Original Research Article

Real-world effectiveness of dimethyl fumarate versus fingolimod in a cohort of patients with multiple sclerosis using standardized, quantitative outcome metrics

Carrie M Hersh (iD), Arman Altincatal*, Nicholas Belviso, Shivani Kapadia, Carl de Moor, Richard Rudick*, James Rhys Williams, Catherine Miller and Irene Koulinska* (iD)

Abstract

Background: Prior studies suggest comparable effectiveness of dimethyl fumarate (DMF) and fingolimod (FTY) in multiple sclerosis (MS) using relapse, Expanded Disability Status Score (EDSS), and magnetic resonance imaging (MRI) lesion metrics.

Objective: Compare the real-world effectiveness of DMF versus FTY using quantitative, validated neuroperformance tests, MRI, and serum neurofilament light chain (sNfL) outcomes while controlling for between-group differences.

Methods: Patients were eligible if on DMF or FTY when first enrolled in the MS Partners Advancing Technology and Health Solutions (MS PATHS) network and had ≥1-year follow-up in MS PATHS. Sensitivity analysis included a subgroup who started DMF/FTY ≤2 years from enrolment. After propensity score weighting, differences in means and in mean 1-year change of neuroperformance and MRI outcomes were compared. sNfL levels were assessed. This was a non-randomized comparison.

Results: In the overall cohort, no significant differences were observed between DMF ($n = 702$) and FTY ($n = 600$) in neuroperformance or MRI outcomes including brain volume loss; mean time (SD) since treatment initiation was 1.98 (0.68) years for DMF and 2.02 (0.75) years for FTY. A sensitivity analysis controlling for DMF and FTY treatment duration yielded similar results.

Conclusion: In this study, DMF and FTY demonstrated similar effects on physical and cognitive neuroperformance and MRI outcomes. Direct comparisons to other fumarates and S1P receptor modulators were not conducted.

Keywords: dimethyl fumarate, disease-modifying therapies, fingolimod, multiple sclerosis, outcome measurement, cognition

Introduction

Multiple sclerosis (MS), a chronic neurodegenerative disease characterized by demyelination and axonal damage, often leads to physical and cognitive disability. While many disease-modifying therapies (DMTs) have been approved for relapsing forms of MS, individualized treatment selection is challenging due to the scarcity of prospective, head-to-head studies and because randomized, placebo-controlled clinical trials enrol a highly selected population, not necessarily representative of the broad spectrum of patients in clinical practice. Two commonly prescribed oral

Correspondence to:
Carrie M Hersh,
Lou Ruvo Center for Brain Health, Cleveland Clinic, Las Vegas, NV, USA.
hershc@ccf.org

*Employee of Biogen at the time the research was conducted.

Carrie M Hersh,
Arman Altincatal,
Lou Ruvo Center for Brain
Health, Cleveland Clinic, Las
Vegas, USA

Nicholas Belviso,
Shivani Kapadia,
Carl de Moor,
Richard Rudick,
James Rhys Williams,
Catherine Miller,
Irene Koulinska,
Biogen, Cambridge, USA

DMTs, dimethyl fumarate (DMF) and fingolimod (FTY), demonstrated comparable efficacy against placebo and active comparator in their respective pivotal clinical trials.[1–4] Previous real-world observational studies demonstrated comparable DMF and FTY effectiveness, as measured by clinical relapses and conventional magnetic resonance imaging (MRI) measures. In a German NeuroTransData registry-based analysis using propensity score (PS)–matched patients with relapsing-remitting MS, DMF and FTY had similar annualized relapse rates, time-to-first-relapse, and time-to-3- and 6-month Expanded Disability Status Scale (EDSS)–confirmed disability progression.[5] Further, DMF and FTY had comparable effects on the proportion of patients and number with relapses, gadolinium-enhancing lesions, and new T2-hyperintense lesions over 24 and 36 months.[6,7] However, real-world comparative effectiveness data using standardized physical and cognitive neuroperformance outcomes, as well as standardized MRI metrics on brain volume and serum neurofilament light chains (sNfL), have not been reported in the literature to date.

MS Partners Advancing Technology and Health Solutions (MS PATHS) is a technology-enabled network of 10 MS centres in the US, Germany, and Spain.[8] MS PATHS data allow for the real-world assessment of clinically meaningful quantitative outcomes in a standardized manner with the ability to adjust for relevant demographics, disease characteristics, and comorbidities that influence treatment selection. For DMF and FTY, accounting for comorbidities, especially cardiovascular disease and diabetes mellitus, is important because they can influence prescribing practices and treatment selection,[9,10] introducing possible indication bias. Further, accounting for potential differences at baseline is important given that cardiovascular disease and diabetes mellitus, among others, can impact physical, cognitive, and MRI outcomes assessed in the course of MS disease monitoring.[11–14] We compared the real-world effectiveness of DMF versus FTY in the MS PATHS network to explore several clinical, radiological, and biomarker outcomes not included in prior comparative effectiveness studies.

