ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 10 | October - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

"SAFETY, EFFICACY, AND ADHERENCE OF DIMETHYL FUMARATE IN PATIENTS WITH MULTIPLE SCLEROSIS- A REAL-WORLD EXPERIENCE"

Neurology

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ABSTRACT

Background: To study the efficacy and safety of DMF (Dimethyl fumarate) and factors related to drug response, switching and adherence of DMF in the Indian population. We aimed to evaluate the efficacy, safety and tolerability of DMF in multiple sclerosis (MS). **Methods**: A chart review was performed for patients treated with DMF in MS from the MS registry maintained at the hospital. We performed analyses to assess relationships between baseline parameters and DMF efficacy, outcome and Expanded Disability Status Scale (EDSS) progression status. **Results:** The study included 37 patients (median follow-up = 27.5 months). The majority had previously been treated with other Disease modifying therapies -DMTs (59.5%). The average EDSS before DMF was 3.5± 1.8 and average EDSS after minimum 6 months of DMF was 3.01±1.9. During the follow-up period, 10 (27%) patients switched treatment; eight were due to clinical or radiological relapse. None of them had tolerability issues. **Conclusions:** We confirm that DMF shows a good efficacy in both drug-naïve patients and patients switching from other first-line DMTs with definite improvement in EDSS.

KEYWORDS

Multiple sclerosis, DMF, dimethyl fumarate

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disease associated with dysregulation of adaptive immunity, leading to tissue damage by the periodic entry of immune cells into the central nervous system (CNS) and oxidative environment imbalance in CNS [1,2]. The rapidly emerging new MS treatment poses a challenge for neurologists to select the most optimal disease modifying therapy (DMT) for their patients.The first oral DMT for RRMS patients, fingolimod, was introduced in 2011 in Europe followed by teriflunomide and dimethyl fumarate (DMF) in 2013[3,4] .DMF exerts its action by activating the nuclear factor (erythroid-derived 2)-like 2 (Nrf2)which is essential in redox homeostasis and responses to reactive oxygen species (ROS).[5–7] Nrf2 is a transcript of the NFE2L2 (Nuclear Factor, Erythroid 2 Like 2) gene. Data on CNS penetration of DMF in lacking though it is ascribed to have cytoprotective effects for CNS cells during inflammation[8,9]. The most likely mechanism of DMF for its clinical and radiological effect has been anti-oxidative property[10,11]. Though DMF is well-known medication used by many neurologists in MS; there are inadequate data from the Indian population. In view of ethnic differences, an attempt was made to study the safety, efficacy and adherence of DMF in patients of Multiple sclerosis

MATERIALS AND METHODS

This is a chart review of the patient records maintained in the MS registry, conducted in the department of Neurology, from a University Teaching hospital from South India. All patients diagnosed with MS (fulfilling McDonald's criteria) were evaluated over a period of 2015-2021. A demographic data including the age, gender, age of onset, duration of illness, number of attacks and type of immunomodulator already tried were recorded. The adverse events noted during the therapy and the reasons for switching the DMF were noted. Patients of MS undergo periodic evaluation with blood counts and yearly MRI brain, that was tabulated. The Expanded Disability Status Scale (EDSS) was obtained from all patients during their periodic evaluation. Oral DMF was prescribed at the dosage of 120 mg twice daily for 1 week followed by 240 mg twice daily for all the patients. The evaluation was done on the basis of a file review which is maintained as a part of medical records documentation updated during every subsequent visit of the patient. MRI were performed on the 3T Inginea (Philips Healthcare, The Netherlands). For the routine diagnostic MRI all T2WI, T1WI, DWI, SWI, T2 coronal fat suppressed images for optic nerve were done. Following that, 3D FLAIR and 3D DIR were acquired in sagittal plain covering whole brain. 3D FLAIR and 3D DIR were reformatted to coronal and axial orientations. Images obtained from MRI were analysed independently by 2 neuroradiologists. Both the readers were blinded for clinical data.

