16.1%; DMF, 12.7%; and fingolimod, 6.4%), most of whom (93.1%) were compliant with the prescribed medications.

The assessment of NEDA-3 status achievement was conducted for 231 patients, with data from five patients excluded due to loss to follow-up, which result in missing information. NEDA-3 status was achieved in 38.5% of all patients, and the individual parameters are summarized in Figure 1. Most patients (54.1%) taking DMT did not experience a relapse. Less than one-third of those on oDMT and more than half of those on IFN had at

Table 1: Characteristics of the enrolled patients

Variables	Total patients (N=236)	Interferon 153 (64.8%)	Oral DMT 83 (35.2%)	Common Odds ratio	95% Confidence Interval	*P*
Demographic characteristics						
Age (years)						
Mean±SD	34.7±9.4	34.5±9.3	35.1±9.7	–	–	0.62
Median (IQR)	34 (28–40)	33 (28–40)	35 (28–40)			
Male	75 (31.8%)	52 (34%)	23 (27.7%)	0.74	0.41–1.33	0.32
Female	161 (68.2%)	101 (66%)	60 (72.3%)		–	0.32
Clinical variables						
Age at diagnosis (years)	27.3±8.7	27.0±8.5	27.7±9.0		–	0.58
Baseline EDSS						
Mean±SD	1.7±1.0	1.8±1.0	1.6±1.0			0.15
Median (IQR)	1.5 (1.0–2.5)	2.0 (1.0–2.5)	1.0 (1.0–2.2)			
Motor	66 (28)	44 (28.8)	22 (26.5)	0.89	0.49–1.62	0.71
Optic neuritis	42 (17.8)	34 (22.2)	08 (3.4)	0.37	0.16–0.85	0.02
Ataxia	43 (18.2)	33 (21.6)	10 (12)	0.49	0.23–1.07	0.07
Cerebellar	62 (26.3)	42 (27.5)	20 (24.1)	0.83	0.45–1.55	0.47
Brainstem	49 (20.8)	28 (18.3)	21 (25.3)	1.51	0.79–2.87	0.20
Sensory	54 (22.9)	43 (28.1)	11 (13.3)	0.39	0.18–0.80	0.01
Incontinence	48 (20.3)	37 (24.2)	11 (13.3)	0.47	0.23–0.99	0.04
Radiological characteristics						
Supratentorial lesions	235 (99.6)	152 (99.3)	83 (100)	0.64	0.58–0.71	0.46
Infratentorial lesions	140 (59.3)	91 (59.5)	49 (59)	0.98	0.57–1.69	0.94
Spinal cord lesions	120 (50.8)	67 (43.8)	53 (63.9)	2.26	1.29–3.94	0.004
MRI brain hyperintense T2 lesions	236 (100)	153 (100)	83 (100)		–	0.158
Gd-enhanced lesions	39 (17.1)	32 (53.7)	7 (8.3)	0.34	0.14–0.82	0.014

EDSS – Expanded Disability Status Scale; SD – Standard deviation; DMT – Disease-modifying treatment; MRI – Magnetic resonance imaging

least one relapse (P <0.01). Clinical relapse, disability progression, and new MRI activity were significantly less frequent in patients administered oDMT than in those who were administered IFN [Figure 2]. At baseline, hyperintense T2 lesions and Gd-enhanced T1 lesions were detected in 17.1% of the patients on MRI. Focal MRI activity, indicating active disease, was detected in 54.1% of the patients during follow-up studies and was the most common parameter contributing to the failure in achieving NEDA-3 status. In addition, new Gd-enhanced T1 lesions were detected in 23% of patients at 6-month follow-up.

The frequencies and likeliness of clinical relapse, disability progression, and new MRI activity according to each prescribed medication are summarized in Table 2. Among all oDMT, DMF had the best outcomes (relapse: 31%; disability progression: 20.7%; new MRI activity: 41.3%), whereas INF had the worse outcomes (relapse: 54.2%; disability progression: 29.4%; new MRI activity: 58.8% [Figure 3].

In the univariate analysis, the highest likelihood of achieving the NEDA-3 status was observed with DMF treatment (OR = 1.86, 95% CI = 1.28-2.71; P =0.001) and the lowest with IFN treatment (OR = 0.72, 95% CI = 0.58–0.89; P <0.001). In the multivariate analysis, the likeliness of achieving NEDA-3 status was significantly higher with oDMTs (OR: 2.49, 95% Cl = 1.34-4.62) than IFN (OR: 0.40, 95% Cl = 0.21–0.74) (P = 0.004) [Table 3].

