Comparative effectiveness of dimethyl fumarate versus fingolimod and teriflunomide among MS patients switching from first-generation platform therapies in the US

Daniel Ontaneda[a], Jacqueline Nicholas[b], Matthew Carraro[c], Jia Zhou[d], Qiang Hou[d], Jaanai Babb[d,e], Katherine Riester[d], Jason P. Mendoza[d], Terrie Livingston[d], Mehul Jhaveri[d,*]

[a] Cleveland Clinic, Mellen Center for MS, Cleveland, OH, United States
[b] OhioHealth Multiple Sclerosis Center, Columbus, OH, United States
[c] Novant Health Center for Multiple Sclerosis, Charlotte, NC, United States
[d] Biogen, Cambridge, MA, United States
[e] MCPHS University, Boston, MA, United States

ARTICLE INFO

ABSTRACT

Background: Previous real-world comparative research of MS disease modifying therapies (DMTs) in the overall population has suggested dimethyl fumarate (DMF) to be comparable to fingolimod (FTY) and more efficacious than teriflunomide (TERI) in reducing relapses. However, there is limited comparative evidence in patients switching from platform DMTs in the US. The objective of the study was to compare the annualized relapse rate (ARR) and risk of relapse in MS patients who have switched from a platform therapy to DMF, FTY, or TERI.

Methods: MS patients (18–65 years old) initiating an oral DMT from June 2013 to March 2015 were identified from the Truven MarketScan® Commercial Claims Database. The index date was the date of first oral DMT fill. Patients were required to have: continuous enrollment in the database for 12 months pre-index date and ≥3 months post-index date; ≥1 MS diagnosis over the pre-index period; discontinuation of a platform DMT with no evidence of oral or infusion DMTs over the pre-index period; and adherence to the index drug for ≥90 days. DMF patients were propensity-score matched (PSM) 3:1 to FTY and to TERI based on age, gender, region, a claims-based MS severity measure, ARR, and number of hospitalizations over the pre-index period. Patients were censored when they dropped out of the database or at the end of the study period (March 31, 2016). Post-index relapses were annualized.

Results: The database included 20,311 oral DMT users. After applying the study criteria, the PSM yielded 1602:534 switch patients for the DMF–FTY matched cohort. DMF–FTY patients were well-matched on all covariates: age (mean = 44 for both), gender (28% vs. 26% male, respectively), MS severity measure (0.99 vs. 1.08), and baseline ARR (0.40 vs. 0.44). PSM yielded 833:279 switch patients for the DMF–TERI match. DMF–TERI patients were well-matched on all covariates: age (mean = 50), gender (24% vs. 25% male), MS severity measure (0.86 vs. 0.99), and baseline ARR (0.23 vs. 0.30). The standardized differences confirmed balance across all covariates for matched cohorts. The matched DMF–FTY cohorts had comparable post-index ARR (Rate Ratio [RR] = 1.07 [95% Cl: 0.861, 1.328]) and risk of relapse (Hazard Ratio [HR] = 0.996 [95% CI: 0.803, 1.236]). Post-index ARR was significantly lower with DMF in comparison to TERI (RR = 0.667 [0.486, 0.914]). The risk of relapse was also significantly lower when switching to DMF than TERI (HR = 0.679 [0.503, 0.917]).

Conclusion: In this analysis, the effectiveness profiles for those oral DMT users specifically switching from platform therapies are consistent with findings from previous research conducted among all oral DMT users, regardless of prior therapy.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system with an estimated worldwide prevalence of 2.3 million (Garg and Smith, 2015). Relapsing remitting MS (RRMS) is characterized by clinical attacks, or relapses, caused by

inflammatory lesions, followed by periods of remission (Kutzelnigg and Lassmann, 2014). Treatment of MS consists of several components, the most important of which are disease-modifying therapies (DMTs) that reduce disease activity and delay disease progression (Rio et al., 2011). Effective treatment of MS with DMTs reduces the occurrence of relapses, slows neurological disability and prevents the decline of patients' quality of life. Interferon β-1b, interferon β-1a, and glatiramer acetate were the earliest DMTs (i.e., 1st-generation) approved for the treatment of MS. The anti-inflammatory properties of these injectable treatments reduced the rate of relapse and decreased disease activity observed with magnetic resonance imaging (MRI) (Torkildsen et al., 2016). Since then, treatment options have broadened to include the orally administered DMTs fingolimod (FTY), teriflunomide (TERI), and dimethyl fumarate (DMF). Phase III clinical trials have shown that, in comparison to placebo, each of these oral DMTs reduced relapse rates, disease activity and disability progression (Calabresi et al., 2014; Confavreux et al., 2014; Fox et al., 2012; Gold et al., 2012; Kappos et al., 2010; O'Connor et al., 2011).

While these clinical trials demonstrated the efficacy of oral DMT treatment, there have not been head-to-head comparisons of oral medications. However, retrospective studies have been used to assess the real-world comparative effectiveness of FTY, DMF, and TERI. Observational studies of DMF and FTY treatment over a 24-month period found comparable effectiveness (Hersh et al., 2016, 2017; Vollmer et al., 2017). A retrospective claims analysis of injectable and oral DMTs found DMF to have comparable effectiveness to FTY and greater effectiveness than TERI (Boster et al., 2017). Several indirect treatment comparison studies of oral DMTs also produced similar results (Fox et al., 2017; Hamidi et al., 2018; Huisman et al., 2017; Hutchinson et al., 2014). Overall, these outcomes suggest that DMF is comparable to FTY and more efficacious than TERI in reducing relapses.

MS patients often switch therapies for a variety of reasons. With the availability of multiple DMTs for the treatment of MS, treatment decisions for MS clinicians are becoming increasingly complex. Previous studies have demonstrated that switching from an injectable platform therapy to FTY reduced relapse rates, disease activity, and was associated with greater patient satisfaction (Bergvall et al., 2014; Fox et al., 2014; He et al., 2015; Meng et al., 2015). Such comparative studies can assist clinicians when considering the most appropriate treatment for their patients. Although there have been comparative effectiveness studies of oral DMTs among the overall MS population, there is limited comparative evidence in patients switching from injectable platform DMTs to oral DMTs. While obtaining such evidence from randomized clinical trials is difficult, observational studies allow direct comparison of medications from real world practices. The objective of the current study was to compare the ARR and time to relapse in MS patients who have switched from an injectable platform therapy to DMF, FTY, and TERI.

2. Patients and methods

2.1. Data source

The study was a retrospective claims analysis using data from the Truven MarketScan® Commercial database for the period of June 1, 2012 to March 31, 2016. Encompassing >60 million employees, spouses, and dependents located in all 10 U.S. census regions, the administrative database contains healthcare claims data from approximately 100 different insurance companies, plans, and third-party administrators. It is a large, national (US), de-identified database that reflects real-world treatment patterns and costs by tracking clinical care received by patients as they travel through the healthcare system (i.e.,

includes inpatient, outpatient, and pharmacy claims). Data is HIPAA compliant by application of synthetic identifiers to patient- and provider-level data, thereby protecting the identities of patient and data contributors.