Data and Statistical analysis:

Data was analysed using SPSS software version 22. Data was expressed using descriptive statistics such as for continuous variables, mean and standard deviation and for categorical variables, frequency and percentage. Paired t test was used to compare means. For analysis of continuous variables, nonparametric test (Mann Whitney test and Mc Neimer tests) was employed. The analysis of categorical variables was done by Fischer's exact test and p value of <0.05 was taken as significant.

RESULTS:

There were 37 (F:M-21:16) patients of multiple sclerosis who were treated with DMF evaluated during the study period from 2015-2021. Average age of onset of patients were 25.1±8.1 years **(table 1).** The average duration of illness after which DMF was started was 6.6±4.9years. Average duration for which DMF was given was 27.46 (Range: 6 to 72) months. The types of MS were: RRMS (26), SPMS (9), PPMS (1) and one patient with RIS with the proprietary drug used by 33 patients, while the rest four patients were on generic brands. DMF was given in few patients of progressive MS in view of unaffordability and not willing to shift to immunosuppressants in view of side effects. Fifteen patients had DMF as first DMT, 11 patients were started as second DMT, 10 patients had 2 immunomodulators tried and 1 patient had 3 immunomodulators before starting DMF.

Table 1- Demographical and clinical characteristics of patients with MS.			
Number of subjects (N=37)	Mean± Standard Deviation		
Age of onset of MS	25.1 ± 8.1 years		
Gender (F:M)	21:16		
Duration of illness	8.16± 5.4 years		
MS course	RRMS	28 (75.7%)	
	RRMS to SPMS	7 (19.9%)	
	PPMS	1 (2.7%)	
	RIS	1 (2.7%)	
Age of distribution(in years)	0-20 years	4(10.8%)	
	20-35 years	25(51.3%)	
	35-50 years	14(37.8%)	
Duration of illness at DMF start(in years)	6.6		
Duration of DMF intake(in months)	27.48		
EDSS prior to start of DMF	3.51± 1.8		
EDSS after start of DMF	3.01±1.9		
No. of immunomodulators already tried	0	15(40.5%)	
	1	11(29.7%)	
	2	10(27%)	
	3	1(2.7%)	
Switch reason	Total patients switch to another drug	N=10	
	efficacy	8(80%)	
	Tolerability	0	
	Financial issues	1(10%)	
	Preferred Inj. Rituximab	1(10%)	
Clinical complications	Number of subjects with clinical complications in patients with generic drugs	With generic drugs N=3(75%)	With proprietary drugs N=4 (12.1%)
	Only epigastric discomfort	0	1
	Epigastric discomfort and constipation	1	0
	Nausea and vomiting	1	0
	Undue fatigue and tiredness	1	1
	Flushing	0	1
	Transient hair loss	0	1
Laboratory complications	Number of subjects with laboratory abnormalities	N=4(100%)	N=5(15.1%)
	Isolated LFT derangement	0	4
	Isolated lymphopenia(grade I to grade II)	1	0
	Combined deranged LFT and grade Ilymphopenia	3	1
Radiological relapse		N=2(50%)	N=6(18.2%)

Adverse events:

