Journal of the Neurological Sciences 407 (2019) 116498

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Comparative discontinuation, effectiveness, and switching practices of dimethyl fumarate and fingolimod at 36-month follow-up☆

Brandi Vollmer[a], Daniel Ontaneda[b], Haleigh Harris[c], Kavita Nair[a], Robert A. Bermel[b], John R. Corboy[a], Robert J. Fox[b], Timothy Vollmer[a], Jeffrey A. Cohen[b], Enrique Alvarez[a], Carrie M. Hersh[c,*]

[a] Rocky Mountain Multiple Sclerosis Center at Anschutz Medical Campus, University of Colorado, Denver, CO, United States
[b] Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic, Cleveland, OH, United States
[c] Lou Ruvo Center for Brain Health, Cleveland Clinic, Las Vegas, NV, United States

ARTICLE INFO

Keywords:
Tecfidera
Gilenya
Comparative effectiveness
DMT discontinuation
Multiple sclerosis
Propensity score analysis
Switching patterns

ABSTRACT

Background: Dimethyl fumarate (DMF) and fingolimod (FTY) are approved oral disease modifying therapies (DMTs) for relapsing multiple sclerosis (MS). There are currently no known head-to-head studies comparing DMF and FTY over 36 months, which leaves their relative effectiveness unknown.
Objective: To assess real-world discontinuation, effectiveness, and switching practices of DMF and FTY over 36 months along with disease activity after switching DMT.
Methods: Patients prescribed DMF ($n = 737$) and FTY ($n = 535$) from two academic MS centers were retrospectively reviewed. Discontinuation and effectiveness outcomes were assessed using propensity score (PS) weighting. PS model covariates included sociodemographics and clinical and MRI characteristics.
Results: Discontinuation was more common in DMF (58.3%) versus FTY (45.2%) over 36 months [OR = 1.81, 95% CI (1.41–2.31), $p < .001$], largely driven by intolerance [OR = 1.63, 95% CI (1.18–1.73), $p < .001$]. There were no differences in clinical relapses [OR = 1.27, 95% CI (0.90–1.79), $p = .17$], gadolinium-enhancing (GdE) lesions [OR = 1.25, 95% CI (0.85–1.84), $p = .26$], or new T2-hyperintense lesions [OR = 0.99, 95% CI (0.74–1.32), $p = .93$]. Within 12 months of DMF/FTY discontinuation, switchers to highly effective therapy (HET) versus other DMTs (injectables/orals) had fewer relapses (DMF/HET, 5.9% versus DMF/Other, 14.2%, $p = .03$; FTY/HET, 11.6% versus FTY/Other, 18.0%, $p = .04$) and fewer GdE lesions post-FTY (DMF/HET, 10.3% versus DMF/Other, 14.3%, $p = .36$; FTY/HET, 11.9% versus FTY/Other, 21.5%, $p = .04$).
Conclusion: This combined analysis showed similar effectiveness for DMF and FTY over 36 months with higher DMF discontinuations. Disease activity was lower in switchers to HET versus injectable/oral therapies after DMF/FTY cessation.

1. Introduction

Dimethyl fumarate (DMF) and fingolimod (FTY) are two commonly prescribed oral disease modifying therapies (DMTs) approved for the treatment of relapsing multiple sclerosis (MS). Separate phase 3 randomized clinical trials (RCTs) for DMF and FTY showed similar efficacy when compared to placebo, including reductions in annualized relapse rate (ARR) of 44%–53% for DMF and 48%–54% for FTY [1–4]. Furthermore, DMF and FTY both demonstrated superior efficacy when compared to injectable therapies. A *post-hoc* comparison of DMF versus glatiramer acetate showed significant reductions in ARR and number of new/enlarging T2-hyperintense lesions over 24 months [2]. Additionally, in two 12-month head-to-head RCTs, FTY showed improved efficacy with respect to ARR compared to interferon beta-1a and glatiramer acetate [3,5].

However, there are notable differences in adverse events (AEs) and tolerability profiles between DMF and FTY that lead to variable prescribing patterns in real world practice. DMF is commonly associated with flushing and gastrointestinal (GI) side effects that are most prominent within the first 1–2 months of treatment [1,2]. Typical FTY AEs include mild to moderate upper respiratory tract infections, headaches, and back pain [3,4]. Additionally, rare serious AEs related to FTY

☆ Statistical analysis conducted by Dr. Carrie Hersh, DO, MSc, Lou Ruvo Center for Brain Health, Cleveland Clinic.

* Corresponding author at: Lou Ruvo Center for Brain Health, Cleveland Clinic, 888 W Bonneville Ave, Las Vegas, NV 89106, United States.
E-mail address: hershc@ccf.org (C.M. Hersh).

https://doi.org/10.1016/j.jns.2019.116498
Received 20 March 2019; Received in revised form 18 August 2019; Accepted 17 September 2019
Available online 15 October 2019

include second degree heart block, cryptococcal meningitis, fatal herpesvirus infections, and macular edema [4]. Both DMTs are associated with a rare risk of progressive multifocal leukoencephalopathy (PML) [6,7].

Currently, there is no consensus on the sequencing of MS therapies, resulting in variable use of DMTs in routine practice. The comparative effectiveness of certain MS DMTs is currently unknown, and indirect comparisons of oral DMTs showed conflicting results [8–10]. Observational studies harnessed from real-world data from clinical practice have valuable implications in decision-making and can answer clinically relevant questions with broad applicability.

Previous real-world studies directly comparing DMF and FTY largely demonstrated similar effectiveness between these DMTs [11–17] and an increased likelihood of DMF discontinuation up to 30 months [11–18]. However, to date, there are no published comparative effectiveness studies investigating DMF versus FTY over 36 months, nor data on switching patterns and effectiveness outcomes following oral DMT discontinuation. We, therefore, directly compared the discontinuation and effectiveness profiles of DMF versus FTY over 36 months in patients treated at two large academic MS centers. In a subgroup analysis of patients who discontinued DMT, we further investigated switching and effectiveness outcomes in the 12 months post- DMF or FTY cessation. We used propensity score (PS) adjusted analyses to reduce the impact of confounding and certain biases prior to reporting treatment effect differences [19].