DISCUSSION

The current study evaluated the response rate to oDMTs and the attainment of NEDA-3 status in PwRRMS from a single center in Saudi Arabia. The findings of this cohort study demonstrate the importance of oDMT prescriptions for the treatment of PwRRMS and provide valuable data regarding the relative efficacy of oDMTs compared with IFN in achieving NEDA-3 status. Prescribing DMTs with higher efficacy early in the course of disease in patients with MS has been considered an appropriate strategy for achieving long-term results.[23] According to our findings, 51.3% of patients on oDMTs attained NEDA-3 status compared with only 32% of patients on IFN. In a similar study from Norway, 38% of patients receiving highly and moderately efficacious DMTs, including oDMTs, achieved NEDA-3.[11] Our results indicating the higher efficacy of oDMTs over IFN in lowering clinical relapse, disability progression, and new focal MRI activity support their use in the treatment of PwRRMS [Table 2].

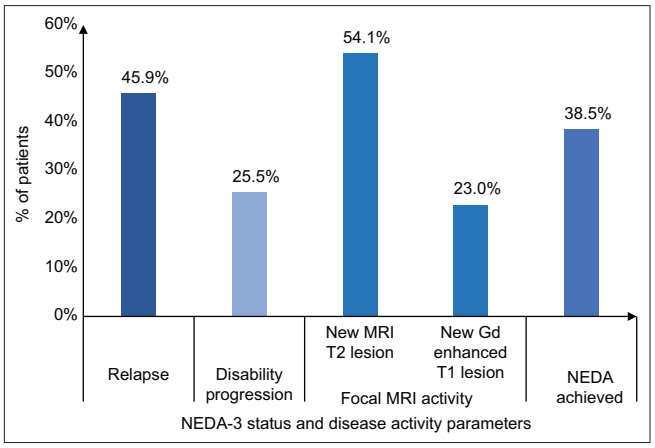

Figure 1: Clinical and radiological parameters indicating disease activity and NEDA-3 status in all patients

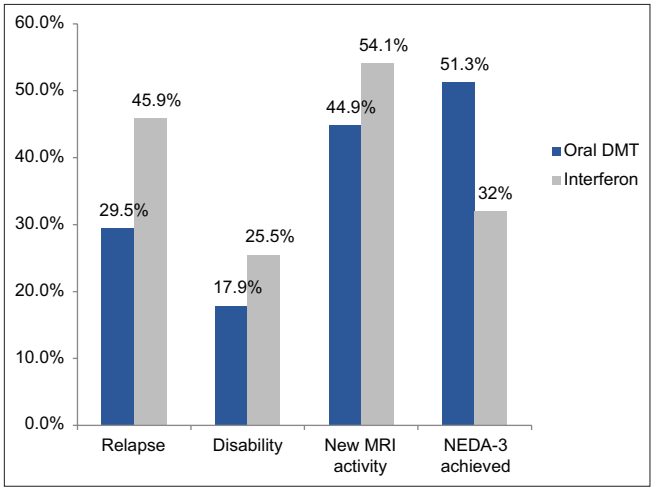

Figure 2: Disease activity parameters and NEDA-3 status in patients receiving oral DMT versus Interferon

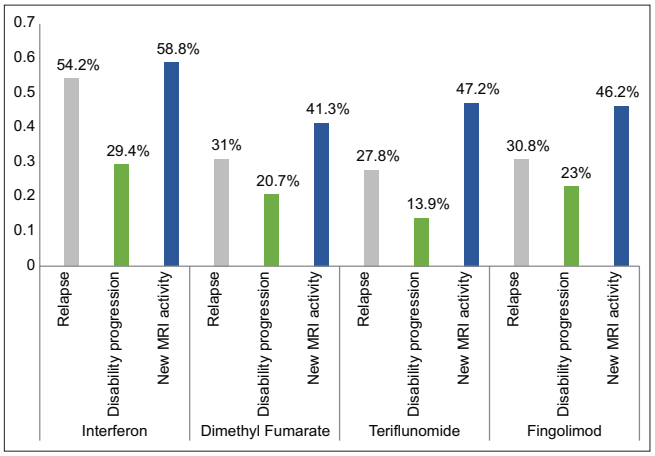

Figure 3: Disease activity parameters for each type of therapy

Several characteristics were explored for their impact on NEDA-3 status in patients during the univariate analysis, including baseline EDSS and early clinical symptoms. The baseline EDSS is a disability measure used to evaluate