The adverse events noted among the cohort were: constipation and epigastric discomfort (1), only epigastric discomfort (1), nausea and vomiting (1), undue fatigue and tiredness (2), flushing (1) and transient hair loss (1). Blood parameters were normal in 27 patients at the end of six months, 4 patients had isolated deranged liver function tests (LFT) with mildly elevated alanine aminotransferase, 2 patients had isolated grade I (absolute lymphocytes count, ALC: 800-999/µl) to grade II (ALC: 500–799/µl) lymphopenia and 4 patients had both deranged LFT and lymphopenia. Patients on **generic brands** were 4 and all 4 patients (100%) had adverse events related to drugs- epigastric discomfort and constipation (1), undue fatigue and weakness (1), Nausea and vomiting (1). Blood parameters revealed grade 1 to grade II lymphopenia (1), combined grade 1 lymphopenia and deranged LFT (3) in various combinations.2 patients among them had radiological relapse(50%). The mean EDSS improvement seen among patients on generic drug was 0.26. 33 patients were on **proprietary drug** and 5 patients (15.1%) among them had adverse events. Adverse events among them were- transient hair loss (1), flushing (1), undue fatigue and tiredness(1), only epigastric discomfort (1). Among blood parameters- isolated deranged LFT were observed in 4 patients, grade 1 to grade II lymphopenia with deranged LFT in 1 patient.6 patients had radiological relapse(18.2%).The mean EDSS improvement for patients on proprietary drug was 0.47. Among them, 27 continued to take DMF and 10 patients were switched from DMF to another immunomodulator for the following reasons: clinical and radiological relapse (6), only radiological worsening (2), unaffordability (1) and non-adherence to daily medication (1). Among the 8 patients with relapse, all patients had duration of illness of more than 5 years and none of them had adherence issues. The EDSS before DMF intake on patient who showed clinical and radiological improvement was 3.32±1.9 and EDSS after at least 6 months of DMF was 2.8±2. Among 8 patients who had relapse EDSS score before DMF was 3.9±1.26 and EDSS after clinical or radiological relapse was 4±1.4.

MRI changes:

The average duration of first MRI to the MRI brain and spine done before at the time of initiation of DMF was 20.6 months. The average duration of imaging after DMF intake was 14.8 months. Table 2 shows the imaging characteristic before starting DMF treatment and Table 3 shows the change in imaging characteristic after initiation of DMF treatment.

Table 3: Description of the Neuroimaging abnormalities in patients of MS in the study cohort after starting DMF

Serial no	New lesions	Deep gray matter involved	Lesion localization(enhancing and non enhancing)					Mineralization	T1 black holes	Enhancement	Diffusion restriction	Cortical atrophy
			PV	JC	Brainstem and cerebellum	Optic nerve	Spinal cord					
1	N	Lt thalamus	>5	N	2	N	C-SS	N	Y	N	N	N
2	N	N	>5	N	1	N	N	N	Y	N	N	N
3	Y	N	>5	2	1	N	N	N	Y	Y	N	N
4	N	N	3	2	3	B/L OA	C-SS-5	N	N	N	N	N
5	N	B/L thalami	>5	>5	>5	B/L OA	C-SS-1 and D-SS-2	N	Y	N	N	N
6	N	N	>5	>5	2	N	C-SS-1;,D-SS-2	Y	Y	N	N	Increased atrophy

7	N	B/L thalami	>5	>5	>5	B/L ON	N	N	N	N	N	N
8	N	B/L caudate	>5	>5	5	B/L OA	C-SS-1, D-SS-2	Y	Y	N	N	increased atrophy
9	N	N	3	N	N	N	N	N	N	N	N	N
10	Y-D-1	B/L thalami	>5	>5	>5	N	C –SS-1, D-SS-2	N	Y	Y	N	N
11	N	Lt GP	>5	>5	2	N	CD-LS	N	Y	N	N	N
12	N	N	>5	2	N	LT ON	N	N	N	N	N	N
13	N	N	>5	>5	1	LT OA	C-SS-1, D-SS-2	N	N	N	N	N
14	Y-centrum semiovale	N	>5	>5	3	B/L OA	C-SS-2	N	Y	Y	N	N
15	N	N	>5	>5	>5	B/L OA	C-SS-1;D–SS-1 and Co-SS-1	N	Y	N	N	N
16	N	Lt putamen, Rt thalamus and GP	>5	>5	>5	B/L OA	C-SS-1, D-SS-2	N	N	N	N	Y
17	N	B/L GP and thalami	>5	>5	>5	B/L OA	C-SS-3	Y	Y	N	N	Increased atrophy
18	N	B/L thalami	>5	>5	>5	B/L OA	C –SS-1, D-SS-1	N	Y	N	N	increased atrophy
19	N	N	>5	3	>5	B/L OA	C-SS-1;D–SS-1 and Co-SS-1	N	N	N	N	Increased atrophy
20	N	Rt thalamus	>5	>5	>5	B/L OA	C –SS-1, D-SS-1	N	N	N	N	Y
21	N	N	>5	3	2	Lt OA	C –SS-2	N	Y	N	N	Y
22	N	N	>5	2	1	N	N	N	N	N	N	N
23	N	N	>5	>5	2	N	C –SS-1, D-SS-1	N	N	N	N	Y
24	N	N	N	N	N	B/L OA	C-SS-1;D–SS-1 and Co-SS-1	N	N	N	N	N
25	N	N	>5	>5	>5	LT OA	C –SS-1, D-SS-1	N	Y	N	N	Y
26	N	N	>5	>5	>5	LT ON	C-SS-1;D–SS-1 and L-SS-1	N	N	N	N	N
27	N	N	>5	>5	>5	NA	N	N	Y	N	N	Increased atrophy
28	N	N	>5	>5	>5	B/L OA	C-SS-2;D–SS-1 and L-SS-1	N	Y	N	N	N
29	N	B/L thalami	>5	>5	>5	RT OA	C- SS-1	N	N	N	N	N
30	N	B/L thalami	>5	>5	>5	B/L OA	C –SS-1, D-SS-1	N	Y	N	N	Y