2. Methods

2.1. Patient population

This retrospective observational study followed MS patients treated with either DMF or FTY at the Cleveland Clinic Mellen Center or the Rocky Mountain MS Center at the University of Colorado (RMMSC at CU). Patients treated at Cleveland Clinic were selected from those starting DMF or FTY within one year of their respective FDA approval. Patients treated at RMMSC at CU were selected from those starting DMF or FTY prior to October 2013. Patients starting DMF and FTY received counseling per standard of care on possible side effects and mitigation strategies. Occasionally, slower DMF titration schedules were implemented at our sites to alleviate AEs, though these data were not consistently captured in this study population. Patients with progressive MS were included in this study to reflect the real-world experience of patients treated in clinical practice. A subgroup analysis was conducted on relapsing-remitting MS (RRMS) patients to better comment on comparative outcomes in a more inflammatory population. An additional analysis was conducted on patients who discontinued DMF and FTY within 36 months of follow-up to comment on sequencing practices and comparative effectiveness in patients switching to injectable/oral therapies versus escalating treatment to highly effective agents.

2.2. Data collection

Following institutional review board approval at each site, the electronic medical records (EMR) of patients who met the inclusion criteria were retrospectively reviewed. Baseline data within 12 months of DMF/FTY initiation and outcomes data up to 36 months after DMT initiation were collected. Patients who discontinued DMF or FTY by ≤36 months with available data were retrospectively followed for an additional 12 months from DMT discontinuation.

Post-baseline follow-up (e.g. MRI frequency/protocols and visits) was similar between groups. For the purpose of this study, clinical relapses were defined as new or worsening neurological symptoms lasting > 24 h, without a coexistent illness or fever. Relapses were determined via clinician report in the available patient charts. The number of new T2-hyperintense brain lesions and semi-quantitative assessment of overall lesion burden were determined manually by C.M.H. at Cleveland Clinic, B.V. at RMMSC at CU, and neuroradiologists at each institution.

Cleveland Clinic data were stored on a secure server using Redcap Software. RMMSC at CU data were encrypted and stored on a secure server using Excel. Data were de-identified by each center prior to being merged into a single Excel database for analysis.

2.3. Outcome measures

The primary outcome of this study was DMT discontinuation by 36-month follow-up. Secondary outcomes included reason for discontinuation (categorized as “Disease Activity,” “Intolerance/Adverse Effects,” or “Other”), time to discontinuation, and proportions with clinical relapse(s), brain MRI gadolinium-enhancing (GdE) lesions, brain MRI new T2-hyperintense lesions, brain MRI activity (a composite measure of GdE and new T2-hyperintense lesions), and absence of disease activity (defined as freedom from clinical relapses and brain MRI activity). All effectiveness endpoints for secondary outcomes were on-treatment measures.

For patients who discontinued therapy ≤36 months and had available data, additional outcomes were collected in the 12 months post-DMF/FTY discontinuation. These data included whether or not the patient switched to a new DMT, the type/efficacy of switched DMT (defined as “low efficacy”- interferon-beta, glatiramer acetate, teriflunomide; “moderate efficacy”- DMF, FTY; or “high efficacy”- natalizumab, rituximab, ocrelizumab, alemtuzumab) [20–21], washout length, and the proportions with clinical relapse activity and brain MRI GdE lesions within 12 months of respective DMT discontinuation. The switched DMT was chosen at the discretion of the treating clinician and patient in a personalized medicine approach [22].

2.4. Statistical analysis

Statistical analyses were conducted using R version 3.5.0 [23]. Two-tailed p-values < .05 were considered statistically significant. For unadjusted estimates, differences between DMF and FTY were evaluated using t-tests for continuous data, χ^2 tests for categorical data, and Cox proportional hazards models and Kaplan-Meier curves for survival outcomes. We used PS methods identical to our 24-month study when conducting adjusted analyses [13].

The PS model was created using logistic regression to calculate the probability of initiating DMF, as compared to FTY, using a priori selected covariates including demographics and baseline clinical and MRI characteristics. All covariates were missing in fewer than 10% of patients. To determine the strength and selection of our PS method, we compared standardized differences in covariates pre- and post-adjustment. Excellent covariate balance was defined as an absolute standardized difference < 10% between the covariate means across DMF and FTY. Before directly observing the study outcomes, we selected the best PS approach to make inferential conclusions on treatment effect differences based on the most complete covariate balance. To identify patients in the DMF and FTY groups with comparable baseline characteristics except for treatment, we derived a PS for each patient used in average treatment effect on the treated (ATT) weighting. We used the same approach as in our previous 12- and 24-month studies to account for missingness patterns [13,15,17].

For binary outcomes, conditional logistic regression was applied after ATT weighting to obtain odds ratio (OR) estimates comparing the treatment groups. Stratified Cox regression and Kaplan-Meier survival curves were used to evaluate survival data. All ORs and hazard ratios (HRs) refer to DMF-treated patients compared to those treated with FTY.