2.2. Patient selection

The study population consisted of adult MS patients (18–65 years) who switched from an injectable platform DMT (interferons or glatiramer acetate) to a single oral DMT (DMF, FTY, or TERI) between June 1, 2013 and March 31, 2015. The date of first oral DMT fill to occur during this period was defined as the index date with the associated DMT defined as the index DMT. Patients were required to have continuous enrollment in the database for 12 months prior to the index date (pre-index period) and for ≥3 months after the index date (post-index period). In accordance with previous studies, patients were required to have ≥1 MS diagnoses (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9] code 340) during the pre-index period (Johnson et al., 2015; Lavery et al., 2016; Livingston et al., 2016; Smith et al., 2015). Furthermore, patients were required to have discontinued an injectable platform DMT and have no evidence of oral DMT (DMF, FTY, or TERI) or infusion DMT (natalizumab, novantrone, or alemtuzumab) use during the pre-index period. Patients were also required have an index DMT treatment duration of ≥90 days. Qualified patients were stratified into three cohorts based on their index DMT. In addition, patients in the DMF cohort were propensity-score matched (PSM) to those in the FTY and TERI cohorts as described in Section 2.4.

2.3. Study measures

Patient demographics at the index date included age, gender, geographic region, and type of health insurance plan. Clinical characteristics assessed during the pre-index period included Charlson comorbidity score (CCI) and the number of MS-related and other, non-MS-related, hospitalizations. In addition, a claims-based MS severity measure based on the number of pre-defined MS-related comorbidities (e.g., visual symptoms, fatigue, etc.; Appendix A, Table 1) present during the pre-index period was determined using an algorithm derived from a multivariate regression model that measured the robustness of these comorbidities in predicting disease severity (Nicholas et al., 2017). Using a previously published algorithm, MS relapses were defined as a hospitalization with a primary diagnosis of MS or an outpatient visit with a diagnosis of MS and one of the following treatments within 30 days of the visit: intravenous steroid treatment, adrenocorticotropic hormone (ACTH) use, ≥500 mg/day prednisone use, or total plasma exchange (Chastek et al., 2010; Nicholas et al., 2018; Ollendorf et al., 2002). Pre-index period relapses were identified by ICD-9 code 340 and used to determine the pre-index ARR as a clinical characteristic. ICD-9 code 340 and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) code G35 were used to identify post-index period MS relapses and determine post-index relapse rate and time to relapse. Post-index ARR was evaluated among the unmatched and PSM patient populations. Time to relapse was assessed among the PSM cohorts and compared pairwise using DMF patients as the reference cohort. Time to relapse was defined as the number of days from the index date to the date of the earliest relapse that occurred during the post-index period. Patients were followed until they dropped out of the database or at the end of the study period (March 31, 2016), whichever occurred earlier.
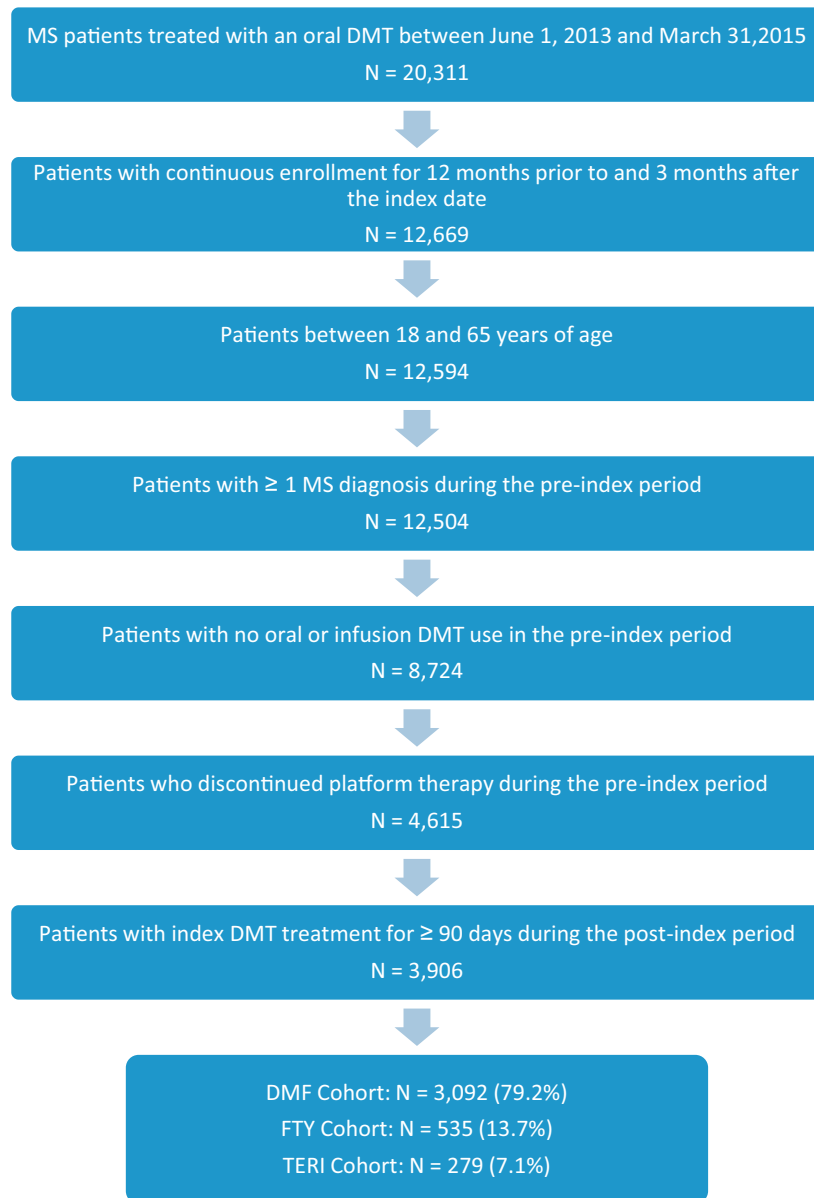
Fig. 1. Patient attrition for the study population. DMF, dimethyl fumarate; DMT, disease modifying therapy; FTY, fingolimod; TERI, teriflunomide.

2.4. Propensity score matching

DMF patients were propensity-score matched 3:1 to FTY and to TERI based on age, gender, and region at the index date; MS severity measure; and ARR, CCI score, and number of hospitalizations over the pre-index period using a logistic regression model. After fitting the propensity score model, trimming was performed to exclude non-overlapping regions of the propensity score by dropping patients in the comparative cohort who had estimated propensity scores less than the smallest value or greater than the largest value of the propensity score among the reference DMF cohort patients. An $8 < -1$ greedy algorithm was used to match patients. If multiple qualified patients were available for matching at any step, random selection was employed. Pre- and post-matching balance in the baseline covariates was assessed by cohort using Wilcoxon rank-sum and chi-square tests to compare unmatched and matched baseline covariates. Density plots and Love plots were generated for the visual inspection of the propensity scores from the PSM process. Matching balance was assessed based on standardized mean differences with a threshold of ≤ 0.20 and expected *p*-values of ≥ 0.05 for corresponding statistical tests.