Table 2: Detailed analysis of NEDA-3 status for different oral DMT and interferon with individual parameters

Type of medication (*n*)	No relapse (*n*=125; 54.1%) *n* (%) OR, 95% CI, *P*	No disability progression (*n*=172; 74.5) *n* (%) OR, 95% CI, *P*	No new MRI activity 106 (45.9%) *n* (%) OR, 95% CI, *P*	NEDA-3 status achieved 89 (38.5) *n* (%) OR, 95% CI, *P*
Interferon (153)	70 (45.8)	108 (70.6)	63 (41.2)	49 (32)
	0.39, 0.24–0.63	0.42, 0.21–0.82	0.62, 0.41–0.92	0.72, 0.58–0.89
All oDMTs (78)	55 (70.5)	64 (82.1)	43 (55.1)	40 (51.3)
	1.47, 1.23–1.76, <0.001	1.34, 1.13–1.58, 0.004	1.28, 1.05–1.55, 0.01	1.86, 1.28–2.71, 0.001
Dimethyl Fumarate (29)	20 (69)	23 (79.3)	17 (58.6)	17 (58.6)
	1.09, 0.99–1.20, 0.08	1.04, 0.93–1.16, 0.49	1.08, 0.98–1.20, 0.10	2.18, 1.09–4.34, 0.02
Teriflunomide (36)	26 (72.2)	31 (86.1)	19 (52.8)	16 (44.4)
	1.18, 1.06–1.31, 0.002	1.19, 1.10–1.29, 0.004	1.08, 0.96–1.21, 0.17	1.53, 0.81–2.91, 0.18
Fingolimod (13)	09 (69.2)	10 (77)	7 (53.8)	7 (53.8)
	1.04, 0.98–1.12, 0.17	1.02, 0.95–1.09, 0.59	1.02, 0.95–1.09, 0.48	2.15, 0.70–6.58, 0.16

oDMT – Oral disease-modifying treatment; CI – Confidence interval; MRI – Magnetic resonance imaging; NEDA-3 – No evidence of disease activity-3

Table 3: Variables having significant association with NEDA-3 status achievement during univariate and multivariate analysis

Parameters	NEDA-3 achieved	NEDA-3 achieved Univariate analysis OR, 95% CI, *P*	NEDA-3 not achieved Univariate analysis OR, 95% CI, *P*	Multivariate analysis OR, 95% CI, *P*
Baseline EDSS	1.46±1.04	0.001	1.93±1.00	0.74, 0.54–1.02, 0.07
Motor (*n*=65)	16	0.53, 0.32–0.87, 0.008	1.24, 1.06–1.45, 0.008	0.49, 0.23–1.03, 0.06
Ataxia (*n*=43)	06	0.26, 0.11–0.59, 0.000	1.25, 1.12–1.40, 0.000	0.46, 0.13–1.61, 0.22
Cerebellar (*n*=62)	14	0.47, 0.27–0.80, 0.003	1.26, 1.09–1.46, 0.003	1.52, 0.56–4.15, 0.40
Urinary incontinence (*n*=48)	11	0.48, 0.26–0.89, 0.01	1.18, 1.04–1.33, 0.01	0.52, 0.21–1.26, 0.15
Interferon	49	0.72, 0.58–0.89, 0.001	1.86, 1.28–2.71, 0.001	0.40, 0.21–0.74
oDMTs	40	1.86, 1.28–2.71, 0.001	0.72, 0.58–0.89, 0.001	2.49, 1.34–4.62, 0.004

EDSS – Expanded disability status scale; OR – odds ratio; CI – Confidence interval; *P* – *P* value; NEDA-3 – No evidence of disease activity-3; oDMT – Oral disease-modifying treatment

patients with MS. In the present study, patients with lower baseline EDSS scores had a higher chance of achieving NEDA-3 status. This indicates that NEDA-3 status is more likely to be attained by patients if oDMT is initiated at a stage when the disease is less disabling. Baseline EDSS was an important confounder in our study; however, it was adjusted for during the multivariate logistic regression to analyze the effect of oDMT. Notably, EDSS scores did not differ between the two groups in our study cohort. This study also found that individuals had a lower chance of achieving NEDA-3 status if they had certain initial clinical manifestations, including motor symptoms, ataxia, and dysarthria. However, none of these clinical symptoms or the EDSS score was found to be significant in the multivariate analysis, except for the type of DMT administered. [Table 3] Treatment with DMF resulted in lower relapse rate, disability progression, and activity compared with other oDMTs, which agrees with the findings of Zilli *et al*.[23] Nevertheless, these data suggest that baseline EDSS and early clinical symptoms may have some influence in achieving NEDA-3 status in PwRRMS, and thus carry some prognostic value that needs to be studied further in larger studies [Table 3].