Abbreviations: PV= periventricular; JC= Juxtacortical; N= No; Y=Yes; ON= Optic neuritis; GP= Globus pallidus; OA= Optic atrophy; D= Dorsal; MCP= Middle cerebellar peduncle; Lt= Left; Rt= Right; C=Cervical; D=Dorsal; L=Lumbar;P= Pons; Co= Conus; SS= short segment; LS= Long segment.

Table 2: Description of the Neuroimaging abnormalities in patients of MS in the study cohort before starting DMF

No.	Deep gray matter involvement	Lesion location					Mineralization	T1 black holes	Enhancement	Diffusion restriction	Cortical atrophy
		PV	JC	Brainstem &cerebellum	Optic nerve	Spinal cord					
1	Lt thalamus	>5	N	2	N	C-SS	N	Y	N	N	N
2	N	>5	N	1	N	N	N	Y	N	N	N
3	N	>5	2	1	N	N	N	Y	N	N	N
4	N	3	2	3	B/L OA	C-SS-5	N	N	Y- SC, P	N	N
5	B/L thalami	>5	>5	>5	B/L OA	C and D-2	N	Y	N	N	N
6	N	>5	>5	2	N	C-SS-1;,D-SS-2	N	Y	N	N	Y
7	B/L thalami	>5	>5	>5	B/L ON	N	N	N	N	N	Y
8	B/L caudate	>5	>5	5	B/L OA	C-SS-1, D-SS-2	Y	Y	N	N	Y
9	N	3	N	N	N	N	N	N	Y	Y	N
10	B/L thalami	>5	>5	>5	N	C –SS-1, D-SS-1	N	Y	N	N	N
11	Lt GP	>5	>5	2	N	CD-LS	N	Y	N	N	N