Materials and methods

Study population
This study included patients from US sites participating in the MS PATHS network as of August 2020.[8] The MS PATHS participating centres are summarized in Supplemental Table 1. This analysis included only US sites to (1) circumvent perceived differences in DMF and FTY patient populations between the EU and US owing to EU label restrictions for FTY as a second-line therapy and (2) maintain a more comparable study population to prior MS PATHS studies that were only from US sites. Participating sites standardized aspects of their clinical and radiological assessments by leveraging technology, patient engagement, and automated data collection to minimize the burden on the providers and system.[8] Patients with a confirmed diagnosis of MS, including clinically isolated syndrome, were eligible to enrol. The investigators and research coordinators were encouraged to invite all patients to participate, with an aim of 80% of MS participants at each site enrolled in MS PATHS. Patients provided permission for sharing pseudoanonymized data with the network investigators and sponsor, and such data sharing was approved by all site institutional review boards. Upon enrolment, patient demographics, MS and other medical history, physical and laboratory assessments, medications, patient-reported outcomes and tests, and MRI-related data were collected at baseline and each routine visit. Patients could opt into an optional biobanking substudy that collected serum, RNA, and DNA at routine clinical visits as often as every 6 months.[8]

We identified patients who initiated DMF or FTY prior to enrolment in MS PATHS and were using DMF or FTY at first visit in MS PATHS. Participants were required to have ≥1-year follow-up and ≥1 MRI in the previous year. When patients provided permission for data sharing, they consented to prospective data collection and any in-scope data for the previous 12 months. For this analysis, data were collected at enrolment in MS PATHS and up to 12 months after enrolment on the same DMT. MRI data from the year prior to MS PATHS enrolment were used to define a baseline assessment for calculating new T2 lesions and change in brain parenchymal fraction (BPF) and grey matter fraction (GMF).

Baseline disease characteristics
Patient demographic information was collected using the MS Performance Test (MSPT)[15,16] and electronic medical records, including age, sex, race, ethnicity, education, employment status, MS and medical history, and DMTs.[8] The MSPT is an iPad®-based self-administered assessment tool that includes 4 previously validated neuroperformance test modules for cognition (Processing Speed Test, PST),[17] upper extremity motor function (Manual Dexterity Test, MDT), vision (Contrast Sensitivity Test, CST), and lower extremity motor function (Walking Speed

Test, WST).[15,16] MSPT was designed to be similar to, and extends, the Multiple Sclerosis Functional Composite (MSFC).[15]

Outcome measures

Outcomes were assessed at routine clinical visits following enrolment in MS PATHS and included PST,[17] MDT, CST, WST,[18] patient-reported relapses, Patient Determined Disease Steps (PDDS),[19] new T2 lesions, gadolinium-enhancing (Gd$^+$) lesions, BPF, and GMF.[20] Neuroperformance was defined as performance on PST, MDT, CST, and WST. For PST and CST, a higher number indicates improvement, while for MDT, WST, and PDDS, a lower number indicates improvement.[17–19,21] The scoring performance is number of correct responses for PST and CST and time to completion for MDT and WST; therefore, there is no upper limit for these measures.[17,18] Longitudinal assessments included data from the first year of follow-up in MS PATHS and the latest MRI assessment available in the year prior to enrolment in MS PATHS as baseline for BPF, new T2 lesions, and GMF. sNfL was analysed in a subset of patients using SIMOA NF-light® Advantage Kit (Quanterix).[22]

BPF, GMF, and new T2 brain MRI lesions were generated from standardized 3D T2-weighted fluid-attenuated inversion recovery (FLAIR) and 3D T1-weighted acquisition sequences on Siemens 3 T scanners via a software prototype (MSPie, MS PATHS image analysis). Gd$^+$ lesions were extracted from radiology reports in the medical records. All longitudinal assessments of these outcomes were utilized in the analysis.

Propensity score model and statistical analysis

A PS model based on inverse probability of treatment weights (IPTW) with trimming to exclude outliers was used to balance DMF- and FTY-treated patients on the following characteristics believed to be potential confounders: age, sex, race, education, MS duration, prior DMTs, and comorbidities that may impact neuroperformance. Comorbidities were defined based on the use of co-medications for cardiovascular disease, chronic obstructive pulmonary disease, depression, diabetes mellitus, dyslipidemia, fatigue, inflammatory bowel disease, osteoporosis, pain, rheumatological conditions, and thyroid disease. Prior DMTs were grouped based on the following broad categories: (1) interferons, glatiramer acetate, and teriflunomide; (2) fumarates and S1P receptor modulators; and (3) natalizumab, B-cell depleting therapies, alemtuzumab, and cladribine.

Since there is no formal consensus on DMT categorization based on the lack of head-to-head clinical trials, data were also assessed by individual DMT in a sensitivity analysis. Standardized differences were calculated pre- and post-IPTW to assess covariate balance between DMF and FTY groups after IPTW.

Generalized estimating equation (GEE) models assessed the differences in means and the mean change from first visit to last visit (1-year change) between DMF- and FTY-treated patients with available data for each outcome. GEE models for PST and MDT were further adjusted for number of assessments to account for the impact of practice effects. Least Squares (LS) Means estimates for DMF- and FTY-treated patients and differences in LS Means estimates for DMF versus FTY were computed across the follow-up for clinical and MRI outcomes and summarized with their 95% CI estimates and p values. All assessments were calculated using DMF as a reference. Statistical significance was defined as $p < 0.05$.

Differences in sNfL levels between treatment groups were analysed as both continuous and binary variables. Elevated sNfL was defined as $\geq 97.5\%$ of age-adjusted normative data derived from healthy controls.[23] T-tests were used for measuring differences in mean sNfL levels. Logistic regression models were used to compare the binary outcome of elevated sNfL "yes/no" between DMF- and FTY-treated groups.

Sensitivity analysis

Patients in the overall study cohort could have initiated DMF or FTY at any time before enrolment in MS PATHS; 418 (59.5%) of DMF-treated and 318 (53.0%) of FTY-treated patients in the overall study population did not report their DMT start date. Therefore, we conducted a sensitivity analysis in the subgroup who reported DMF or FTY start dates and initiated DMT within 2 years prior to MS PATHS. While FTY was FDA-approved 3 years earlier than DMF, the comparison conducted in this study was between patients treated with DMF or FTY contemporaneously in the same calendar years. By limiting DMT start date to the time period of up to 2 years prior to MS PATHS enrolment and then following those patients for another 1 year in MS PATHS, we theoretically studied a patient population with follow-up spanning between 1 year (those who initiated DMT immediately prior to enrolment in MS PATHS) and 3 years (those who initiated 2 years prior to enrolment in MS PATHS). By applying these criteria, the sensitivity subgroup population

started DMT an average of 10 months prior to MS PATHS enrolment. In this context, the duration of DMF and FTY treatment in our subgroup population was similar to what has been assessed in prior studies.[5–7,24] Outcome assessments in this subgroup accounted for time since DMT initiation in the PS model.