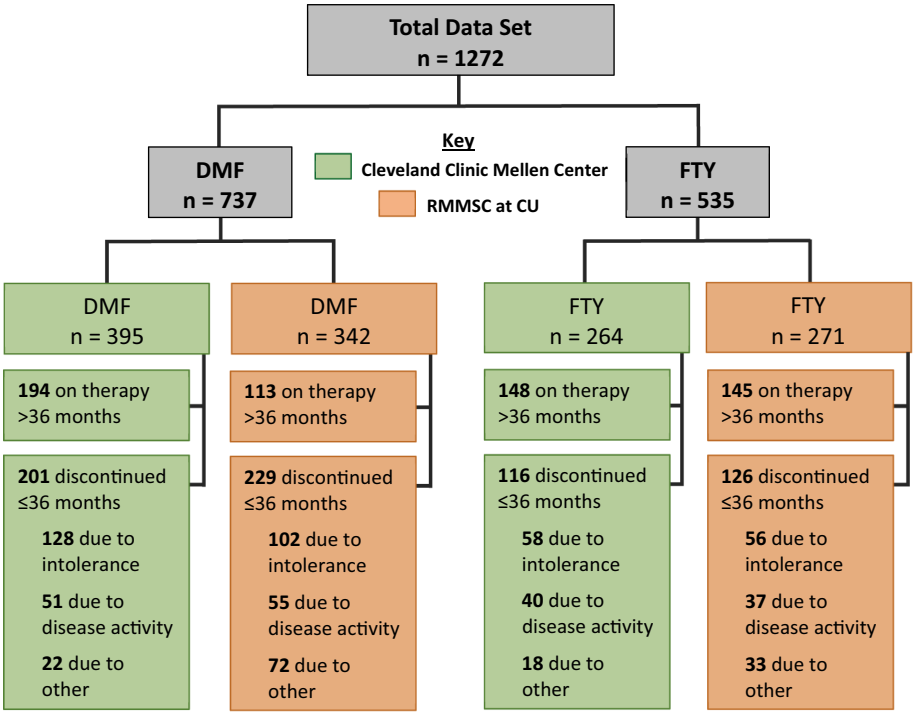

Fig. 1. Study flow diagram.
RMMSC at CU: Rocky Mountain Multiple Sclerosis Center at the University of Colorado; DMF: dimethyl fumarate; FTY: fingolimod. Discontinuations due to other include pregnancy, insurance issues, patient preference, loss to follow up, etc.

3. Results

3.1. Baseline characteristics

Fig. 1 demonstrates the overall study flow. A total of 1272 patients were included in this study with baseline characteristics presented in Table 1. Between 24 and 36 months of follow-up, 786 patients had available data (DMF $n = 428$, FTY $n = 358$). Differences between cohorts were observed in age, race, MS phenotype, last DMT prior to DMF or FTY, and baseline MRI lesion burden.

3.2. Propensity score model

The PS model assigned higher PS to DMF compared to FTY with substantial PS overlap across the two DMTs (Fig. S1), demonstrating adequate comparability between the two treatment groups and confirming the appropriateness of using PS-adjusted techniques. The groups were not well-balanced prior to PS adjustment, as demonstrated by 4 covariates with absolute standardized differences > 10% (Fig. S2) [13]. Further, the absolute value of the standardized difference of the linear PS was 51.8%, comparing DMF to FTY. Through ATT weighting, we achieved well-balanced groups with no covariates having an absolute standardized difference > 10% and a comparable linear PS distribution with a standardized difference of 4.3%, well under the 50% standard proposed by Rubin [24]. Missing data among covariates in the PS model did not meaningfully change overall covariate balance after PS analysis.

3.3. Discontinuation and effectiveness outcomes

Tables 2 and 3 present unadjusted and PS-adjusted primary and secondary outcome estimates using ATT weighting. Discontinuations among DMF-treated patients were more frequent (58.3%) compared to FTY (45.2%) by ≤36 months [OR = 1.81, 95% CI (1.41–2.31), $p < .001$] and occurred earlier in DMF patients [HR = 1.53, 95% (CI 1.32–1.77), $p < .001$], as further demonstrated through a Kaplan-Meier analysis (Fig. 2). Fig. 3 demonstrates the proportion of discontinuations for each drug stratified by year.

While intolerance was the leading cause of discontinuation for both DMF and FTY, DMF patients had greater odds of discontinuing DMT due to AEs [OR = 1.63, 95% CI (1.18–1.73), $p < .001$]. Of those who discontinued due to intolerance, the most common AEs for DMF were GI-related concerns, and the most common AEs for FTY were infections (Table S4). There were no cases of PML or other serious opportunistic infections while on treatment. Discontinuations due to disease activity were similar [OR = 1.01, 95% CI (0.49–1.12), $p = .923$].

PS-adjusted analyses demonstrated no differences between DMF and FTY in any of the clinical or radiographic effectiveness outcomes, including relapses [OR = 1.27, 95% CI (0.90–1.79), $p = .173$], GdE lesions [OR = 1.27, 95% CI (0.90–1.79), $p = .171$], new T2-hyperintense lesions [OR = 0.99, 95% CI (0.74–1.32), $p = .932$], and brain MRI activity [OR = 0.99, 95%CI (0.74–1.31), $p = .935$]. Relapses per patient were low at 0.16 and 0.14 for DMF and FTY ($p = .397$), respectively. By 36 months, 55.8% of DMF patients demonstrated absence of disease activity versus 55.9% of FTY patients [OR = 1.00, 95% CI (0.78–1.12), $p = .997$]. A subgroup analysis for RRMS patients demonstrated consistent results for discontinuation and effectiveness endpoints, as compared to the overall cohort (Table S1-S3).

3.4. Outcomes after DMF/FTY discontinuation

A total of 573 patients had additional 12-month follow-up data after DMF or FTY discontinuation. Table 4 summarizes the baseline characteristics and outcomes of this sub-group population. Patients switching from FTY to an alternative DMT experienced a longer mean washout duration (2.3 months) compared to those transitioning off of DMF (1.7 months) ($p = .010$).

Overall, disease activity within 12 months of DMF/FTY withdrawal was low and comparable. Following PS-adjustment, of patients who switched to HET, those previously on DMF compared to those

Table 1
Baseline characteristics of study population.

	DMF		FTY		p-value
	n = 737		*n* = 535		
	n or mean	% or SD	n or mean	% or SD	
Age (years, SD)	46.4	11.6	43.3	10.4	< **0.001**[b]
Female	516	70.0%	382	71.4%	0.635[c]
Race					**0.008**[c]
White	614	83.3%	476	89.0%	
Black	59	8.0%	22	4.1%	
Other	31	4.2%	14	2.6%	
Not reported	33	4.5%	23	4.3%	
Disease Duration (years, SD)	13.4	9.3	13.3	8.6	0.771[b]
Relapsing-Remitting MS	558	75.7%	459	85.8%	< **0.001**[c]
Secondary Progressive MS	119	16.1%	53	9.9%	**0.010**[c]
Primary Progressive MS	60	8.1%	23	4.3%	**0.030**[c]
Last therapy prior to DMF or FTY					< **0.001**[c]
None[a]	282	38.3%	159	29.7%	
Interferon	127	17.2%	103	19.3%	
Glatiramer	198	26.9%	110	20.6%	
Natalizumab	91	12.3%	139	26.0%	
Teriflunomide	2	0.3%	0	0.0%	
Immunosuppressive therapy	26	3.5%	15	2.8%	
Other	11	1.5%	9	1.7%	
MRI available for review	686	93.1%	489	91.4%	0.843[c]
Disease burden on MRI					< **0.001**[c]
Mild	374	55.2%	193	40.0%	
Moderate	245	36.2%	210	43.6%	
Severe	58	8.6%	79	16.4%	
GdE Lesion on MRI	133	19.4%	115	23.5%	0.115[β]