2.5. Statistical analysis

Categorical variables were summarized by frequencies and proportions and continuous variables were summarized by means, standard deviations (SD), and medians. Wilcoxon rank-sum and chi-square tests were used to compare study measures among the unmatched and matched populations by cohort as appropriate. ARR was estimated

Table 1a

Demographic and clinical characteristics of the unmatched and propensity-score matched dimethyl fumarate (DMF) and fingolimod (FTY) cohorts. *p*-values were estimated using Wilcoxon rank-sum and chi-square tests. ARR, annualized relapse rate; CCI, Charlson comorbidity index; CDHP, Consumer Directed Health Plan; EPO, Exclusive Provider Organization; HDHP, High Deductible Health Plan; HMO, Health Maintenance Organization; POS, Point of Service; PPO, Preferred Provider Organization.

| | Unmatched patients | | | 3:1 Matched patients | | |
| | DMF | FTY | *p*-Value | DMF | FTY | *p*-Value |
	N = 3092	N = 535		N = 1602	N = 534	
Age, mean	47.00	44.20	< 0.0001	44.27	44.24	0.9441
Age groups, *n* (%)						
≤ 34 years	378 (12.2)	91 (17.0)		295 (18.4)	90 (16.9)	
35–44 years	830 (26.8)	176 (32.9)		504 (31.5)	176 (33.0)	
45–54 years	1049 (33.9)	172 (32.2)		510 (31.8)	172 (32.2)	
55–65 years	835 (27.0)	96 (17.9)		293 (18.3)	96 (17.9)	
Gender, %			0.3675			0.3989
Male	23.8%	25.6%		27.5%	25.7%	
Female	76.2%	74.4%		72.5%	74.3%	
MS severity measure, mean	1.07	1.08	0.8116	0.99	1.08	0.1279
MS severity measure groups, *n* (%)						
0	1301 (42.1)	221 (41.3)		702 (43.8)	221 (41.4)	
1–2	1403 (45.4)	250 (46.7)		727 (45.4)	249 (46.6)	
3–4	334 (10.8)	51 (9.5)		153 (9.6)	51 (9.6)	
> 4	54 (1.7)	13 (2.4)		20 (1.2)	13 (2.4)	
CCI score, mean	0.11	0.10	0.2961	0.08	0.10	0.1828
CCI score groups, *n* (%)						
0	2781 (89.9)	490 (91.6)		1491 (93.1)	489 (91.6)	
1 – 2	307 (9.9)	45 (8.4)		110 (6.9)	45 (8.4)	
3 – 4	4 (0.1)	–		1 (0.1)	–	
Pre-index ARR, mean	0.33	0.44	0.0015	0.40	0.44	0.3411
Pre-index hospitalizations, mean						
MS-related	0.03	0.04	0.2091	0.03	0.04	0.3514
Other	0.09	0.07	0.4152	0.06	0.07	0.3380
Region, %			0.4137			0.7461
Northeast	22.3%	23.7%		21.3%	23.8%	
North Central	23.7%	25.6%		26.0%	25.5%	
South	32.7%	32.7%		33.7%	32.8%	
West	18.9%	15.5%		17.0%	15.5%	
Unknown	2.4%	2.4%		2.1%	2.4%	
Health plan type, %						
Comprehensive	85 (2.7)	13 (2.4)		44 (2.7)	13 (2.4)	
EPO	33 (1.1)	3 (0.6)		22 (1.4)	3 (0.6)	
HMO	344 (11.1)	64 (12.0)		178 (11.1)	64 (12.0)	
PPO	1958 (63.3)	307 (57.4)		1004 (62.7)	306 (57.3)	
POS	221 (7.1)	30 (5.6)		112 (7.0)	30 (5.6)	
POS with capitation	18 (0.6)	8 (1.5)		7 (0.4)	8 (1.5)	
CDHP	264 (8.5)	58 (10.8)		149 (9.3)	58 (10.9)	
HDHP	130 (4.2)	41 (7.7)		62 (3.9)	41 (7.7)	
Missing	39 (1.3)	11 (2.1)		24 (1.5)	11 (2.1)	

based on the total number of relapses and total follow up time. The treatment effect for ARR and 95% CI was estimated from a GEE Poisson model with an offset for index-therapy exposure and a robust error variance to account for over-dispersion (Stokes et al., 2012). Parameter estimates from the model were exponentiated to convert to relapse rates and rate ratios. The proportion of subjects who relapsed during the post-index period was analyzed using Kaplan–Meier methods. The time to the first relapse to occur during the post-index period was evaluated using a Cox marginal proportional hazard model taking the clustered nature of the data into consideration. Proportional hazard assumptions were assessed by visual inspection of the Kaplan–Meier survival functions and a Kolmogorov-type Supreman test (Lin et al., 1993). Covariates considered for both analysis models included age, gender, region, clinical characteristics measurements (CCI score, MS severity measure), pre-index hospitalization, and pre-index ARR. Groups were well balanced after propensity score matching and therefore covariates were not included in the final models.

2.6. Subgroup and sensitivity analysis

The primary analysis was carried out on the basis of intent-to-treat. Although some DMTs may need ≥ 6 months for full effect, a treatment duration of ≥ 90 days was used in order to capture those relapses that may occur during the interim in a real-world setting. An on-treatment subgroup analysis was performed on the primary endpoints of post-index relapse rate and time to relapse to evaluate the impact of treatment duration. On-treatment was defined as the time period during which a patient received continuous index DMT treatment, starting at the index date and ending at treatment discontinuation, the end of the study (March 31, 2016), or at the end of enrollment, whichever was earliest. Treatment discontinuation was defined as a gap of ≥ 60 days from the end of the previous days of supply of the index DMT to the next prescription claim date with no other DMTs present during the gap.

To investigate the robustness of the findings to unmeasured

Table 1b

Demographic and clinical characteristics of the unmatched and propensity-score matched dimethyl fumarate (DMF) and teriflunomide (TERI) cohorts. *p*-values were estimated using Wilcoxon rank-sum and chi-square tests. ARR, annualized relapse rate; CCI, Charlson comorbidity index; CDHP, Consumer Directed Health Plan; EPO, Exclusive Provider Organization; HDHP, High Deductible Health Plan; HMO, Health Maintenance Organization; POS, Point of Service; PPO, Preferred Provider Organization.

	Unmatched patients			3:1 Matched patients		
	DMF N = 3092	TERI N = 279	*p*-Value	DMF N = 833	TERI N = 279	p-Value
Age, mean	47.00	49.96	< 0.0001	49.97	49.96	0.9838
Age groups, n (%)						
≤34 years	378 (12.2)	18 (6.5)		52 (6.2)	18 (6.5)	
35–44 years	830 (26.8)	53 (19.0)		178 (21.4)	53 (19.0)	
45–54 years	1049 (33.9)	109 (39.1)		307 (36.9)	109 (39.1)	
55–65 years	835 (27.0)	99 (35.5)		296 (35.5)	99 (35.5)	
Gender, %			0.6295			0.6854
Male	23.8%	25.1%		23.9%	25.1%	
Female	76.2%	74.9%		76.1%	74.9%	
MS severity measure, mean	1.07	0.99	0.2768	0.86	0.99	0.1051
MS severity measure groups, *n* (%)						
0	1301 (42.1)	124 (44.4)		404 (48.5)	124 (44.4)	
1–2	1403 (45.4)	128 (45.9)		360 (43.2)	128 (45.9)	
3–4	334 (10.8)	20 (7.2)		63 (7.6)	20 (7.2)	
>4	54 (1.7)	7 (2.5)		6 (0.7)	7 (2.5)	
CCI score, mean	0.11	0.17	0.0127	0.13	0.17	0.1411
CCI score groups, n (%)						
0	2781 (89.9)	234 (83.9)		736 (88.4)	234 (83.9)	
1–2	307 (9.9)	45 (16.1)		96 (11.5)	45 (16.1)	
3–4	4 (0.1)	–		1 (0.1)	–	
Pre-index ARR, mean	0.33	0.30	0.4887	0.23	0.30	0.1061
Pre-index hospitalizations, mean						
MS-related	0.03	0.03	0.7391	0.02	0.03	0.4995
Other	0.09	0.07	0.5036	0.05	0.07	0.1746
Region, %			0.6083			0.6494
Northeast	22.3%	22.9%		21.9%	22.9%	
North Central	23.7%	22.9%		27.6%	22.9%	
South	32.7%	35.1%		33.4%	35.1%	
West	18.9%	17.9%		16.3%	17.9%	
Unknown	2.4%	1.1%		0.8%	1.1%	
Health plan type, %						
Comprehensive	85 (2.7)	15 (5.4)		24 (2.9)	15 (5.4)	
EPO	33 (1.1)	1 (0.4)		9 (1.1)	1 (0.4)	
HMO	344 (11.1)	36 (12.9)		85 (10.2)	36 (12.9)	
PPO	1958 (63.3)	170 (60.9)		526 (63.1)	170 (60.9)	
POS	221 (7.1)	22 (7.9)		56 (6.7)	22 (7.9)	
POS with capitation	18 (0.6)	–		6 (0.7)	–	
CDHP	264 (8.5)	27 (9.7)		74 (8.9)	27 (9.7)	
HDHP	130 (4.2)	5 (1.8)		39 (4.7)	5 (1.8)	
Missing	39 (1.3)	3 (1.1)		14 (1.7)	3 (1.1)	