Results

Patient characteristics

There were 702 patients treated with DMF and 600 patients treated with FTY. Mean time (SEM) since treatment initiation was 1.98 (0.68) years for DMF and 2.02 (0.75) years for FTY. Average number of follow-up assessments per patient in the first year following enrolment in MS PATHS was comparable between groups (clinical, 2.3 [DMF, n = 674; FTY, n = 582]; MRI, 1.9 [DMF, n = 149; FTY, n = 138]; sNfL, 1.0 [DMF, n = 174; FTY, n = 134]). At baseline prior to IPTW, patients treated with DMF were older at symptom onset and first visit, had longer education duration, were more likely to have cardiovascular comorbidities, and were more likely to have been treated with interferons and glatiramer acetate versus FTY (Table 1). PDDS, patient-reported relapses, and smoking were balanced between the groups.

At first visit and before any covariate adjustment, PST scores were significantly worse for DMF-treated patients compared to FTY-treated patients (mean [SD], 48.6 [13.0] in DMF [n = 632] vs 50.6 [12.3] in FTY [n = 541]; $p < 0.01$), and the prevalence of cardiovascular disease was significantly higher among patients treated with DMF versus FTY (46% vs 39%; $p = 0.01$). There were no significant differences for the other neuroperformance metrics at first visit (Table 1). In those patients without cardiovascular comorbidities, the PST score between treatment groups did not differ (mean [SD], 50.6 [13.0] in DMF [n = 337]; 52.1 [12.4] in FTY [n = 328]; $p = 0.10$).

IPTW derived a balanced population among the baseline covariates with standardized differences <0.05 (Supplemental Table 2). In a post-hoc sensitivity analysis using individual DMTs rather than DMT categories to construct probability weights, there were no differences in directionality or statistical significance (data not shown).

Comparison of outcomes in the overall IPTW patient cohort

Using all available longitudinal assessments for each measure starting at MS PATHS enrolment, the differences in means and mean 1-year change from baseline in PST, MDT, WST, CST, PDDS, and patient-reported relapses were comparable between treatment groups after IPTW (Table 3). BPF, new T2 lesions, and GMF also showed similar results (all p values >0.05). Absolute differences were minimal and not statistically significant across treatment groups for any of the outcomes assessed.

Sensitivity analysis in patients initiating DMF or FTY within 2 years of enrolment in MS PATHS

A subgroup of 135 DMF- and 134 FTY-treated patients fit the sensitivity analysis criteria, enabling control for DMT start date. Mean (SD) time since treatment initiation was 11.2 months (7.3) for the DMF group (n = 135) and 10.1 months (6.9) for the FTY group (n = 134). The average number of assessments was similar between groups (DMF [n = 131]: clinical = 2.5, MRI = 2.0, biomarker = 1.0; FTY [n = 132]: clinical = 2.3, MRI = 2.1, biomarker = 1.0). Prior to IPTW, baseline characteristics were similar except DMF-treated patients were older at first visit (42.9 vs 39.9, $p = 0.01$), more likely to be treated with interferons, glatiramer acetate, and teriflunomide (53% vs 44%), less likely to be treated with fumarates and S1P receptor modulators (4% vs 18%) and natalizumab and B-cell depleting therapies (2% vs 17%), and less likely to have rheumatological conditions (22% vs 34%, $p = 0.03$) compared to FTY-treated patients. Following IPTW, all baseline covariates were well-balanced with standardized mean differences <0.06, as in the overall cohort. Treatment outcomes after IPTW were also similar to the overall cohort, with the exception of a significant difference in mean (95% CI) 1-year change from baseline between treatment groups for MDT (−0.60 [−1.14, −0.05]; $p = 0.03$; Table 4), favouring DMF.

SNfL levels

Among patients with available data (DMF: n = 174; FTY: n = 134), mean (SD) sNfL was 9.5 (5.6) for DMF versus 12.3 (10.5) for FTY (t-test, $p = 0.01$); 17/174 (9.8%) DMF-treated patients and 26/134 (19.4%) FTY-treated patients had elevated sNfL levels at first year follow-up assessment after MS PATHS enrolment. Mean (SD) estimated time from MS PATHS baseline visit to sNfL measurement (n = 308) was 7.1 (5.2) months. A logistic regression model comparing patients with elevated sNfL (≥97.5% of age-adjusted normative data) demonstrated a significant difference favouring DMF (odds ratio, 0.450; 95% CI, 0.233, 0.869; $p = 0.02$).

Table 1. Baseline demographics, MS disease characteristics, and comorbidities at first visit in MS PATHS.