Abbreviations: DMF: dimethyl fumarate; FTY: fingolimod; GdE: gadolinium-enhancing lesions; MS: multiple sclerosis.
Bolded *P*-values indicate statistically significant with $p < .05$.
[a] Patients who were remote switchers (> 3 months since last DMT) or first line users.
[b] *t*-test.
[c] Chi-Squared test.

previously on FTY had similar odds of experiencing a clinical relapse [OR = 0.61, 95% CI (0.34–1.09), $p = .093$] and GdE lesions [OR = 0.79, 95% CI (0.38–1.62), $p = .516$]. Similarly, of patients who switched to oral/injectable DMTs, those previously treated with DMF compared to FTY had comparable clinical relapses [OR = 0.75, 95% CI (0.34–1.66), $p = .483$)] and GdE lesions [OR = 0.60, 95% CI (0.23–1.55), $p = .293$]. When directly comparing DMF switchers to HET (DMF/HET) versus DMF switchers to other DMTs (DMF/Other), DMF/HET had fewer relapses (5.9% versus 14.2%, $p = .03$), but similar GdE lesions (10.3% versus 14.3%, $p = .36$). When directly comparing FTY switchers to HET (FTY/HET) versus FTY switchers to other DMTs (FTY/Other), FTY/HET had both fewer relapses (11.6% versus 18.0%, $p = .04$) and lower GdE lesions (11.9% versus 21.5%, p = .04). In a subgroup analysis of patients laterally switching from DMF to FTY and FTY to DMF, disease activity remained low, and there were no significant differences in relapses or GdE lesions within the first 12 months of DMT discontinuation (Table 4). Further, there were no cases of PML or other serious opportunistic infections during this time period.

4. Discussion

While RCTs provide the highest level of evidence for DMT safety and efficacy, comparing individual therapies in a pairwise fashion in robust clinical trials is cost- and time-prohibitive and have more limited applications in the clinical setting due to restrictive inclusion criteria [25]. Further, the anticipated approval of new MS medications that are not available at the time of trial initiation decreases the overall impact of such studies. However, advanced statistical methods such as PS-adjustment produce comparable cohorts using real-world data to allow head-to-head comparisons that can inform decision-making in routine practice with broad applicability.

We conducted a real-world, PS-adjusted, study directly comparing DMF versus FTY over 36 months in clinical practice. Individual sample sizes achieved by each center were similar to those used in the respective phase 3 clinical trials [1–4]. Additionally, owing to our sizable proportions of discontinuations across both DMTs, we examined switching patterns and effectiveness outcomes in a subset of patients after discontinuing either DMF or FTY.

Table 2
Summary of unadjusted outcomes at 36-month follow-up.

	DMF		FTY		p-value
	n = 737 (428)		n = 535 (358)		
	n	% or SD	n	% or SD	
Discontinued drug ≤ 36 months	430	58.3%	242	45.2%	< **0.001**[c]
Disease activity	106	14.4%	77	14.4%	0.932[c]
Intolerance/adverse effects	230	31.2%	114	21.3%	< **0.001**[c]
Other	94	12.8%	51	9.5%	0.101[c]
Clinical relapse ≤ 36 months	116	15.7%	75	14.0%	0.442[c]
Relapses per patient (mean)	0.16	0.4	0.14	0.4	0.397[b]
MRI available ≤ 36 months on DMT	598	81.1%	461	86.2%	0.132[c]
Disease activity on MRI ≤ 36 months on DMT	192	32.1%	147	31.9%	0.992[c]
GdE lesion	77	13.1%	64	13.9%	0.771[c]
New T2 lesions	179	30.7%	146	31.7%	0.775[c]
MRI available 24–36 months on DMT	281	65.7%	211	58.9%	0.768[c]
MRI activity between 24 and 36 months on DMT	43	15.3%	31	14.7%	0.952[c]
GdE lesion	7	2.5%	8	3.8%	0.704[c]
New T2 lesions	35	12.5%	34	16.1%	0.406[c]
Absence of disease activity ≤ 36 months[a]	336	55.8%	260	55.9%	0.999[c]

(Numbers in parentheses) represent number of patients with available 36-month follow-up and were used as the denominator for data between 24 and 36 months.
Abbreviations: DMF: Dimethyl fumarate; DMT: disease modifying therapy; FTY: fingolimod; GdE: gadolinium-enhancing lesions.
Bolded *P*-values indicate statistically significant with $p < .05$.
[a] Proportion of patients free of clinical relapses, GdE lesions, and new T2 lesions calculated from those with complete data available by 36-month follow-up (DMF $n = 602$, FTY $n = 465$).
[b] *t*-test.
[c] Chi-Squared test.

Table 3
Unadjusted and adjusted outcomes of DMF versus FTY at 36 months.

Study endpoints	Unadjusted			Propensity adjusted		
	Odds or hazards ratio	95% CI	p-value	Odds or hazards ratio	95% CI	p-value
DMT discontinuation	1.70	1.35–2.12	< **0.001**	1.81	1.41–2.31	< **0.001**
Disease activity	1.00	0.50–1.24	0.958	1.01	0.49–1.12	0.923
Intolerance	1.68	1.27–2.16	< **0.001**	1.63	1.18–1.73	< **0.001**
Time to discontinuation	1.46	1.24–1.70	< **0.001**	1.53	1.32–1.77	< **0.001**
Clinical relapse ≤ 36	1.15	0.84–1.57	0.427	1.27	0.90–1.79	0.173
Brain MRI activity ≤ 36 months	1.01	0.78–1.31	0.947	0.99	0.74–1.31	0.935
GdE lesions	0.93	0.65–1.33	0.716	1.25	0.85–1.84	0.259
New T2 Lesions	0.95	0.73–1.24	0.737	0.99	0.74–1.32	0.932
Brain MRI activity 24–36 months	1.05	0.64–1.73	0.899	1.10	0.64–1.88	0.731
GdE lesions	0.91	0.25–2.00	0.603	0.95	0.29–2.48	0.770
New T2 lesions	0.88	0.47–1.26	0.363	0.93	0.44–1.35	0.363
Absence of disease activity ≤ 36 months[a]	1.00	0.78–1.27	1.000	1.01	0.78–1.12	0.997

Unadjusted analysis used simple logistic regression. Propensity adjusted methods used conditional logistic regression after average treatment effect on the treated (ATT) weighting for propensity scores.
Abbreviations: DMF: dimethyl fumarate; DMT: disease modifying therapy; FTY: fingolimod; GdE: gadolinium-enhancing lesions.
Bolded *P*-values indicate statistically significant with $p < .05$.
[a] Proportion of patients free of clinical relapses, GdE lesions, and new T2 lesions calculated from those with complete data available.