Table 2

Post-index annualized relapse rates (ARR) among the unmatched and propensity-score matched dimethyl fumarate (DMF) and fingolimod (FTY) cohorts. *p*-values and relapse rates estimated by a generalized estimating equation Poisson model without further covariate adjustment. Relapse rate ratios (RR) and confidence intervals (CI) were determined using FTY patients as the reference cohort.

| Cohort	*N*	ARR	RR (95% Cl)	*p*-Value
Unmatched				
DMF	3092	0.216	1.020 (0.869, 1.198)	0.809
FTY	535	0.212		
Matched				
DMF	1602	0.229	1.070 (0.861, 1.328)	0.543
FTY	534	0.214		

Table 3

Post-index annualized relapse rates (ARR) among the unmatched and propensity-score matched dimethyl fumarate (DMF) and teriflunomide (TERI) cohorts. *p*-values and relapse rates estimated by a generalized estimating equation Poisson model without further covariate adjustment. Relapse rate ratios (RR) and confidence intervals (CI) were determined using TERI patients as the reference cohort.

Cohort	*N*	ARR	RR (95% Cl)	*p*-Value
Unmatched				
DMF	3092	0.216	0.800 (0.664, 0.964)	0.019
TERI	279	0.270		
Matched				
DMF	833	0.176	0.667 (0.486, 0.914)	0.012
TERI	279	0.264		

confounders, a sensitivity analysis as described by Lin et al., (1998) was conducted. Under a conditional independence assumption between the unmeasured and the measured confounders, an approximate algebraic

relationship exists between the true effect estimate and the estimate when ignoring the unmeasured confounder. This was used to derive the adjusted effect estimates under various combinations of sensitivity parameters.
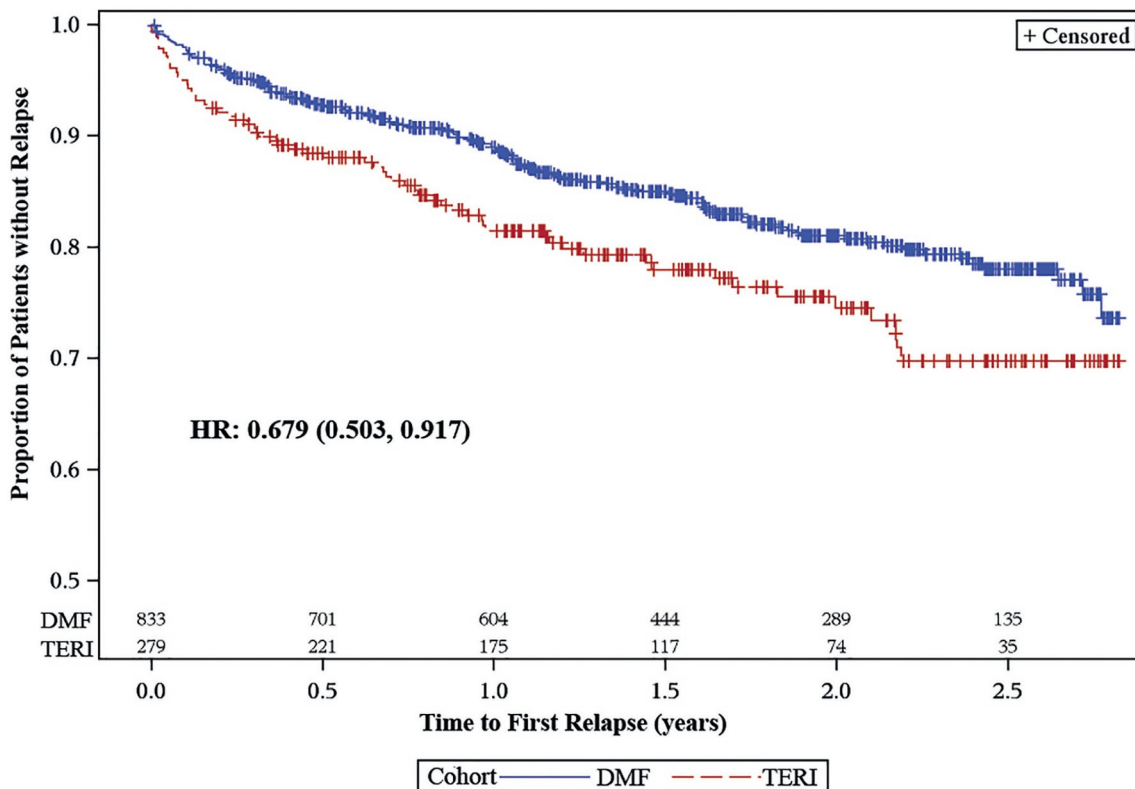
A. DMF vs. FTY
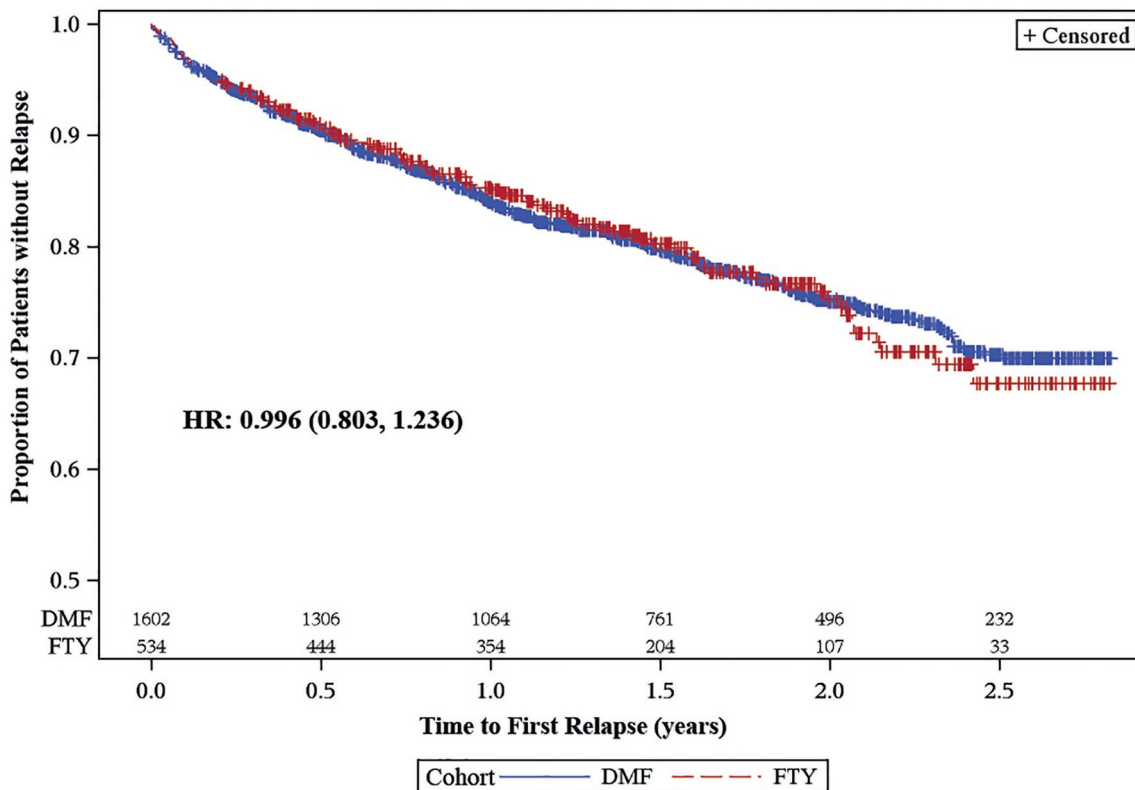
B. DMF vs. TERI