Characteristics	N	DMF	N	FTY	p value
Age at first visit, years, mean [SD]	702	47 [10]	600	44 [10]	<0.001
Age at first symptom, years, mean [SD]	697	33 [11]	599	31 [10]	<0.001
Female, n (%)	703	510 (73)	600	433 (72)	0.88
Race, n (%)	703		600		0.08
Black/African American		88 (13)		53 (9)	
Asian		1 (<1)		4 (<1)	
White		579 (82)		511 (85)	
Other		35 (5)		32 (5)	
Education, years, mean [SD]	702	15.1 [2.6]	600	14.7 [2.4]	0.01
Full-time employment, yes, n (%)	701	375 (53)	599	309 (52)	0.49
Smoking, yes, n (%)	701	310 (44)	599	251 (42)	0.40
Patient-reported relapses (in the past year)					0.71
Mean [SD]	694	0.8 [1.0]	598	0.7 [1.0]	0.39
0, n (%)		390 (56)		339 (57)	0.58
1, n (%)		145 (21)		135 (23)	
2, n (%)		90 (13)		77 (13)	
≥ 3, n (%)		69 (10)		47 (8)	
MS duration, years, mean [SD]	690	11.9 [8.4]	587	11.5 [7.7]	0.40
PDDS Score, mean [SD]	697	1.7 [2.0]	595	1.6 [1.8]	0.33
Prior DMT use, n (%)[a]	702		600		<0.001
Interferons, glatiramer acetate, teriflunomide		445 (63)		324 (54)	
Glatiramer acetate		229 (33)		138 (23)	
Interferon beta-1a, intramuscular		117 (17)		98 (16)	
Interferon beta-1a, subcutaneous		63 (9)		53 (9)	
Interferon beta-1b		27 (4)		24 (4)	
Teriflunomide		4 (1)		6 (1)	
Peginterferon beta-1a		5 (1)		4 (1)	
Interferon-beta[b]		0 (0)		1 (0)	
Fumarates, S1P receptor modulators[c]		39 (6)		84 (14)	
Dimethyl fumarate		12 (2)		74 (12)	
Fingolimod		27 (4)		10 (2)	
Natalizumab, B-cell depleting therapies, alemtuzumab, cladribine		45 (6)		73 (12)	
Natalizumab		43 (6)		70 (12)	
Rituximab		0 (0)		3 (1)	
Alemtuzumab		1 (0)		0 (0)	
Ocrelizumab		1 (0)		0 (0)	
Cladribine		0 (0)		0 (0)	
Immunosuppressive therapy[d]		0 (0)		2 (<1)	
No Prior DMT		174 (25)		117 (20)	
Comorbidities, n (%)	702		600		
Cardiovascular		324 (46)		236 (39)	0.01
Chronic obstructive pulmonary disease		103 (15)		90 (15)	0.87
Depression		373 (53)		332 (55)	0.43
Diabetes mellitus		52 (7)		38 (6)	0.45
Dyslipidemia		159 (23)		137 (23)	0.94
Fatigue		215 (31)		191 (32)	0.64
Inflammatory bowel disease		5 (<1)		4 (<1)	0.92

(continued)

Table 1. Continued.

Characteristics	N	DMF	N	FTY	p value
Osteoporosis		34 (5)		15 (3)	0.03
Pain		442 (63)		342 (57)	0.03
Rheumatological conditions		162 (23)		156 (26)	0.22
Thyroid disease		82 (12)		63 (11)	0.50
Neuroperformance values, mean [SD]					
PST	632	48.6 [13.0]	541	50.6 [12.3]	0.01
MDT	598	27.1 [6.5]	523	26.8 [6.4]	0.35
CST	366	33.1 [12.9]	323	33.2 [13.3]	0.91
WST	597	7.1 [3.6]	522	7.0 [3.8]	0.83

CST = contrast sensitivity test; DMF = dimethyl fumarate; DMT = disease-modifying therapy; FTY = fingolimod; MDT = manual dexterity test; MS = multiple sclerosis; MS PATHS, MS Partners Advancing Technology and Health Solutions; PDDS = patient-determined disease score; PST = processing speed test; SD = standard deviation; WST = walking speed test.

[a]Prior DMT was patient-reported.

[b]Interferon beta use self-reported by patient without additional details on interferon type or administration.

[c]No patients in this study were previously treated with any of the other approved fumarates (diroximel fumarate, monomethyl fumarate) or S1P receptor modulators (siponimod, ozanimod, posenimod) to date.

[d]Immunosuppressive therapy included mycophenylate mofetil and methotrexate in this cohort.

There were no patients who self-reported prior use of daclizumab, pulse intravenous methylprednisolone, or intravenous immune globulin.

Data shown in this table are prior to trimming with calculated inverse probability weighting.

Comorbidities were defined based on the use of comedications.

In the sensitivity analysis, only 46 DMF- and 30 FTY-treated patients had sNfL assessments. Among those, mean (SD) sNfL was 8.7 (4.2) for DMF and 10.2 (11.8) for FTY ($p = 0.50$). After 1 year of enrolment in MS PATHS, 5 DMF-treated (10.9%) and 4 FTY-treated (13.3%) patients had elevated sNfL ($p = 0.75$).

Discussion

The current study compared the effectiveness of DMF and FTY in a large heterogeneous real-world cohort of patients from the MS PATHS network by assessing standardized neuroperformance measures of physical and cognitive impairment (MDT, WST, CST, and PST), MRI metrics of active disease and brain volume change, and sNfL levels. Results were consistent with and further strengthen prior findings showing comparable effectiveness of DMF and FTY on the risk of relapses and Gd+ lesions.[5–7] Importantly, we demonstrated that DMF and FTY have similar effects on PST, BPF, and GMF while accounting for the presence of cardiovascular disease and diabetes mellitus, among other potential confounders measured.