Overall, our findings are in line with those of earlier studies that demonstrated the efficacy of oDMTs in reducing disease activity and improving the outcomes of PwRRMS.[7,8,11] Notably, the findings of the efficacy and side effects of oDMTs in a set of Saudi populations from Riyadh were in line with those of studies from the rest of the world. In that study, the authors emphasized the need for further large-scale studies of these therapies within the local context, as 80% of their patients were switching therapies, indicating a higher proportion of patients not continuing IFN.[17] Prior studies have also reported that nearly half of the patients prescribed injectable DMTs were non-adherent after 1 year.[24,25] In one study comparing injectable and oral DMTs, patients reported that oral medicine treatment was more convenient.[26] Remarkably, according to real-world data from the Italian Multiple Sclerosis Register, first-line oDMTs appear to be less likely to cause a fresh relapse and medication discontinuation than injectable DMTs.[27]

Interestingly, the *post hoc* analyses of data from different pivotal clinical trials of oDMTs including fingolimod, DMF, TF, and cladribine revealed comparable effects for these oDMTs across the main clinical outcomes: annual relapse rate, clinical disability progression, and new MRI activity.[28] Another study, comparing both DMF and TF, revealed that patients on DMF had a longer duration without relapse than the TF group after the first 38 months of treatment.[29] Remarkably, our patients receiving DMF had a higher incidence of NEDA-3 accomplishment than

those receiving fingolimod and TF. These results indicate that DMF is particularly useful in helping PwRRMS achieve ideal illness management. The efficacy and safety of DMF as an oDMT for MS have previously been investigated in a study conducted in China, the findings of which corroborate the beneficial profile of DMF in the treatment of MS; however, limited data from Chinese patients were considered.[30] Positive outcomes from clinical trials have also been observed, including notable decreases in relapse rates when compared to placebo.[31-33] Notwithstanding the fact that there have been several studies, including the current study, providing evidence to support the effectiveness of oDMTs for MS, yet there is a lack of comprehensive studies examining the benefits of these treatments on a broader scale, such as in a multi-center study from Saudi Arabia with a larger sample size with a longer study duration. Therefore, the effectiveness and value of using different oDMTs in the treatment of MS warrant further exploration, particularly in multicenter trials with larger sample sizes.

The prevalence of MS is high in the Arabian Gulf countries (AGC) (54.8–85.0/100,000), a trend that has only continued to increase over the past few decades. As such, local governmental health authorities are actively investigating the therapeutic paradigm, and taking measures to reduce the disability associated with this disease.[28,34] Developing countries within the AGC, including Saudi Arabia, have access to all US Food and Drug Administration-approved treatments for PwRRMS. Furthermore, in the AGC, all governmental health services provide DMTs free of charge to their nationals with PwRRMS. As injectable DMTs use is affected by suboptimal patient adherence, the approval of several oDMTs has reduced the burden of injection, which improves patient satisfaction and adherence.[29] Another achievement of such measures is the recent development of Saudi Consensus recommendations by a group of experts for the management of MS patients under the supervision of the Ministry of Health for adults[34] and for children and adolescents.[35]

Overall, these findings add to the increasing amount of available data demonstrating the efficacy of oDMTs in the management of RRMS. This study highlights the significance of oDMT prescriptions and the necessity of addressing the obstacles or causes underlying the underutilization of these therapies in our region. Lack of literature could possibly be a barrier in the uptake of oDMTs among clinicians, and thus there is need for further studies to elucidate the efficacy, safety, and overall impact of oDMTs in achieving NEDA-3 status on local communities.

Limitations

This is a retrospective study and has its inherent limitations, including not being able to determine a cause-and-effect relationship. In addition, the generalizability of the findings may be limited because of the small sample size. Therefore, further studies with larger sample sizes and prospective methods are needed to confirm the findings of the current study.