Fig. 2. Kaplan–Meier analysis of time to relapse among the propensity-score matched cohorts. DMF, dimethyl fumarate; FTY, fingolimod; HR, hazard ratio; TERI, teriflunomide.

Table 4
Post-index annualized relapse rate (ARR) on-treatment sub-group analysis of the propensity-score matched dimethyl fumarate (DMF)-fingolimod (FTY) and DMF-teriflunomide (TERI) cohorts. *p*-values and relapse rates were estimated from Poisson regression model using robust standard errors. Relapse rate ratios (RR) and confidence intervals (CI) were determined using FTY or TERI patients as the reference where appropriate.

Cohort	N	ARR	RR (95% CI)	*p*-Value
DMF	1602	0.180	1.076 (0.871, 1.329)	0.4957
FTY	534	0.167		
DMF	833	0.137	0.574 (0.437, 0.753)	< 0.0001
TERI	279	0.238		

Table 5
Post-index time to relapse on-treatment sub-group analysis of the propensity-score matched dimethyl fumarate (DMF)-fingolimod (FTY) and DMF-teriflunomide (TERI) cohorts. *p*-values, hazard ratios (HR) and confidence intervals (CI) were estimated from marginal Cox proportional hazards regression model taking into account the clustered nature of the matched design. FTY or TERI patients were used as the reference where appropriate.

Cohort	N	# with Relapse	HR (95% CI)	*p*-Value
DMF vs. FTY	2136	330	0.867 (0.679, 1.107)	0.2522
DMF vs. TERI	1112	156	0.543 (0.391, 0.754)	0.0003

3. Results

3.1. Patient attrition

Between June 1, 2013 and March 31, 2015, a total of 20,311 MS patients with oral DMT treatment were identified from the database. After applying the study inclusion and exclusion criteria, the overall study population included 3906 patients of whom 3092 (79.2%) switched from an injectable platform therapy to DMF, 535 (13.7%) switched to FTY, and 279 (7.1%) switched to TERI (Fig. 1). After PSM, there were 833:279 switch patients for the DMF–TERI matched cohorts and 1602:534 switch patients for the DMF–FTY matched cohorts.

3.2. Demographics and clinical characteristics

Prior to matching, patients who switched to FTY were younger (44.2 vs. 47.0 years, *p* < 0.0001) and had a higher pre-index ARR (0.44 vs. 0.33 relapses/year, *p* = 0.002) compared to DMF users (Table 1a). In contrast, patients that switched to TERI were older (50.0 vs. 47.0 years, *p* < 0.0001) and had higher pre-index CCI scores (0.17 vs. 0.11, *p* = 0.013) than DMF users (Table 1b) prior to matching. After PSM, DMF–FTY patients were well-matched on all covariates: age (44.3 vs. 44.2, *p* = 0.944), male gender (28% vs. 26%, *p* = 0.399), MS severity measure (0.99 vs. 1.08, *p* = 0.128), CCI score (0.08 vs. 0.10, *p* = 0.183) and pre-index ARR (0.40 vs. 0.44, *p* = 0.341) (Table 1a). Similarly, the DMF-TERI patients were also well-matched on all covariates: age (50 years for both, *p* = 0.984), male gender (24% vs. 25%, *p* = 0.685), MS severity measure (0.86 vs. 0.99, *p* = 0.105), CCI score (0.13 vs. 0.17, *p* = 0.141) and baseline ARR (0.23 vs. 0.30, *p* = 0.106) (Table 1b). The improvement in covariate balance was also evident in the standardized differences. After matching, standardized differences were below 10% in absolute value for all covariates for the DMF versus FTY comparison

as well as for the DMF versus TERI comparison, with the exception of pre-index ARR (10.7%), MS severity measure (10.8%) and region (11.1%) (Supplemental Figs. 1 and 2).

3.3. Relapse rates

There was no difference in the post-index period ARRs between the unmatched or matched DMF and FTY cohorts (Table 2). In contrast, comparison of the unmatched DMF–TERI cohorts revealed that patients treated with DMF had a 20% lower post-index period ARR compared to TERI (RR = 0.800 [0.664, 0.964], *p* = 0.019, Table 3). A similar trend was observed among the matched cohorts where the ARR over the post-index period was 33% lower among patients that switched to DMF than those who switched to TERI (RR = 0.667 [0.486, 0.914], *p* = 0.012).

3.4. Time to relapse

Kaplan–Meier curves of the time to relapse are shown in Fig. 2. Among the 454 patients within the matched DMF–FTY cohorts who relapsed during the post-index period, there was no evidence of a difference in the risk of relapse between patients who switched to DMF versus FTY (Hazard Ratio [HR] = 0.996 [95% Cl: 0.803, 1.236]). 202 of the 1112 patients within the matched DMF–TERI cohorts relapsed during the post-index period. Risk of relapse was 32% lower among patients who switched to DMF compared to those who switched to TERI (HR = 0.679 [0.503, 0.917]).

3.5. Subgroup and sensitivity analyses

There was no difference in the ARR and risk of relapse between the DMF and FTY patients regardless if they were on-treatment or not (Tables 4 and 5). Subgroup analyses of the post-index ARR among the DMF–TERI cohorts were largely consistent with the results of the primary analysis where ARRs were significantly lower among DMF patients who were on-treatment (Table 4, Appendix Tables 2 and 3). Analysis of time to relapse among DMF–TERI cohort patients who were on-treatment resulted in a significantly lower risk of relapse with DMF versus TERI (HR = 0.543 [0.391, 0.754], *p* = 0.0003).

Post hoc sensitivity analyses to assess the robustness of study findings found that the ARR endpoint was fairly robust but demonstrated that the significant effect of DMF versus TERI on ARR could be changed with a confounder with a rate ratio of 2.5 and an imbalance between the prevalence in the groups of 20% (prevalence of 30% in the DMF group and 10% in the TERI group). Time to relapse results were less robust and suggested that the significant effect of DMF versus TERI could be changed with a confounder with a hazard rate as low as 1.5 and 20% imbalance or a hazard rate of 2.5 and a 10% imbalance in the prevalence.