Cognitive impairment is common in MS and can have a major impact on quality of life, activities of daily living, and employability.[25] Thus, assessment of cognition is an important complement to conventional measures of MS disease activity. Volume loss in both whole brain and regional brain (thalamic and cortical grey matter) correlate with cognitive decline in MS and impaired processing speed.[26–28] Cognitive decline differs based on MS disease course, with cognitive decline in early relapsing-remitting MS predictive of white matter integrity damage, and cognitive decline in late relapsing-remitting and progressive MS predictive of cortical atrophy.[29] Cognitive decline can also be impacted by age, education, cardiovascular disease, and other chronic comorbidities. In a previous MS PATHS analysis, patients initiating DMF had worse baseline PST scores independent of age, MS type (relapsing vs progressive), and education than patients initiating FTY and had baseline characteristics associated with a worse prognosis.[30] Such baseline imbalance can lead to residual confounding in comparative effectiveness studies given that cardiovascular comorbidities have also been associated with lower cognition scores[31–34] and more advanced brain atrophy.[13] Accordingly, the lower PST scores observed at baseline in DMF versus FTY in this study may have been related to a higher prevalence

Table 2. Standardized differences of PS model covariates before and after IPTW.

Characteristic[a]	Standardized difference	
	Before IPTW	After IPTW
Age	0.30	0.01
Sex	0.01	0.00
Race	0.14	0.03
Education	0.15	−0.01
MS duration	−0.05	0.01
Prior DMT	0.37	0.00
Cardiovascular disease	0.14	0.00
Diabetes mellitus	0.04	0.00

DMT = disease-modifying therapy; IPTW = inverse probability of treatment weights; MS = multiple sclerosis; PS = propensity score.
[a]Comorbidities were defined based on the use of comedications.

of cardiovascular comorbidities in the DMF group; in the subgroup of patients without cardiovascular comorbidities at baseline, the PST scores of DMF-versus FTY-treated patients were not significantly different. While the specific contribution of MS disease versus non-MS factors (e.g. cardiovascular comorbidity, age, education, and other chronic conditions) to cognitive decline could not be assessed in this study, baseline differences in PST between study groups became non-significant at 1-year follow-up after adjusting for several covariates, including age and cardiovascular disease. This finding highlights the importance of including comorbidities as covariates in comparative effectiveness studies, especially when cognition and measures of brain atrophy are assessed.

Our study was also unique in that it analysed standardized, quantitative neuroperformance outcomes such as MDT, WST, and CST, which are typically not available from real-world cohorts because they are not routinely assessed.[35] The use of MSPT in MS PATHS enabled standardized digital collection of such data for the present investigation. Further, analysis of real-world MRI data is typically restricted by different image acquisitions via a variety of MRI protocols and scanners, often making comparisons across patients difficult. Use of a standardized MRI protocol on Siemens 3 T scanners avoided this limitation in the current study. However, interpretation of MRI outcomes is limited due to the smaller size of the subgroup in the primary analysis population

who had available MRI data and known DMT start date, comprising 270 patients.

Age-adjusted sNfL was also assessed. Most patients had normal sNfL levels based on references from a normative population.[23] Recently, similar decreases in sNfL concentrations were shown in patients treated with DMF or FTY for at least 4 months.[36] In this study, while the means were higher in FTY patients, interpretation of such findings is restricted by (1) the small magnitude of the difference, (2) smaller sample size of patients with available sNfL, and (3) mostly cross-sectional nature of the analysis given that only one sample per patient was available; therefore, we could not assess change from baseline for this biomarker.

A key limitation of this study is the inclusion of patients who had initiated DMF or FTY before enrolment in MS PATHS. Therefore, results were reflective of DMT performance in patients who were already established on DMT, resulting in missing clinical information at DMT start and shortening the time interval available to assess the slope of change in metrics over time. Approximately half of patients did not have a reliable DMT start date reported, limiting our ability to account for time since DMT initiation. To address this limitation, we conducted a sensitivity analysis that included only patients whose available start times were restricted to reflect an overall DMF and FTY treatment duration similar to that of prior real-world comparative effectiveness studies (i.e. ranging from 1 to 3 years). As such, results are reflective of treatment effectiveness in patients who were on therapy for ~1 year (mean treatment initiation in the sensitivity cohort was 10 months prior to MS PATHS), given that patients who might have discontinued therapy earlier were not included. The results of this sensitivity analysis were consistent with results from the overall cohort, as well as from prior real-world studies.[5–7]

The current study was also limited by retrospectively collected and missing data (e.g. MRI and sNfL measures), in addition to hidden biases of unmeasured covariates. Although prior DMTs were known and included in the PS model to adjust for indication bias, the study was limited by inaccessible data on number of switched DMTs and sequencing strategies prior to DMF and FTY start. Further, while we adjusted for prior DMTs in the PS model, it is difficult to measure their impact on the future MS disease course and whether their impact on the immune

Table 3. Neuroperformance and MRI outcomes following IPTW analysis (overall cohort).