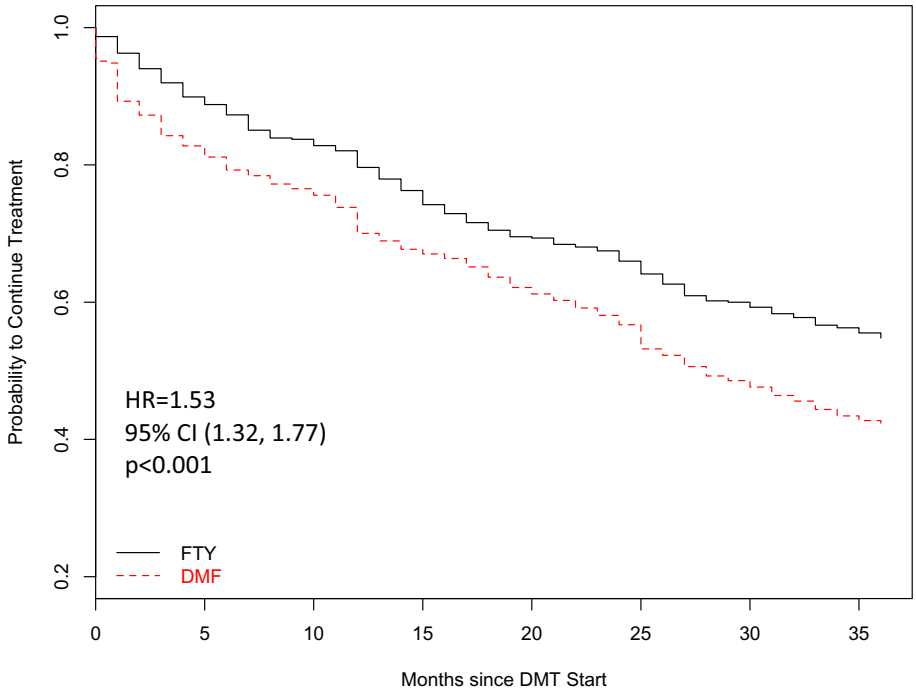

Fig. 2. Kaplan-Meier Plot of DMT discontinuation 0–36 months.
Abbreviations: DMF: dimethyl fumarate; DMT: disease modifying therapy; FTY: fingolimod.

DMF-treated patients demonstrated higher odds of discontinuation compared to FTY-treated patients by 36 months, largely driven by intolerance. Our results also showed relatively greater DMF discontinuations compared to FTY, as were also reported by other observational studies [11,12,16,18,26,27]. Interestingly, when accounting for patient censoring, there appeared to be a bimodal relationship of DMT discontinuation stratified by year of follow-up. For example, DMF patients had significantly greater odds of discontinuation between 0 and 12 months and 24–36 months, while discontinuations between 12 and 24 months were lower and comparable. This finding was further substantiated by our Kaplan-Meier analysis (Fig. 2). One explanation is that AEs more commonly expected with early DMF treatment, such as GI AEs and flushing, largely contributed to discontinuation patterns between 0 and 12 months. Other AEs, such as DMF-associated lymphopenia, which was the third leading cause of DMT cessation in our study, became more prominent as a reason for discontinuation during later treatment. This may have been due to the clinical recognition of the risks of sustained DMF-associated lymphopenia, as opposed to the time course of lymphopenia, for previous studies showed absolute lymphocyte count reductions occur commonly in the first year after DMF initiation [28,29]. Additionally, during this study, revisions to DMF labeling recommended treatment interruption if prolonged lymphopenia occurred due to opportunistic infection risks (e.g. PML), which were observed in the open-label extension study and post-marketing experience [28–30]. In this context, these concerns likely drove our clinicians to discontinue DMF as risks became apparent based on later published research, not necessarily immediately after lymphopenia occurred in earlier treated patients. Further, there was no significant difference in discontinuation due to disease activity over 36 months, or when stratified by year of treatment [13–16].

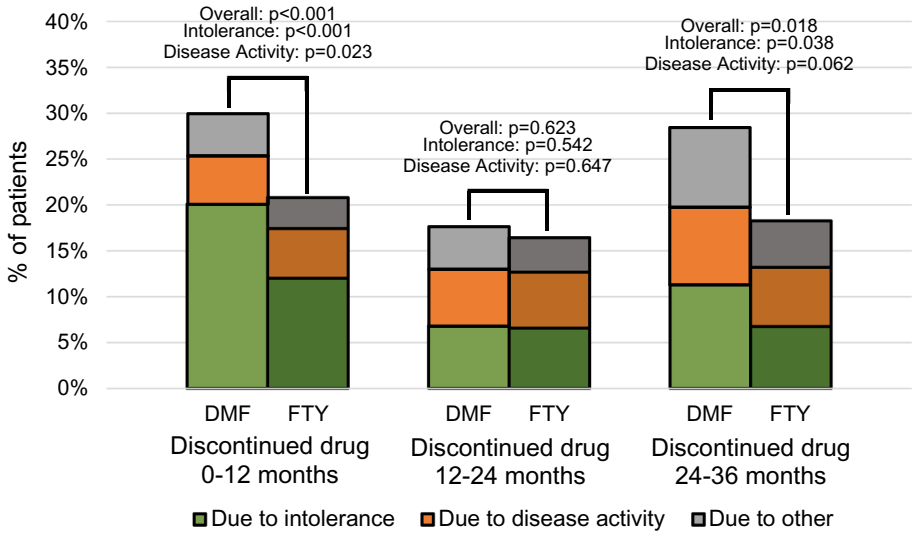

Fig. 3. Distribution of discontinuations by year.
Percentages calculated as number of patients on drug at start of each year (at 0 months, 12 months, and 24 months). Abbreviations: DMF: dimethyl fumarate; FTY: fingolimod.