4. Discussion

In the event of suboptimal response or treatment failure, switching between injectable platform therapies has been shown to result in lower ARR (Gajofatto et al., 2009; Rio et al., 2011). However, oral DMTs have demonstrated greater efficacy compared to platform therapies and although switching from platform therapies to FTY was found to lower ARR and increase time to relapse (Bergvall et al., 2014; Braune et al., 2016; He et al., 2015; Meng et al., 2015), there is limited information

on the effectiveness of switching to other oral DMTs. In this analysis, the effectiveness profiles of oral DMT users specifically switching from platform therapies are consistent with findings from previous research conducted among all oral DMT users, regardless of prior therapy (Boster et al., 2017), with comparable effectiveness between DMF and FTY and greater effectiveness with DMF in comparison to TERI.

In addition, recent studies from Hersh et al. (2016, 2017) and Vollmer et al. (2017) reported comparable effectiveness with both DMF and FTY treatment and a retrospective, international medical record review revealed similar relapse rates with both DMF and FTY treatment as well (Sloane et al., 2017). Indirect comparisons of the efficacy of DMF and FTY using clinical trial patient data also found that both DMTs had comparable ARR and disability progression (Fox et al., 2017; Hamidi et al., 2018; Huisman et al., 2017; Hutchinson et al., 2014). In accordance with the results of these studies, there was no evidence of a difference between the post-index ARR of propensity-score matched DMF and FTY patients in the current analysis, suggesting comparable effectiveness.

The current analysis also found significantly lower post-index ARR and risk of relapse among DMF patients compared to their matched TERI counterparts, suggesting greater effectiveness. Correspondingly, studies utilizing the international MSBase Neuro-Immunology registry, German NeuroTransData (NTD) MS registry and Swiss Federation for Common Tasks of Health Insurances Registry each revealed that TERI treatment was associated with higher ARR and a greater risk of relapse in comparison to DMF (Braune et al., 2017; Kalincik et al., 2017; Lorscheider et al., 2017; Spelman et al., 2016). Indirect comparisons also determined that DMF treatment resulted in significantly lower ARR in comparison to TERI treatment (Hamidi et al., 2018; Hutchinson et al., 2014).

Unlike randomization, propensity score matching can only adjust for balance in measured covariates and consequently, results may be impacted by unmeasured covariates. In addition, the study was limited by a lower number of controls for the treated patients making a 1:1 matching algorithm infeasible. As a result, a 3:1 matching algorithm was used to maximize the number DMF subjects included in the analysis. After matching, a review of the standardized differences between DMF subjects and the FTY and TERI controls indicated that the groups were balanced.

There are also limitations inherent to the use of claims data. The MarketScan database consists of claims submitted by healthcare providers to insurance companies for reimbursement on behalf of individuals employed by various companies. Such claims are subject to possible coding errors, coding for the purpose of rule-out rather than actual disease, and under-coding, without the possibility of verifying reported diagnoses. Studies using administrative claims typically employ algorithms to select an appropriate study population. However, the clinical data necessary to validate these algorithms is often unavailable. While published algorithms were used to identify both MS patients and relapses in this study, only the relapse algorithm was validated with a positive predicative value (Chastek et al., 2010). However, mild relapses would likely not be captured as these may not be treated with steroids. The paucity of clinical detail in claims data also restricts the use of disability and safety measures. While the frequency of MRI procedures can be determined, the results of such testing are unavailable for analysis. As a result, disease severity is often difficult to evaluate.

In addition, the databases are based on a sample that is not random and may fail to generalize well to other populations. The database utilized in the study is comprised of claims from private insurance companies. As a result, the study population is less likely to include patients who are older or on disability. For medications captured in the outpatient pharmacy, presence of a claim for a filled prescription does not indicate that the medication was consumed or that it was taken as prescribed. Finally, patients may switch drugs for many reasons (e.g., poor response, tolerability issues, convenience of administration, etc.) which are not captured by claims data. Although PSM was used to reduce confounders of treatment use, this method, unlike randomization, cannot remove confounding of unknown and unmeasured confounders.

A key strength of this analysis is that it provides a better understanding of the comparative effectiveness of oral DMTs in real world clinical practice for patients switching from injectable platform therapies. While MS disability measures were not available in this database, platform DMTs have been typically prescribed early in the treatment pathway and the study design infers a population that has switched to an oral DMT earlier in their disease course. Since MS patients often require switch in therapy to properly manage this chronic disease, this comparative effectiveness research addresses an important gap in this subset of MS patients.

Another key strength of this study is the generalizability of the study findings given the large, national dataset. For instance, the study includes older MS patients who are often under-represented in MS clinical trials. In addition, patient histories prior to treatment are well observed in the data, as well as the patient's post-treatment experience. Finally, since prescribing patterns in the real-world are broader and less limiting, this study provides a more comprehensive picture of the MS patients that require a switch from platform therapies, the breakdown by which patients are being switched to oral DMTs from platform therapies in routine practice, and the differences in clinical and patient characteristics of these separate cohorts. In regard to real-world prescribing practices, we would like to note that rituximab is not approved for the treatment of MS by the FDA in the US and may be used for other conditions, and it was not included as part of the exclusion criteria in this study. Upon review of the study cohorts, there were only 2 patients with a claim for rituximab in the pre-index period.

5. Conclusions

The effectiveness of DMF was greater than that of TERI and comparable to that of FTY as measured by ARR and the risk of relapse in MS patients switching from platform therapy. These findings are largely consistent with past comparative effectiveness studies and provide additional real-world data to help support decision-making in routine clinical practice in order to achieve optimal therapeutic benefit for patients.

Appendix A

Appendix Table A1

ICD-9 codes for symptom categories and Healthcare Common Procedure Coding System (HCPCS) codes suggesting mobility problems or severe disability that were used for the MS severity measure.

ICD-9 codes

Visual symptoms

377.00, 377.10, 377.15, 377.3x, 377.41, 377.49, 368.10, 368.11, 368.12, 368.13, 368.15, 368.40, 368.41, 368.42, 368.43, 368.44, 368.8

Brainstem symptoms (e.g., facial neuralgia, vertigo, dizziness)

350.1x, 350.2, 368.2x, 386.00, 386.10, 386.11, 386.2, 386.30, 780.4x, 787.2x

Difficulty walking/gait problems

719.7, 781.2x

Cerebellar symptoms (e.g., movement disorders, ataxia, tremor)

333.1, 333.99, 438.84, 781.0x, 781.3x

Pyramidal symptoms (e.g., weakness, paralysis, spasticity/muscle symptoms)

342.xx, 344.0x, 344.1, 344.2, 344.3x, 344.4x, 344.5, 344.9, 728.2, 728.85, 729.2, 781.4x

Sensory symptoms

438.6, 782.0x

Speech symptoms

784.5

Bladder/bowel symptoms/sexual dysfunction

302.7, 564.0, 596.54, 788.2x, 788.3x, 788.63

Cerebral symptoms/cognitive impairment

331.83, 331.9, 780.97, 784.3

General symptoms (e.g., fatigue)

780.71, 780.79

HCPCS codes

Specialty beds

E0250, E0251, E0255, E0256, E0260, E0261, E0265, E0266, E0270, E0271, E0272, E0273, E0274, E0275, E0276, E0277, E0280, E0290, E0291, E0292, E0293, E0294, E0295, E0296, E0297, E0300, E0301, E0302, E0303, E0304, E0305, E0310, E0315, E0316

Wheelchair

E0950, E0951, E0952, E0955, E0956, E0957, E0958, E0959, E0960, E0961, E0966, E0967, E0968, E0969, E0970, E0971, E0973, E0974, E0978, E0980, E0981, E0982, E0983, E0984, E0985, E0986, E0988, E0990, E0992, E0994, E0995, E1002, E1003, E1004, E1005, E1006, E1007, E1008, E1009, E1010, E1011, E1014, E1015, E1016, E1017, E1018, E1020, E1028, E1029, E1030, E1031, E1035, E1036, E1037, E1038, E1039, E1050, E1060, E1070, E1083, E1084, E1085, E1086, E1087, E1088, E1089, E1090, E1092, E1093, E1100, E1110, E1130, E1140, E1150, E1160, E1161, E1170, E1171, E1172, E1180, E1190, E1195, E1200, E1220, E1221, E1222, E1223, E1224, E1225, E1226, E1227, E1228, E1229, E1230, E1231, E1232

Walker

E0130, E0135, E0140, E0141, E0143, E0144, E0147, E0148, E0149, E0153, E0154, E0155, E0156, E0157, E0158, E0159

Cane

E0100, E0105

Appendix Table A2

Representative results of sensitivity analysis on the dimethyl fumarate (DMF) vs. teriflunomide (TERI) comparison for the annualized relapse rate (ARR) endpoint. This analysis assumes the unmeasured confounder is binary. RR, rate ratio; CI, confidence interval.