	LS means (95% CI)[a]		Difference in means between groups (95% CI)	p value	Change in LS means (95% CI)[c]		Difference in mean 1-year change from baseline between groups (95% CI)	p value
	DMF	FTY			DMF	FTY		
Neuroperformance								
PST[b]	49.2 (48.1, 50.3)	50.4 (49.3, 51.6)	−1.19 (−2.68, 0.29)	0.12	0.68 (0.41, 0.96)	0.66 (0.36, 0.97)	0.02 (−0.37, 0.41)	0.92
MDT[c]	27.0 (26.4, 27.3)	26.7 (26.1, 27.3)	0.28 (−0.47, 1.04)	0.46	−0.49	−0.36	−0.13 (−0.44, 0.18)	0.42
WST[c]	7.18 (6.86, 7.50)	7.04 (6.72, 7.36)	0.14 (−0.31, 0.60)	0.53	−0.04 (−0.69, −0.28)	0.01 (−0.61, −0.11)	−0.05 (−0.23, 0.12)	0.55
CST[b]	33.1 (31.9, 34.2)	32.9 (31.6, 34.1)	0.20 (−1.49, 1.88)	0.82	0.51 (−0.20, 0.11)	0.53 (−0.09, 0.11)	−0.02 (−0.73, 0.70)	0.96
PDDS	1.64 (1.49, 1.79)	1.52 (1.37, 1.68)	0.12 (−0.10, 0.33)	0.28	−0.02 (−0.01, 1.00)	−0.03 (−0.03, 1.08)	0.01 (−0.05, 0.08)	0.68
Patient-reported relapses, number	0.58 (0.52, 0.60)	0.54 (0.48, 0.60)	0.04 (−0.05, 0.13)	0.36	−0.21 (−0.06, 0.03)	−0.20 (−0.07, 0.02)	−0.01 (−0.08, 0.05)	0.67
Magnetic resonance imaging								
New T2 lesions (cumulative)	0.51 (0.37, 0.65)	0.45 (0.28, 0.62)	0.06 (−0.16, 0.28)	0.61	0.96 (0.72, 1.21)	0.77 (0.50, 1.04)	0.20 (−0.17, 0.56)	0.29
Gd+ lesions (continuous)	0.05 (0.01, 0.09)	0.03 (0.005, 0.05)	0.02 (−0.02, 0.07)	0.32	0.11 (−0.05, 0.27)	−0.03 (−0.08, 0.02)	0.14 (−0.03, 0.31)	0.10
Brain parenchymal fraction	0.86 (0.85, 0.86)	0.85 (0.85, 0.86)	−0.0009 (−0.005, 0.005)	0.74	−0.0005 (−0.0008, −0.0003)	−0.0006 (−0.001, −0.0002)	0.0001 (−0.0004, 0.0005)	0.79
Grey matter fraction	0.47 (0.47, 0.48)	0.48 (0.47, 0.48)	−0.004 (−0.008, 0.0005)	0.09	−0.002 (−0.003, −0.0004)	−0.003 (−0.005, −0.002)	0.002 (−0.0008, 0.004)	0.18

CST = contrast sensitivity test; DMF = dimethyl fumarate; FTY = fingolimod; Gd+ = gadolinium enhancing; GEE = generalized estimating equation; LS = least squares; MDT = manual dexterity test; PDDS = patient determined disease step; PS = propensity score; PST = processing speed test; WST = walking speed test.
[a]DMF is the reference for this comparison. The LS Means estimates are derived from GEE models with repeated measure data; each patient can contribute multiple measures to the analysis.
[b]PST and CST scores indicate the number of correct responses.
[c]MDT and WST scores are measured in number of seconds to complete the test.

Table 4. Neuroperformance and MRI outcomes following IPTW analysis (subgroup population of patients with known DMT start date).

	LS means (95% CI)[a]		Difference in means between groups (95% CI)	p value	Change in LS means (95% CI)[a]		Difference in mean 1-year change from baseline between groups (95% CI)	p value
	DMF	FTY			DMF	FTY		
Neuroperformance								
PST[b]	52.9 (50.6, 55.2)	54.5 (52.1, 56.8)	−1.56 (−4.7, 1.6)	0.34	0.81 (0.26, 1.35)	0.85 (0.10, 1.6)	−0.04 (−0.91, 0.84)	0.45
MDT[c]	25.8 (24.6, 26.9)	25.9 (24.8, 26.9)	−0.093 (−1.54, 1.35)	0.74	−0.97 (−1.40, −0.55)	−0.38 (−0.75, −0.002)	−0.60 (−1.14, −0.05)	0.03
WST[c]	6.68 (6.11, 7.25)	6.50 (5.90, 7.11)	0.18 (−0.65, 1.01)	0.42	−0.21 (−0.53, 0.11)	0.08 (−0.15, 0.31)	−0.29 (−0.67, 0.08)	0.13
CST[b]	36.3 (34.3, 38.4)	36.7 (34.4, 39.0)	−0.38 (−3.5, 2.7)	0.81	0.60 (−0.43, 1.64)	0.29 (−0.80, 1.37)	0.32 (−1.15, 1.78)	0.67
PDDS	1.17 (0.86, 1.47)	1.09 (0.79, 1.40)	0.07 (−0.36, 0.50)	0.74	−0.001 (−0.09, 0.08)	−0.07 (−0.15, 0.002)	0.07 (−0.04, 0.18)	0.20
Patient-reported relapses, number	0.60 (0.46, 0.73)	0.54 (0.42, 0.67)	0.05 (−0.13, 0.24)	0.57	−0.32 (−0.44, −0.20)	−0.27 (−0.37, −0.17)	−0.05 (−0.20, 0.10)	0.52
Magnetic resonance imaging								
New T2 lesions (cumulative)	0.41 (0.12, 0.70)	0.64 (0.20, 1.08)	−0.23 (−0.73, 0.27)	0.37	0.69 (0.30, 1.08)	1.08 (0.48, 1.67)	−0.39 (−1.14, 0.37)	0.32
Gd^{+} lesions (continuous)	0.06 (−0.014, 0.130)	0.03 (−0.001, 0.067)	0.02 (−0.057, 0.104)	0.57	−0.0003 (−0.005, 0.004)	−0.042 (−0.123, 0.039)	0.042 (−0.039, 0.122)	0.31
Brain parenchymal fraction	0.87 (0.86, 0.87)	0.87 (0.86, 0.87)	0.002 (−0.01, 0.01)	0.72	−0.001 (−0.002, −0.0001)	−0.002 (−0.001, 0.004)	−0.001 (−0.002, 0.0003)	0.17
Grey matter fraction	0.48 (0.47, 0.49)	0.48 (0.47, 0.49)	−0.003 (−0.012, 0.005)	0.47	−0.004 (−0.007, −0.001)	−0.003 (−0.006, −0.0003)	−0.0005 (−0.005, 0.004)	0.83

CST = contrast sensitivity test; DMF = dimethyl fumarate; FTY = fingolimod; Gd^{+} = gadolinium enhancing; GEE = generalized estimating equation; LS = least squares; MDT = manual dexterity test; PDDS = patient determined disease step; PST = processing speed test; WST = walking speed test.