12	N	>5	2	N	LT ON	N	N	N	N	N	N
13	N	>5	>5	1	LT OA	C-SS-1, D-SS-2	N	N	N	N	N
14	N	>5	>5	3	B/L OA	C-SS-2	N	N	N	N	N
15	N	>5	>5	>5	B/L OA	C-SS-1;D–SS-1 and Co-SS-1	N	N	N	N	N
16	Lt putamen, Rt thalamus and GP	>5	>5	>5	B/L OA	C-SS-1, D-SS-2	N	N	N	N	Y
17	B/L GP and	>5	>5	>5	B/L OA	C-SS-3	Y	Y	N	N	Y
18	B/L thalami	>5	>5	>5	B/L OA	C –SS-1, D-SS-1	N	N	N	N	Y
19	N	>5	3	>5	B/L OA	C-SS-1;D–SS-1 and Co-SS-1	N	N	N	N	Y
20	Rt thalamus	>5	>5	>5	B/L OA	C –SS-1, D-SS-1	N	N	Y-1-PV	N	Y
21	N	>5	3	2	Lt OA	C –SS-2	N	N	N	N	N
22	N	>5	2	1	N	N	N	N	Y	Y	N
23	N	>5	>5	2	N	C –SS-1, D-SS-1	N	N	N	N	N
24	N	N	N	N	B/L OA	C-SS-1;D–SS-1 and Co-SS-1	N	N	Y-C	N	N
25	N	>5	>5	>5	LT OA	C –SS-1, D-SS-1	N	N	N	N	Y
26	N	>5	>5	>5	LT ON	C-SS-1;D–SS-1 and L-SS-1	N	N	Y	N	N
27	N	>5	>5	>5	NA	N	N	N	N	N	Y
28	N	>5	>5	>5	B/L OA	C-SS-2;D–SS-1 and L-SS-1	N	N	N	N	N
29	B/L thalami	>5	>5	>5	RT OA	C- SS-1	N	N	N	N	N
30	B/L thalami	>5	>5	>5	B/L OA	C –SS-1, D-SS-1	N	N	N	N	Y

Abbreviations: PV= periventricular; JC= Juxtacortical; N= No; Y=Yes; ON= Optic neurtitis; GP= Globus pallidus; OA= Optic atrophy; D= Dorsal; MCP= Middle cerebellar peduncle; Lt= Left; Rt= Right; C=Cervical; D=Dorsal; L=Lumbar;P= Pons; Co= Conus; SS= short segment; LS= Long segment.

Out of 30 patients whose follow up imaging were present, 3 patients follow-up MRI showed new enhancing lesions (case no 3,10,14 – Table 1 and 2, case 3-Figure no-1), 6 patients showed improvement in the enhancement and disappearance of diffusion restriction in their imaging (case no. 4,9,20,22,24,26, case 20- figure no-3), 1 patient did not have major changes in their imaging findings in terms of enhancement or diffusion restriction (figure no 2). 6 patients follow-up MRI showed subjective increased cerebral atrophy.

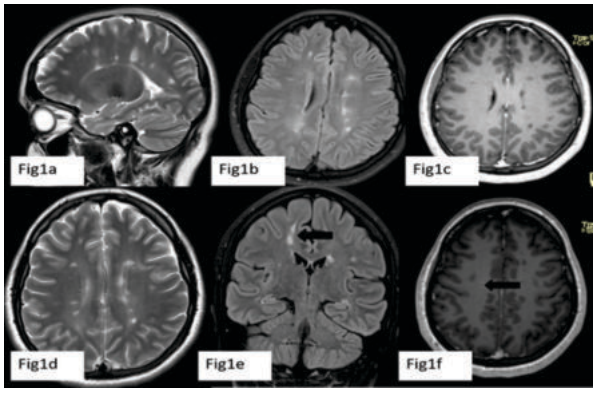

Figure 1:
Case 3: Saggital T2WI (Figure 1a)of brain showing T2 hyperintense lesions involving periventricular white matter oriented perpendicular to the corpus calllosum. Axial FLAIR (Figure 1b) of brain showing FLAIR hyperintense lesions involving periventricular white matter along perivenular distribution. Axial T1 post contrast (Figure 1c) of brain no enhancement in the lesion. Follow up MRI after 6months of DMF therapy, Axial T2WI (Figure 1d) of brain showing T2 hyperintense lesions involving periventricular white matter along perivenular distribution. Coronal FLAIR (Figure 1e) of brain showing new onset FLAIR hyperintense lesion involving right centrum semiovale (black arrow). Axial T1 post contrast (Figure 1f) of brain showing incomplete ring enhancement of the new onset lesion (black arrow).