RR of unmeasured covariate	Difference in prevalence of the unmeasured confound between DMF and TERI group		Adjusted	
	Proportion DMF	Proportion TERI	RR	95% CI
2.5	0.3	0.1	1.24	0.99, 1.54
4.5	0.5	0.2	0.97	0.78, 1.20
5.0	0.5	0.2	0.97	0.76, 1.17
5.0	0.7	0.5	1.24	0.99, 1.53

Appendix Table A3

Representative results of sensitivity analysis on the dimethyl fumarate (DMF) vs. teriflunomide (TERI) comparison for the time to relapse endpoint. This analysis assumes the unmeasured confounder is binary. HR, hazard ratio; CI, confidence interval.

HR of unmeasured covariate	Difference in prevalence of the unmeasured confound between DMF and TERI group		Adjusted	
	Proportion DMF	Proportion TERI	HR	95% CI
1.5	0.1	0.3	1.34	0.997, 1.81
2.5	0.4	0.5	1.35	0.998, 1.82
4.5	0.2	0.5	0.91	0.675, 1.23

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2018.09.038.

References

Bergvall, N., Makin, C., Lahoz, R., Agashivala, N., Pradhan, A., Capkun, G., Petrilla, A.A., Karkare, S.U., McGuiness, C.B., Korn, J.R., 2014. Relapse rates in patients with multiple sclerosis switching from interferon to FTY or glatiramer acetate: a US claims database study. PLoS One 9 (2), e88472 Feb 6.

Boster, A., Nicholas, J., Wu, N., Yeh, W.S., Fay, M., Edwards, M., Huang, M.Y., Lee, A., 2017. Comparative effectiveness research of disease-modifying therapies for the management of multiple sclerosis: analysis of a large health insurance claims database. Neurol. Ther. 6 (1), 91–102 Jun.

Braune, S., Lang, M., Bergmann, A., NeuroTransData Study Group, 2016. Efficacy of FTY is superior to injectable disease modifying therapies in second-line therapy of relapsing remitting multiple sclerosis. J. Neurol. 263 (2), 327–333 Feb.

Braune, S., Grimm, S., van Hövell, P., Freudensprung, U., Hyde, R., Bergmann, A., NeuroTransData Study Group, 2017. Delayed-release dimethyl fumarate demonstrated no evidence of difference in clinical outcomes vs fingolimod in patients with RRMS: a propensity-matched comparative effectiveness analysis of the German NeuroTransData registry. In: Proceedings of the Poster session presented at: 7th Joint ECTRIMS-ACTRIMS Meeting. Paris, France. Oct 25–28.

Calabresi, P.A., Radue, E.W., Goodin, D., Jeffery, D., Rammohan, K.W., Reder, A.T., Vollmer, T., Agius, M.A., Kappos, L., Stites, T., Li, B., Cappiello, L., von Rosenstiel, P., Lublin, F.D., 2014. Safety and efficacy of FTY in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 13 (6), 545–556 Jun.

Chastek, B.J., Oleen-Burkey, M., Lopez-Bresnahan, M.V., 2010. Medical chart validation of an algorithm for identifying multiple sclerosis relapse in healthcare claims. J. Med. Econ. 13 (4), 618–625.

Confavreux, C., O'Connor, P., Comi, G., Freedman, M.S., Miller, A.E., Olsson, T.P., Wolinsky, J.S., Bagulho, T., Delhay, J.L., Dukovic, D., Truffinet, P., Kappos, L., TOWER Trial Group, 2014. Oral TERI for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 13 (3), 247–256 Mar.

Fox, E., Edwards, K., Burch, G., Wynn, D.R., LaGanke, C., Crayton, H., Hunter, S.F., Huffman, C., Kim, E., Pestreich, L., McCague, K., Barbato, L., EPOC study investigators, 2014. Outcomes of switching directly to oral FTY from injectable therapies: results of the randomized, open-label, multicenter, Evaluate Patient OutComes (EPOC) study in relapsing multiple sclerosis. Mult. Scler. Relat. Disord. 3 (5), 607–619 Sep.

Fox, R.J., Miller, D.H., Phillips, J.T., Hutchinson, M., Havrdova, E., Kita, M., Yang, M., Raghupathi, K., Novas, M., Sweetser, M.T., Viglietta, V., Dawson, K.T., CONFIRM Study Investigators, 2012. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N. Engl. J. Med. 367 (12), 1087–1097 Sep 20.

Fox, R.J., Chan, A., Zhang, A., Xiao, J., Levison, D., Lewin, J.B., Edwards, M.R., Marantz, J.L., 2017. Comparative effectiveness using a matching-adjusted indirect comparison between delayed-release DMF and FTY for the treatment of multiple sclerosis. Curr. Med. Res. Opin. 33 (2), 175–183 Feb.

Gajofatto, A., Bacchetti, P., Grimes, B., High, A., Waubant, E., 2009. Switching first-line disease-modifying therapy after failure: impact on the course of relapsing-remitting multiple sclerosis. Mult. Scler. 15 (1), 50–58 Jan.

Garg, N., Smith, T.W., 2015. An update on immunopathogenesis, diagnosis, and treatment of multiple sclerosis. Brain Behav. 5 (9), e00362 Sep.

Gold, R., Kappos, L., Arnold, D.L., Bar-Or, A., Giovannoni, G., Selmaj, K., Tornatore, C., Sweetser, M.T., Yang, M., Sheikh, S.I., Dawson, K.T., DEFINE Study Investigators, 2012. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N. Engl. J. Med. 367 (12), 1098–1107 Sep 20.

Hamidi, V., Couto, E., Ringerike, T., Klemp, M., 2018. A multiple treatment comparison of eleven disease-modifying drugs used for multiple sclerosis. J. Clin. Med. Res. 10 (2), 88–105 Feb.

He, A., Spelman, T., Jokubaitis, V., Havrdova, E., Horakova, D., Trojano, M., Lugaresi, A., Izquierdo, G., Grammond, P., Duquette, P., Girard, M., Pucci, E., Iuliano, G., Alroughani, R., Oreja-Guevara, C., Fernandez-Bolaños, R., Grand'Maison, F., Sola, P., Spitaleri, D., Granella, F., Terzi, M., Lechner-Scott, J., Van Pesch, V., Hupperts, R., Sánchez-Menoyo, J.L., Hodgkinson, S., Rozsa, C., Verheul, F., Butzkueven, H., Kalincik, T., MSBase Study Group, 2015. Comparison of switch to FTY or interferon beta/glatiramer acetate in active multiple sclerosis. JAMA Neurol. 72 (4), 405–413 Apr.