[a] DMF is the reference for this comparison. The LS Means estimates are derived from GEE models with repeated measure data; each patient can contribute multiple measures to the analysis.

[b] PST and CST scores indicate the number of correct responses.

[c] MDT and WST scores are measured in number of seconds to complete the test.

system affected subsequent DMT response. Prior DMTs and relapses were patient-reported and not confirmed by a physician, and data on number of prior DMTs were not collected. Importantly, this investigation focused specifically on DMF and FTY. While similar findings would be expected with other fumarates (e.g. diroximel fumarate, monomethyl fumarate) and S1P receptor modulators (e.g. siponimod, ozanimod, ponesimod), direct comparisons were not conducted in this analysis. Additional research efforts will further the understanding of comparative effectiveness of newer DMT treatment options.

Although there was a larger percentage of FTY-treated vs DMF-treated patients with prior use of high efficacy therapies, we sought to correct this important indicator for DMT selection by including prior DMT as a covariate in the IPTW model to reduce indication bias. We also note that DMF-treated patients were more likely to have osteoporosis. While there may be a relationship between chronic steroid use and osteoporosis, there are other contributory factors such as sex, race, level of physical disability and mobility restrictions limiting weight-bearing, body mass index, smoking, and presence of other autoimmune conditions. In this context, sex, race, and smoking were well-balanced between the 2 cohorts in this study. Since infused steroids are not reliably captured in the MS PATHS database, and patient-reported use of steroids would only span the time enrolled in MS PATHS, we were unable to reliably comment on its association with osteoporosis in this cohort nor any differential effects between DMF and FTY. Finally, this was a non-randomized comparison.

Regardless of the limitations of the dataset, the results from the sensitivity analysis including only patients whose available DMT start dates were known confirmed the findings from the larger cohort. Additionally, clinical, MRI, and biomarker data demonstrated comparable effectiveness of DMF and FTY in this cohort, which are consistent with prior studies using different methodologies, outcomes, and data sources.

Conclusions

In this real-world study, DMF and FTY showed similar findings across measures related to neuroperformance, cognition, brain volume, and sNfL levels in the MS PATHS dataset while incorporating comorbidities known to affect MS outcomes in our statistical model. These data confirm and expand upon prior reports demonstrating comparable effectiveness, including equivalent MRI outcomes, of DMF and FTY in the first 2 to 3 years of therapy[1–5] and may facilitate personalized treatment choices.

Authors' contributions

Carrie M Hersh contributed to the study concept and design, patient recruitment, acquisition and interpretation of data, and drafting and critical revision of the manuscript. Arman Altincatal and Nicholas Belviso provided statistical analysis, interpretation of data, and critical revision of the manuscript for intellectual content. Shivani Kapadia and Catherine Miller contributed to drafting and critical revision of the manuscript. Carl de Moor contributed to the study concept and design, statistical analysis, and interpretation of data. Richard Rudick contributed to patient recruitment, acquisition and interpretation of data, and drafting and critical revision of the manuscript. James Rhys Williams contributed to patient recruitment, acquisition of data, and critical revision of the manuscript for intellectual content. Irene Koulinska contributed to the study concept and design, interpretation of data, and drafting and critical revision of the manuscript for intellectual content.

ORCID iDs

Carrie M Hersh https://orcid.org/0000-0002-5716-5645
Irene Koulinska https://orcid.org/0000-0002-4918-4045

Supplemental material

Supplemental material for this article is available online.