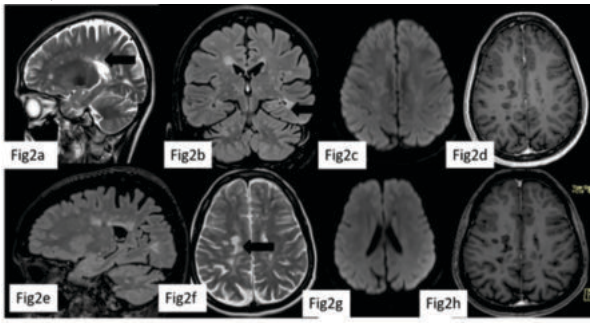

Figure 2:
Case 13: Saggital T2WI (Figure 2a)of brain showing T2 hyperintense lesions involving periventricular white matter oriented perpendicular to the corpus calllosum. Coronal FLAIR (Figure 2b) of brain showing FLAIR hyperintense lesions involving periventricular white matter along left temporal horn (black arrow). Axial DWI image (Figure2c) showing no diffusion restriction of the lesion. Axial T1 post contrast (Figure 2d) of brain no enhancement in any of the lesion. Follow up MRI after 6months of DMF therapy, saggital FLAIR (Figure 2e) of brain showing FLAIR hyperintense lesions involving periventricular white matter oriented perpendicular to the corpus callosum. Axial T2WI (Figure 2f) of brain showing perivenular distribution of the T2 hyperintense lesions appears static in nature. Axial DWI image

(Figure2g) showing no diffusion restriction of the lesion. Axial T1 post contrast (Figure 2h) of brain showing no enhancement in any of the lesion confirming no new onset lesion.

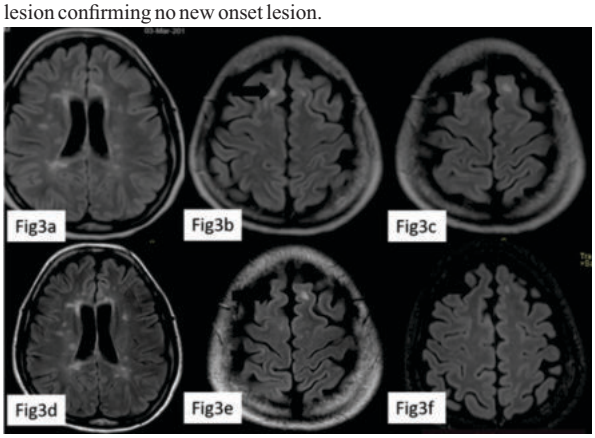

Figure 3:
Case 20: Baseline Axial FLAIR images at lateral ventricle level (Fig3a) and high frontal levels (Fig3b, 3c) showing multiple T2 hyperintense lesions in periventricular and juxta cortical location. After 5months of the DMF therapy axial FLAIR image at the lateral ventricle level (Fig3d) showing no change in morphology and number of the lesion. Axial FLAIR images at the high frontal levels (Fig3e & f) showing lesion located in juxta cortical white matter of right superior frontal gyrus is disappeared (black arrows).

DISCUSSION:

Interferons revolutionised the management of Multiple sclerosis when it was initially introduced. But, the fear of needles, difficulty with self-injection, injection-site reactions, and a range of infusion-associated reactions (headache, rash, pyrexia, nausea and flushing), favoured the second line of medications - oral forms of therapy like DMF with favourable efficacy led to gradually gaining more acceptance among the MS patients[12–15]. In our cohort, 27% of patients discontinued DMF, mainly due to relapse (21.6%). Mean time to first relapse was 10.6 ± 4.9 months. The relapse rate in our study is much higher than the multicentric study done where 8.8% presented at least one relapse with mean time to first relapse being 9.7 ± 5.9 months [15]. Gold et al. evaluated the effect of different doses of DMF in patients with MS. They stated that delayed-release DMF could successfully improve clinical outcomes based on EDSS scale. The mean EDSS scores in the control group, as well as twice and thrice daily administered DMF groups were 2.2, 2.1, and 2.0 respectively[16]. Our patients showed mild to moderate improvement in EDSS with twice daily schedule of DMF with reduction in EDSS score from 3.5±1.8 to 3.01± 1.9. D'Amico et al, demonstrated that those patients who were treated with DMF had lower EDSS score compared to those who were treated by teriflunomide[17].