To our knowledge, there are no direct head-to-head published studies comparing DMF and FTY > 30 months. The current study provides unique extension data to comment on the comparative effectiveness of DMF and FTY over 36 months of treatment. Clinical and radiological outcomes during this time period in our investigation remained low with similar disease activity between DMF and FTY, as was previously observed in other PS-adjusted analyses during shorter time intervals [10,12,31,32], though conflicting data showed reduced ARR among FTY- vs. DMF-treated patients in an international observational MS cohort study [18].

Our results demonstrated no differences in absence of disease activity between DMF and FTY in the overall cohort and RRMS subgroup. As previously discussed [13], there are conflicting reports in the literature regarding comparative NEDA (no evidence of disease activity), which may in part, be related to study logistics and methods of analysis. In a recently published 7-center Italian study, Prosperini et al demonstrated no differences in the probability of achieving NEDA in their overall RRMS cohort (p = .078), though a subgroup analysis indicated favorable NEDA status among switchers from self-injectable drugs to FTY versus DMF [11]. When assessing outcomes individually, Prosperini et al, found no significant differences with the exception of disability worsening (p = .011), which the authors acknowledged to be related to shorter study follow-up (18 month median follow-up). In this context, the inclusion of disability worsening likely contributed to NEDA differences and a probable reason for differences in our report.

To date, no other study has reported switching patterns and comparative outcomes after discontinuing DMF versus FTY. In our study, approximately one third of DMF and FTY patients switched to HET, while more FTY patients switched to moderately effective therapy, likely due to later approval of DMF. In our PS-adjusted analysis, there were no significant differences in clinical relapses or GdE lesions in the 12 months following DMF discontinuation compared to the 12 months following FTY discontinuation, despite the longer washout period in the latter group. Further, there were no differences in relapses or GdE lesions in patients laterally switching to other moderately effective therapies, and overall disease activity remained low in this subgroup. Overall, DMF and FTY discontinuers who switched to HET had less disease activity compared to those switching to injectable and oral therapies. These results align with a large population-based study of patients with breakthrough disease who had reduced ARR and time to first relapse after switching to HET versus moderately effective DMT [32]. It is important to note that the FTY mechanism of action [33] likely played a role in the increased proportion of GdE lesions, relative to on-treatment, when transitioning to other therapies (in particular, non-HET DMTs). This finding underscores the importance of minimizing FTY washout duration and considering a switch to more highly efficacious therapies when clinically appropriate. Our data were also reassuring from a safety standpoint in that no cases of PML or other opportunistic infections occurred in any of our patients on DMF/FTY or within 12 months of transitioning to an alternative DMT.

The current investigation had limitations owing to the assumptions inherent in observational studies, even after the application of PS techniques. While PS adjustment improved the overall baseline covariate balance between DMF and FTY, there are likely residual and hidden biases of unmeasured covariates. However, we believe the a priori covariates included in our PS model are important and well-representative of those used in DMT decision making in clinical practice. As a strength, we were able to include clinical and MRI data that are often unavailable through other sources, such as claims and some population-based data repositories. However, we were limited by retrospectively collected clinician-reported measurements (e.g. relapse) and missing data, which are integral limitations of retrospective observational studies. In addition, our investigation included older and progressive patients representative of the general MS population treated in clinical practice, for which the low inflammatory profiles may have obscured treatment effect differences. To address this, we included a separate subgroup analysis of RRMS patients, which allowed us to ascertain treatment effects in a population of patients similar to those in phase 3 clinical trials. Reassuringly, effectiveness outcomes in this subgroup were comparable to the overall cohort and adds further value to the observed endpoints. Finally, this study included data from two large academic MS centers, which may lessen generalizability to smaller community-based clinics that may differ in DMT prescribing practices and counseling.

5. Conclusion

Our results demonstrate comparable clinical and radiographic effectiveness of DMF and FTY in clinical practice over 36 months of treatment. We found increased odds of DMF discontinuation compared to FTY, largely driven by intolerance. In our cohort, there appeared to be a small rise in DMF discontinuations after the second year on therapy, which deserves further investigation. Reassuringly, patients transitioning from DMF and FTY to an alternative DMT demonstrated

Table 4
Summary of baseline characteristics and outcomes after DMF or FTY discontinuation.

	DMF		FTY		p-value
	n = 364		*n* = 209		
	n	% or SD	n	% or SD	
Baseline characteristics[a]					
Age (years, SD)	46.1	11.9	42.4	11.5	< **0.001**[e]
Female	264	72.5%	146	70.0%	0.623[f]
Disease duration (years, SD)	13.2	9.2	13.2	9.0	0.993[e]
Relapsing-remitting MS	277	76.1%	169	80.9%	0.243[f]
Disease burden on MRI					< **0.001**[f]
Mild	215	59.2%	76	36.5%	
Moderate	127	34.9%	90	42.9%	
Severe	22	5.9%	43	20.6%	
Gadolinium enhancement on MRI	71	19.4%	50	23.9%	0.214[f]
Washout between DMF/FTY and Switched DMT (months)	1.7	1.6	2.3	1.7	**0.010**[e]
DMT After DMF/FTY discontinuation					< **0.001**[f]
HET	118	32.4%	69	33.0%	
Natalizumab	44	12.1%	24	11.5%	
Immunosuppressive therapy[b]	74	20.3%	45	21.5%	
Moderate	56	15.4%	69	33.0%	
Dimethyl fumarate	0	0.0%	69	33.0%	
Fingolimod	56	15.4%	0	0.0%	
Low	84	23.1%	30	14.3%	
Interferon	21	5.8%	9	4.3%	
Glatiramer acetate	49	13.5%	18	8.6%	
Teriflunomide	14	3.8%	3	1.4%	
None	105	28.8%	40	19.1%	
Clinical relapse ≤ 12 months after DMF/FTY discontinuation	37	10.2%	29	13.9%	0.191[g]
Relapse per patient (mean, SD)	0.10	0.3	0.14	0.4	0.149[e]
Of those who switched to HET	7/118	5.9%	8/69	11.6%	0.093[g]
Of those who switched to moderate/low	20/140	14.3%	18/99	18.2%	0.483[g]
Of those who switched to FTY/DMF[d]	5/56	8.9%	7/69	10.1%	0.602[f]
GdE lesions ≤ 12 months after DMF/FTY discontinuation[c]	28	12.4%	21	16.3%	0.398[g]
GdE lesions per patient (mean, SD)	0.12	0.3	0.16	0.4	0.316[e]
Of those who switched to HET	9/87	10.3%	5/42	11.9%	0.516[g]
Of those who switched to moderate/low	12/84	14.3%	14/65	21.5%	0.293[g]
Of those who switched to FTY/DMF[d]	5/84	5.6%	5/65	7.7%	0.589[f]