References

1. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med* 2012; 367: 1087–1097.
2. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012; 367: 1098–1107.
3. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010; 362: 387–401. 2010/01/22.
4. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010; 362: 402–415. 2010/01/22.
5. Braune S, Grimm S, van Hövell P, et al. Comparative effectiveness of delayed-release dimethyl fumarate versus interferon, glatiramer acetate, teriflunomide, or fingolimod: results from the German NeuroTransData registry. *J Neurol* 2018; 265: 2980–2992. 2018/10/18.
6. Vollmer B, Ontaneda D, Bandyopadhyay A, et al. Discontinuation and comparative effectiveness of dimethyl fumarate and fingolimod in 2 centers. *Neurol Clin Pract* 2018; 8: 292–301. 2018/08/25.
7. Vollmer B, Ontaneda D, Harris H, et al. Comparative discontinuation, effectiveness, and switching practices of dimethyl fumarate and fingolimod at 36-month follow-up. *J Neurol Sci* 2019; 407: 2019. /10/24.
8. Mowry EM, Bermel R, Williams JR, et al. Harnessing real-world data to inform decision-making: Multiple Sclerosis Partners Advancing Technology and Health Solutions (MS PATHS). *Front Neurol* 2020; 632 11. DOI: 10.3389/fneur.2020.00632
9. Novartis. Gilenya (fingolimod) highlights of prescribing information, https://www.novartis.us/sites/www.novartis.us/files/gilenya.pdf (2019, accessed November 6 2020).
10. Biogen Inc. TECFIDERA® (dimethyl fumarate) delayed-release capsules, for oral use, https://www.tecfidera.com/content/dam/commercial/multiple-sclerosis/tecfidera/pat/en_us/pdf/full-prescribing-info.pdf (accessed July 26, 2019.).
11. Van Dyken P and Lacoste B. Impact of metabolic syndrome on neuroinflammation and the blood-brain barrier. *Front Neurosci* 2018; 12: 930. 2019/01/09.
12. Lorefice L, Frau J, Coghe G, et al. Assessing the burden of vascular risk factors on brain atrophy in multiple sclerosis: a case-control MRI study. *Mult Scler Relat Disord* 2019; 27: 74–78. 2018/10/22.
13. Kappus N, Weinstock-Guttman B, Hagemeier J, et al. Cardiovascular risk factors are associated with increased lesion burden and brain atrophy in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2016; 87: 181–187. 2015/02/28.
14. Jakimovski D, Gandhi S, Paunkoski I, et al. Hypertension and heart disease are associated with development of brain atrophy in multiple sclerosis: a 5-year longitudinal study. *Eur J Neurol* 2019; 26: 87–e88. 2018/08/14.
15. Rao SM, Galioto R, Sokolowski M, et al. Multiple sclerosis performance test: validation of self-administered neuroperformance modules. *Eur J Neurol* 2020; 27: 878–886. 2020/02/06.
16. Rhodes JK, Schindler D, Rao SM, et al. Multiple sclerosis performance test: technical development and usability. *Adv Ther* 2019; 36: 1741–1755. 2019/05/06.
17. Rao SM, Losinski G, Mourany L, et al. Processing speed test: validation of a self-administered, iPad®-based tool for screening cognitive dysfunction in a clinic setting. *Mult Scler* 2017; 23: 1929–1937. 2017/01/13.
18. Learmonth YC, Dlugonski DD, Pilutti LA, et al. The reliability, precision and clinically meaningful change of walking assessments in multiple sclerosis. *Mult Scler* 2013; 19: 1784–1791. 2013/04/17.
19. Young PS, Middleton RG, Vasukutty NL, et al. Primary and revision THA using a stemless metaphyseal-loading implant above distorted proximal femoral anatomy. *Hip Int* 2013; 23: 40–45. 2012/12/20.
20. Fisher E, Kober T, Tsang A, et al. Magnetic resonance imaging (MRI) metrics in routine clinical practice: proof of concept in MS PATHS (multiple sclerosis partners advancing technology for health solutions). *Neurology* 2020; 94: 1356.
21. Learmonth YC, Motl RW, Sandroff BM, et al. Validation of patient determined disease steps (PDDS) scale scores in persons with multiple sclerosis. *BMC Neurol* 2013; 13: 37. 2013/04/27.
22. Kuhle J, Barro C, Andreasson U, et al. Comparison of three analytical platforms for quantification of the neurofilament light chain in blood samples: ELISA, electrochemiluminescence immunoassay and simoa. *Clin Chem Lab Med* 2016; 54: 1655–1661. 2016/04/14.
23. Sotirchos E, Filippatou A, Fitzgerald K, et al. Elevated serum neurofilament light chain is associated with accelerated inner retinal layer thinning in multiple sclerosis. *Mult Scler* 2019; 25(S2): 274.
24. Hersh C, Lei Y, de Moor C, et al. Multiple sclerosis patients initiating dimethyl fumarate versus fingolimod in the real-world setting have baseline characteristics associated with worse clinical prognosis. *Mult Scler* 2019; 25(S2): 866–867.
25. Benedict RH, DeLuca J, Phillips G, et al. Validity of the symbol digit modalities test as a cognition performance

outcome measure for multiple sclerosis. *Mult Scler* 2017; 23: 721–733. 2017/02/17.

26. Sanfilipo MP, Benedict RH, Weinstock-Guttman B, et al. Gray and white matter brain atrophy and neuropsychological impairment in multiple sclerosis. *Neurology* 2006; 66: 685–692. 2006/03/15.

27. Rocca MA, Riccitelli GC, Meani A, et al. Cognitive reserve, cognition, and regional brain damage in MS: a 2-year longitudinal study. *Mult Scler* 2019; 25: 372–381. 2018/01/06.

28. Zivadinov R, Sepcic J, Nasuelli D, et al. A longitudinal study of brain atrophy and cognitive disturbances in the early phase of relapsing-remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2001; 70: 773–780. 2001/06/01.

29. Eijlers AJC, van Geest Q, Dekker I, et al. Predicting cognitive decline in multiple sclerosis: a 5-year follow-up study. *Brain* 2018; 141: 2605–2618. 2018/09/01.

30. Hersh C, Lei Y, de Moor C, et al. Multiple sclerosis patients initiating dimethyl fumarate versus fingolimod in the real-world setting have baseline characteristics associated with worse clinical prognosis. *Mult Scler J* 2019; 23: 866–867.

31. Leritz EC, McGlinchey RE, Kellison I, et al. Cardiovascular disease risk factors and cognition in the elderly. *Curr Cardiovasc Risk Rep* 2011; 5: 407–412. 2011/12/27.

32. Hu P, Lee J, Beaumaster S, et al. Cognitive function and cardiometabolic-inflammatory risk factors among older Indians and Americans. *J Am Geriatr Soc* 2020; 68: S36–S44. 2020/08/21.

33. Shin SY, Katz P, Wallhagen M, et al. Cognitive impairment in persons with rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012; 64: 1144–1150. 2012/04/17.

34. Yaffe K, Bahorik AL, Hoang TD, et al. Cardiovascular risk factors and accelerated cognitive decline in midlife: the CARDIA study. *Neurology* 2020; 95: e839–e846. 2020/07/17.

35. LaRocca NG, Hudson LD, Rudick R, et al. The MSOAC approach to developing performance outcomes to measure and monitor multiple sclerosis disability. *Mult Scler* 2018; 24: 1469–1484. 2017/08/12.

36. Delcoigne B, Manouchehrinia A, Barro C, et al. Blood neurofilament light levels segregate treatment effects in multiple sclerosis. *Neurology* 2020; 94: e1201–e1212. 2020/02/13.