Gastrointestinal symptoms were the primary side effects accounting to 8.1% but these symptoms did not lead to discontinuation as it was mild and gradually subsided unlike results from phase III clinical trials, which report a global suspension rate of 12–16% and GI symptom-related discontinuation of 5–6%[18,19] and results from published real-world data which reported a suspension rate for GI symptoms that range from 10 to 15%[20,21] Flushing was present is only one patient (2.7%) in our cohort which appears consistent with those from the DEFINE and CONFIRM studies (1-4% in phase III trials)[18,19]. In our study, lymphopenia was observed in 8.1 % of patients, and 1 patient (2.7%) developed grade II lymphopenia. None of the patient had developed grade III lymphopenia. The incidence rate of lymphopenia in post-marketing studies of DMF is extremely variable, ranging from 10% to 30%, and that of grade III lymphopenia varies from 2.5 to 11% [22].

A French comparative study showed a discontinuation rate for DMF of 8.5% due to a lack of effectiveness compared with 14.5% of patients who received TRF, while DMF achieved the best results in terms of radiological activity. However, after 2 years of treatment, 21% of patients treated with TRF reported AE compared with 16% of patients treated with DMF [23]. In our cohort, 27% patients were switched from DMF to another immunomodulator for the following reasons of which majority i.e., 80% were due to relapse and rest i.e., 20% were due to non affordability and non-compliance. The high rate of relapse can be explained by starting of DMF in these MS patients in their advanced stage of MS and after failure of other DMTs. Unlike other studies none of our patients had lymphopenia as the cause of drug discontinuation [24–26].

Gold et al. demonstrated that different doses of DMF could have different effects on contrast enhanced lesions. According to their results, contrast enhanced lesions were higher in twice daily administration of DMF compared to thrice daily administration[16] Saida et al. also evaluated the efficacy of delayed-release DMF (240 mg BID) and found that DMF could successfully reduce new contrast enhanced lesions from baseline to week 24 by 75% and reduce the number of relapses by 42% over a 24-week period[27].While in our study we used 240 mg of DMF twice daily, we achieved a significant reduction in contrast enhanced lesions where all 6 patients who had gadolinium enhancement before start of DMF showed no further enhancement on follow up imaging after at least 6 months of DMF intake. None of our patient had thrice daily administration of DMF.

The results of our study confirm that treatment with DMF is safe and effective in real-world clinical practice and its overall effectiveness of DMF remain unaffected by the usage of previous DMTs. However, there are some limitations to this study due to its retrospective and observational nature as well as the limited number of patients. But, the major advantage of this study is the availability of real-world data from low social economic country like India where such data are unavailable, gives data on generic drugs vs proprietary drugs that is important as most of our patients have economical constraints in the usage of higher-cost DMTs and non-coverage of insurance for the medications. The interesting observation that we had on treatment aspect was the profile of side effects differences among patient treated with generic and proprietary drugs, All patients on generic drugs presented with either or both clinical and laboratory parameters derangement whereas only 15.1% patients on proprietary drugs showed adverse events. Though the number of patients on each type of generic vs. proprietary medications is limited; it gives real-world data for the usage of generic DMF.

The rapidly changing treatment paradigms in the treatment of MS landscape especially with he availability of B-cell depletors and wide range of disease modifying therapies available in the armamentarium of MS therapy, poses a challenge to the neurologist in selection of appropriate DMT for patients of MS. In conclusions, this study from India, confirm a good tolerability and efficacy profile of DMF, both on naïve and on drug-switchers as well as in both shorter and longer disease duration of MS patients. Both clinical and radiological efficacy is noted with oral DMF with relapse seen in few cases. Larger study is required to further confirm our findings.

Declarations: None

Financial Disclosure/Conflict of Interest: None of the authors have any financial disclosure or Conflicts of interest.

Source of funding: Nil

Acknowledgements: None

Data Availability: Data is available with the authors. Anonymised data will be shared if ethically indicated.

Ethics approval: Obtained from both the respective hospitals

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