Abbreviations: DMF: dimethyl fumarate; DMT: disease modifying therapy; FTY: fingolimod; GdE: gadolinium-enhancing lesions; SD: standard deviation.
When comparing DMF switchers to HET versus moderate/low DMTs and FTY switchers to HET versus moderate/low DMTs, switchers to HET had fewer relapses (DMF, $p = .03$; FTY, $p = .05$) and lower gadolinium-enhancing lesions post-FTY (DMF, $p = .36$; FTY, $p = .05$).
Bolded P-values indicate statistically significant with $p < .05$.

[a] Baseline characteristics 12 months prior to DMF/FTY start.
[b] Immunosuppressive Therapy: rituximab, ocrelizumab, alemtuzumab.
[c] Brain MRI availablewithin 6–12 months of DMF/FTY discontinuation.
[d] Patients who switched from DMF to FTY and patients who switched from FTY to DMF.
[e] *t*-test.
[f] Chi-Squared test.
[g] Conditional logistic regression using average treatment effect on the treated (ATT) weighting for propensity scores.

relatively low disease activity over the next 12 months, particularly when switching to HET. Future multi-center studies investigating the long-term comparative effectiveness profiles of DMF and FTY will provide further clinical insight on the use of these commonly prescribed oral DMTs in routine clinical practice.

Acknowledgments

The authors thank the patients and clinicians at the Cleveland Clinic Mellen Center and Rocky Mountain Multiple Sclerosis Clinic at the University of Colorado who helped formulate and implement the fingolimod and dimethyl fumarate treatment protocols.

Author disclosures

Brandi Vollmer reports no disclosures.

Dr. Daniel Ontaneda has received research support from NIH, NMSS, PCORI, Race to Erase, Genzyme, Genentech, and Novartis. Consulting fees from Biogen Idec, Genentech, Genzyme, Merck, and Novartis.

Haleigh Harris reports no disclosures.

Dr. Kavita Nair has consulted and/or received research support from Astellas, Genentech, Novartis, and Biogen.

Dr. Robert Bermel has received consulting fees from Biogen, Genentech, Genzyme, and Novartis; and receives research support from Biogen and Genentech.

Dr. John R. Corboy has received grant support from Novartis, Med Day, NMSS, and PCORI; sits on a steering committee for a clinical trial with Novartis; consults with Mylan on a legal issue; receives honorarium for speaking from the Rocky Mountain MS Center and PRIME CME, and receives compensation as editor of Neurology Clinical Practice.

Dr. Robert J. Fox has received personal consulting fees from Actelion, Biogen, EMD Serono, Genentech, Novartis, and Teva. I have served on advisory committees for Actelion, Biogen, and Novartis, and received clinical trial contract and research grant funding from Biogen and Novartis.

Dr. Timothy Vollmer has received compensation for activities such

as advisory boards, lectures and consultancy with the following companies and organizations: Academic CME; Alcimed; Anthem Blue Cross; Genentech/Roche; Biogen IDEC; Novartis; Celgene; EMD Serono; Epigene; Rocky Mountain MS Center; GLG Consulting; Ohio Health; TG Therapeutics; Topaz Therapeutics; Dleara Lawyers; and Teva Neuroscience; Biogen Australia & New Zealand; Sironax. He received research support from the following: Teva Neuroscience; NIH/NINDS; Rocky Mountain MS Center; Biogen; Actelion; Roche/Genentech; UT Southwestern; F. Hoffman-La Roche, Ltd. and TG Therapeutics, Inc.

Dr. Jeffrey A. Cohen reports personal compensation for consulting for Alkermes, Biogen, Convelo, EMD Serono, ERT, Gossamer Bio, Novartis, and ProValuate; speaking for Mylan and Synthon; and serving as an Editor of Multiple Sclerosis Journal.

Dr. Enrique Alvarez has consulted for Biogen, Genzyme, Genentech, Teva, and Novartis; and received research funding from Rocky Mountain MS Center, Biogen, Novartis, Acorda, and Alkermes.

Dr. Carrie Hersh has received speaking and consulting fees from Biogen, Novartis, Genentech, Genzyme, EMD Serono. She has received research support paid directly to her institution by PCORI and Biogen.

Funding

This study received no funding.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.116498.