CONCLUSION

This study showed that in patients with relapsing–remitting multiple sclerosis, treatment with oDMTs significantly increases the likeliness of achieving NEDA-3 status compared with treatment with IFN. The importance of oDMTs in the management of patients with relapsing–remitting multiple sclerosis is highlighted by their efficacy in reducing disease activity and improving outcomes. Further investigation is required to compare the efficacy of various oDMTs and identify ways to encourage their wider use in clinical settings in Saudi Arabia.

Ethical considerations

The study was approved by the Institution Review Board of Imam Abdulrahman Bin Faisal University (IRB no.: IRB-2020-01-211), Dammam, Saudi Arabia. Requirement for patient consent was waived owing to the study design. The study adhered to the principles of the Declaration of Helsinki, 2013.

Peer review

This article was peer-reviewed by two independent and anonymous reviewers.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Conceptualization: F.J.G.A. and A.Z.; Methodology: A.Z., R.M.A., and S.N.; Data analysis: A.Z.; Writing–original draft preparation: A.Z. and R.M.A.; Writing – review and editing: F.J.G.A., Z.Y., R.S., E.S., and N.S.; Supervision: F.J.G.A.

All authors have read and agreed to the published version of the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Compston A, Coles A. Multiple sclerosis. Lancet 2002;359:1221-31.
2. Al-Saeed OM, Albogami MF, Hatem M. Multiple sclerosis in Saudi Arabia: A literature review. Saudi J Health Sci 2021;10:160-4.
3. AlJumah M, Otaibi HA, Al Towaijri G, Hassan A, Kareem A, Kalakatawi M, *et al*. Familial aggregation of multiple sclerosis: Results from the national registry of the disease in Saudi Arabia. Mult Scler J Exp Transl Clin 2020;6:2055217320960499.
4. Daif AK, Al-Rajeh S, Awada A, Al Bunyan M, Ogunniyi A, AbdulJabar M, *et al*. Pattern of presentation of multiple sclerosis in Saudi Arabia: Analysis based on clinical and paraclinical features. Eur Neurol 1998;39:182-6.
5. Nazish S, Shahid R, Zafar A, Alshamrani F, Sulaiman AA, Alabdali M, *et al*. Clinical presentations and phenotypic spectrum of multiple sclerosis at a University Hospital in Saudi Arabia. J Clin Neurol 2018;14:359-65.
6. Algahtani H, Shirah B, Bayazeed A, Alghamdi A, Almailabi M, Algharib M, *et al*. Assessment of the burden of multiple sclerosis patients' caregivers in Saudi Arabia. Cureus 2020;12:e6658.
7. Liu Z, Liao Q, Wen H, Zhang Y. Disease modifying therapies in relapsing-remitting multiple sclerosis: A systematic review and network meta-analysis. Autoimmun Rev 2021;20:102826.
8. Fuh-Ngwa V, Charlesworth JC, Zhou Y, van der Mei I, Melton PE, Broadley SA, *et al*. The association between disability progression, relapses, and treatment in early relapse onset MS: An observational, multi-centre, longitudinal cohort study. Sci Rep 2023;13:11584.
9. Giovannoni G, Tomic D, Bright JR, Havrdová E. "No evident disease activity": The use of combined assessments in the management of patients with multiple sclerosis. Mult Scler 2017;23:1179-87.
10. Rotstein DL, Healy BC, Malik MT, Chitnis T, Weiner HL. Evaluation of no evidence of disease activity in a 7-year longitudinal multiple sclerosis cohort. JAMA Neurol 2015;72:152-8.
11. Simonsen CS, Flemmen HØ, Broch L, Brekke K, Brunborg C, Berg-Hansen P, *et al*. Rebaseline no evidence of disease activity (NEDA-3) as a predictor of long-term disease course in a Norwegian multiple sclerosis population. Front Neurol 2022;13:1034056.
12. Zafar A, AlShamrani FJ. No evidence of disease activity-3 (NEDA-3) status in patients with relapsing remitting multiple sclerosis: Evidence from Saudi cohort receiving mainly interferon. Mult Scler Relat Disord 2021;51:102875.
13. Garg N, McCarthy M, Karmarkar A. Oral therapies for MS. Pract Neurol 2019;Nov–Dec.
14. Hincapie AL, Penm J, Burns CF. Factors associated with patient preferences for disease-modifying therapies in multiple sclerosis. J Manag Care Spec Pharm 2017;23:822-30.
15. Wilson LS, Loucks A, Gipson G, Zhong L, Bui C, Miller E, *et al*. Patient preferences for attributes of multiple sclerosis disease-modifying therapies: Development and results of a ratings-based conjoint analysis. Int J MS Care 2015;17:74-82.
16. Araujo L, Geertsen SS, Amedume A, Higuchi K, van Wingerden J. Persistence, adherence, and switching to higher-cost therapy in patients with multiple sclerosis initiating oral disease-modifying therapies: A retrospective real-world study. Neurol Ther 2022;11:1735-48.
17. Al Turaiki AM, Al Ammari MA, Alabdulkarim DA, Althemery AU. Assessment of safety and effectiveness of oral multiple sclerosis medication. Saudi Med J 2019;40:1116-22.
18. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, *et al*. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292-302.
19. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, *et al*. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162-73.
20. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An Expanded Disability Status Scale (EDSS). Neurology 1983;33:1444-52.
21. Weinstock-Guttman B, Medin J, Khan N, Korn JR, Lathi E, Silversteen J, *et al*. Assessing 'No Evidence of Disease Activity' status in patients with relapsing-remitting multiple sclerosis receiving fingolimod in routine clinical practice: A retrospective analysis of the multiple sclerosis clinical and magnetic resonance imaging outcomes in the USA (MS-MRIUS) study. CNS Drugs 2018;32:75-84.
22. Banwell B, Giovannoni G, Hawkes C, Lublin F. Editors' welcome and a working definition for a multiple sclerosis cure. Mult Scler Relat Disord 2013;2:65-7.
23. Zilli C, Scribani Rossi P, Di Stadio A, Fratino M, Giuliani G, Annecca R, *et al*. Assessing 'No Evidence of Disease Activity' status in patients with relapsing-remitting multiple sclerosis: A long-term follow-up. Front Neurol 2023;14:1187851.
24. Bergvall N, Petrilla AA, Karkare SU, Lahoz R, Agashivala N, Pradhan A, *et al*. Persistence with and adherence to fingolimod compared with other disease-modifying therapies for the treatment of multiple sclerosis: A retrospective US claims database analysis. J Med Econ 2014;17:696-707.
25. Agashivala N, Wu N, Abouzaid S, Wu Y, Kim E, Boulanger L, *et al*. Compliance to fingolimod and other disease modifying treatments in multiple sclerosis patients, a retrospective cohort study. BMC Neurol 2013;13:138.
26. Hojjati S, Ernerudh J, Vrethem M, Mellergård J, Raffetseder J. Dimethyl fumarate treatment in relapsing remitting MS changes the inflammatory CSF protein profile by a prominent decrease in T-helper 1 immunity. Mult Scler Relat Disord 2023;80:105126.
27. D'Amico E, Zanghì A, Romeo M, Cocco E, Maniscalco GT, Brescia Morra V, *et al*. Injectable versus oral first-line disease-modifying therapies: Results from the Italian MS register. Neurotherapeutics 2021;18:905-19.
28. Deleu D, Mesraoua B, Canibaño B, Melikyan G, Al Hail H, El-Sheikh L, *et al*. Oral disease-modifying therapies for multiple sclerosis in the middle Eastern and North African (MENA) region: An overview. Curr Med Res Opin 2019;35:249-60.
29. D'Amico E, Zanghì A, Sciandra M, Lanzillo R, Callari G, Cortese A, *et al*. Dimethyl fumarate versus teriflunomide: An Italian time-to-event data analysis. J Neurol 2020;267:3008-20.
30. Gold R, Barnett M, Chan A, Feng H, Fujihara K, Giovannoni G, *et al*. Clinical use of dimethyl fumarate in multiple sclerosis treatment: An update to include China, using a modified Delphi method. Ther Adv Neurol Disord 2023;16:17562864231180734.
31. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, *et al*. Placebo- controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012;367:1098-107.
32. Gold R, Arnold DL, Bar-Or A, Fox RJ, Kappos L, Mokliatchouk O, *et al*. Long-term safety and efficacy of dimethyl fumarate for up to 13 years in patients with relapsing-remitting multiple sclerosis: final ENDORSE study results. Mult Scler 2022; 28: 801–816.
33. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, *et al*. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012;367:1087-97.
34. Bomprezzi R. Dimethyl fumarate in the treatment of relapsing-remitting multiple sclerosis: An overview. Ther Adv Neurol Disord 2015;8:20-30.
35. Alroughani R, Ahmed SF, Behbahani R, Khan R, Thussu A, Alexander KJ, *et al*. Increasing prevalence and incidence rates of multiple sclerosis in Kuwait. Mult Scler 2014;20:543-7.