References

[1] R. Gold, L. Kappos, D.L. Arnold, et al., Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis, N. Engl. J. Med. 367 (2012) 1098–1107.
[2] R.J. Fox, D.H. Miller, J.T. Phillips, et al., Placebo-controlled phase 3 study of Oral BG-12 or glatiramer in multiple sclerosis, N. Engl. J. Med. 367 (2012) 1087–1097.
[3] J.A. Cohen, F. Barkhof, G. Comi, et al., Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis, N. Engl. J. Med. 362 (2010) 402–415.
[4] L. Kappos, E.-W. Radue, P. O'Connor, et al., A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis, N. Engl. J. Med. 362 (2010) 387–401.
[5] Novartis, Novartis announces new data from the first direct head-to-head trial to demonstrate superior efficacy of Gilenya® over Copaxone® in patients with relapsing remitting multiple. Sclerosis, https://www.novartis.com/news/media-releases/novartis-announces-new-data-from-first-direct-head-head-trial-demonstrate-superior-efficacy-gilenya-over-copaxone-patients-relapsing-remitting-multiple (2018) (accessed 28 Jan 2019).
[6] J.R. Berger, Classifying PML risk with disease modifying therapies, Mult. Scler. Relat. Disord. 12 (2017) 59–63.
[7] J. Van Schependom, J. Gielen, J. Laton, G. Nagels, Assessing PML risk under immunotherapy: if all you have is a hammer, everything looks like a nail, Mult. Scler. J. 22 (2016) 389–392.
[8] R. Nixon, N. Bergvall, D. Tomic, N. Sfikas, G. Cutter, G. Giovannoni, No evidence of disease activity: indirect comparisons of oral therapies for the treatment of relapsing–remitting multiple sclerosis, Adv. Ther. 31 (2014) 1134–1154.
[9] M.S. Freedman, X. Montalban, A.E. Miller, et al., Comparing outcomes from clinical studies of oral disease-modifying therapies (dimethyl fumarate, fingolimod, and teriflunomide) in relapsing MS: assessing absolute differences using a number needed to treat analysis, Mult. Scler. Relat. Disord. 10 (2016) 204–212.
[10] R.J. Fox, A. Chan, A. Zhang, et al., Comparative effectiveness using a matching-adjusted indirect comparison between delayed-release dimethyl fumarate and fingolimod for the treatment of multiple sclerosis, Curr. Med. Res. Opin. 33 (2017) 175–183.
[11] L. Prosperini, M. Lucchini, S. Haggiag, et al., Fingolimod vs dimethyl fumarate in multiple sclerosis. A real-world propensity score-matched study, Neurology 91 (2018) e153–e161.
[12] S. Braune, S. Grimm, P. van Hövell, et al., Comparative effectiveness of delayed-release dimethyl fumarate versus interferon, glatiramer acetate, teriflunomide, or fingolimod: results from the German NeuroTransData registry, J. Neurol. 265 (2018) 2980–2992.
[13] B. Vollmer, D. Ontaneda, A. Bandyopadhyay, et al., Discontinuation and comparative effectiveness of dimethyl fumarate and fingolimod in 2 centers, Neurol. Clin. Pract. 8 (2018) 292–301.
[14] B. Vollmer, K.V. Nair, S.H. Sillau, J. Corboy, T. Vollmer, E. Alvarez, Comparison of fingolimod and dimethyl fumarate in the treatment of multiple sclerosis: two-year experience, Mult. Scler. J. 3 (2017) 2055217317725102.
[15] C.M. Hersh, T.E. Love, A. Bandyopadhyay, et al., Comparative efficacy and discontinuation of dimethyl fumarate and fingolimod in clinical practice at 24-month follow-up, Mult. Scler. J. 3 (2017) 2055217317715485.
[16] P. Wicks, L. Rasouliyan, B. Katic, B. Nafees, E. Flood, R. Sasané, The real-world patient experience of fingolimod and dimethyl fumarate for multiple sclerosis, BMC Res. Notes 9 (2016) 434.
[17] C.M. Hersh, T.E. Love, S. Cohn, et al., Comparative efficacy and discontinuation of dimethyl fumarate and fingolimod in clinical practice at 12-month follow-up, Mult. Scler. Relat. Disord. 10 (2016) 44–52.
[18] T. Kalincik, E.K. Havrdova, D. Horakova, et al., Comparison of fingolimod, dimethly fumarate, and teriflunomide for multiple sclerosis, J. Neurol. Neurosurg. Psychiatry 90 (2019) 458–468.
[19] R. Rosenbaum, D.B. Rubin, The central role of the propensity score in observational studies for causal effects, Biometrika 70 (1983) 41–55.
[20] A. Rae-Grant, G.S. Day, R.A. Marrie, et al., Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the guideline development, dissemination, and implementation subcommittee of the American Acadmy of Neurology, Neurology 90 (17) (2018), https://doi.org/10.1212/WNL.0000000000005347.
[21] D.M. Wingerchuk, J.L. Carter, Multiple sclerosis: current and emerging disease-modifying therapies and treatment strategies, Mayo Clin. Proc. 89 (2) (2014) 225–240.
[22] T. Derfuss, Personalized medicine in multiple sclerosis: hope or reality? BMC Med 10 (2012) 116, https://doi.org/10.1186/1741-7015-10-116.
[23] Team RDC, R: A Language and Environment for Statistical Computing.: Vienna, Austria: The, R Foundation for Statistical Computing, 2014.
[24] D.B. Rubin, Using propensity scores to help design observational studies: application to the tobacco litigation, Health Serv. Outcome. Res. Methodol. 2 (2001) 169–188.
[25] X. Montalban, Review of methodological issues of clinical trials in multiple sclerosis, J. Neurol. Sci. 311 (2011) S35–S42.
[26] K.M. Johnson, H. Zhou, F. Lin, J.J. Ko, V. Herrera, Real-world adherence and persistence to oral disease-modifying therapies in multiple sclerosis patients over 1 year, J. Manag. Care Specialty Pharmacy 23 (2017) 844–852.
[27] M. Granqvist, M. Boremalm, A. Poorghobad, et al., Comparative effectiveness of rituximab and other initial treatment choices for multiple sclerosis, JAMA Neuro. 75 (2018) 320–327.
[28] R. Gold, D.L. Arnold, A. Bar-Or, et al., Long-term effects of delayed-release dimethyl fumarate in multiple sclerosis: interim analysis of ENDORSE, a randomized extension study, Mult. Scler. (Houndmills, Basingstoke, England) 23 (2017) 253–265.
[29] T. Rosenkranz, M. Novas, C. Terborg, PML in a patient with lymphocytopenia treated with dimethyl fumarate, N. Engl. J. Med. 372 (2015) 1476–1478.
[30] US Food and Drug Administration, TECFIDERA™ (dimethyl fumarate); highlights of prescribing information https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/204063s017lbl.pdf, (2017) (accessed 28 Jan 2019).
[31] A. Boster, J. Nicholas, N. Wu, et al., Comparative effectiveness research of disease-modifying therapies for the management of multiple sclerosis: analysis of a large health insurance claims database, Neurol. Therapy (2017) 1–12.
[32] T. Spelman, T. Kalincik, M. Trojana, et al., Comparative analysis of MS outcomes in dimethyl fumarate-treated patients relative to propensity matched fingolimod, interferon, glatiramer acetate, or teriflunomide (P6.372), Neurology 88 (2017) (P6.372).
[33] T.A. Chalmer, T. Kalincik, B. Laursen, et al., Treatment escalation leads to fewer relapses compared with switching to another moderately effective therapy, J. Neurol. 266 (2019) 306–315.