Hersh, C.M., Love, T.E., Cohn, S., Hara-Cleaver, C., Bermel, R.A., Fox, R.J., Cohen, J.A., Ontaneda, D., 2016. Comparative efficacy and discontinuation of DMF and FTY in clinical practice at 12-month follow-up. Mult. Scler. Relat. Disord. 10, 44–52 Nov.

Hersh, C.M., Love, T.E., Bandyopadhyay, A., Cohn, S., Hara-Cleaver, C., Bermel, R.A., Fox, R.J., Cohen, J.A., Ontaneda, D., 2017. Comparative efficacy and discontinuation of DMF and FTY in clinical practice at 24-month follow-up. Mult. Scler. J. Exp. Transl. Clin. 3 (3), 2055217317715485 Aug 24.

Hutchinson, M., Fox, R.J., Havrdova, E., Kurukulasuriya, N.C., Sarda, S.P., Agarwal, S., Siddiqui, M.K., Taneja, A., Deniz, B., 2014. Efficacy and safety of BG-12 (DMF) and other disease-modifying therapies for the treatment of relapsing-remitting multiple sclerosis: a systematic review and mixed treatment comparison. Curr. Med. Res. Opin. 30 (4), 613–627 Apr.

Huisman, E., Papadimitropoulou, K., Jarrett, J., Bending, M., Firth, Z., Allen, F., Adlard, N., 2017. Systematic literature review and network meta-analysis in highly active relapsing-remitting multiple sclerosis and rapidly evolving severe multiple sclerosis. BMJ Open 7 (3), e013430 Mar 10.

Kalincik, T., Spelman, T., Jokubaitis, V., Horakova, D., Havrdova, E., Izquierdo, G., Prat, A., Girard, M., Duquette, P., Lugaresi, A., Grammond, P., Alroughani, R., Lechner-Scott, J., Prevost, J., Terzi, M., Grand'Maison, F., Boz, C., Trojano, M., Van Wijmeersch, B., Pucci, E., Granella, F., Turkoglu, R., Sola, P., Ferraro, D., McCombe, P., Solaro, C., Van Pesch, V., Ozakbas, S., Slee, M., Spitaleri, D., Sanchez-Menoyo, J.L., Ampapa, R., Hodgkinson, S., Karabudak, R., Vucic, S., Butzkueven, H., MSBase Study Group, 2017. Effectiveness of fingolimod, dimethyl fumarate and teriflunomide in relapsing-remitting multiple sclerosis: a comparative longitudinal study. In: Proceedings of the Poster session presented at: 7th Joint ECTRIMS-ACTRIMS Meeting. Paris, France. Oct 25–28.

Johnson, B.H., Bonafede, M.M., Watson, C., 2015. Platform therapy compared with natalizumab for multiple sclerosis: relapse rates and time to relapse among propensity score-matched US patients. CNS Drugs 29 (6), 503–510 Jun.

Kappos, L., Radue, E.W., O'Connor, P., Polman, C., Hohlfeld, R., Calabresi, P., Selmaj, K., Agoropoulou, C., Leyk, M., Zhang-Auberson, L., Burtin, P., FREEDOMS Study Group, 2010. A placebo-controlled trial of oral FTY in relapsing multiple sclerosis. N. Engl. J. Med. 362 (5), 387–401 Feb 4.

Kutzelnigg, A., Lassmann, H., 2014. Pathology of multiple sclerosis and related inflammatory demyelinating diseases. Handb. Clin. Neurol. 122, 15–58.

Lavery, A.M., Banwell, B.L., Liu, G., Waldman, A.T., 2016. Hospital admission rates for pediatric multiple sclerosis in the United States using the Pediatric Health Information System (PHIS). Mult. Scler. Relat. Disord. 9, 5–10 Sep.

Lin, D.Y., Psaty, B.M., Kronmal, R.A., 1998. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. Biometrics 54 (3), 948–963 Sep.

Lin, D.Y., Wei, L.J., Ying, Z., 1993. Checking the Cox model with cumulative sums of martingale-based residuals. Biometrika 80 (30), 557–572 Sep.

Livingston, T., Fay, M., Iyer, R., Wells, W., Pill, M.W., 2016. Quantifying differences in health care consumption for the management of multiple sclerosis within privately and publicly insured health care programs. J. Manag. Care Spec. Pharm. 22 (12), 1385–1391 Dec.

Lorscheider, J., Benkert, P., Lienert, C., Hänni, P., Schmid, J., Derfuss, T., Kuhle, J., Kappos, L., Yaldizli, Ö., 2017. Fingolimod vs. dimethyl fumarate in relapsing-remitting multiple sclerosis: propensity score matched comparison in a large observational data set. In: Proceedings of the Poster session presented at: 7th Joint ECTRIMS-ACTRIMS Meeting. Paris, France. Oct 25–28.

Meng, X., Chin, P.S., Hashmonay, R., Zahur Islam, M., Cutter, G., 2015. Effect of switching from intramuscular interferon β-1a to oral FTY on time to relapse in patients with relapsing-remitting multiple sclerosis enrolled in a 1-year extension of TRANSFORMS. Contemp. Clin. Trials 41, 69–74 Mar.

Nicholas, J., Ontaneda, D., Carraro, M., Wu, N., Jhaveri, M., Yang, K., Jones, D., Livingston, T., 2017. Development of an algorithm to identify multiple sclerosis (MS) disease severity based on healthcare costs in a US administrative claims database. In: Proceedings of the Poster session presented at: 69th Annual American Academy of Neurology Meeting. Boston, MA. Apr 22–28.

Nicholas, J., Boster, A., Wu, N., Yeh, W.S., Fay, M., Kendter, J., Huang, M.Y., Lee, A., 2018. Comparison of disease-modifying therapies for the management of multiple sclerosis: analysis of healthcare resource utilization and relapse rates from US insurance claims data. Pharmacoecon. Open 2 (1), 31–41 Mar.

O'Connor, P., Wolinsky, J.S., Confavreux, C., Comi, G., Kappos, L., Olsson, T.P., Benzerdjeb, H., Truffinet, P., Wang, L., Miller, A., Freedman, M.S., TEMSO Trial Group, 2011. Randomized trial of oral TERI for relapsing multiple sclerosis. N. Engl. J. Med. 365 (14), 1293–1303 Oct 6.

Ollendorf, D.A., Jilinskaia, E., Oleen-Burkey, M., 2002. Clinical and economic impact of glatiramer acetate versus beta interferon therapy among patients with multiple sclerosis in a managed care population. J. Manag. Care Pharm. 8 (6), 469–476 Nov-Dec.

Rio, J., Comabella, M., Montalban, X., 2011. Multiple sclerosis: current treatment algorithms. Curr. Opin. Neurol. 24, 230–237.

Sloane, J., Phillips, J.T., Calkwood, J., Van der Walt, A., Min, J., Okwuokenye, M., Taylor, C., 2017. Delayed-release dimethyl fumarate demonstrated no difference in clinical outcomes versus fingolimod in patients with relapsing-remitting multiple sclerosis: results from the real-world EFFECT study. In: Proceedings of the Poster session presented at: 7th Joint ECTRIMS-ACTRIMS Meeting. Paris, France. Oct 25–28.

Smith, M.Y., Sabidó-Espin, M., Trochanov, A., Samuelson, M., Guedes, S., Corvino, F.A., Richy, F.F., 2015. Postmarketing safety profile of subcutaneous interferon beta-1a

given 3 times weekly: a retrospective administrative claims analysis. J. Manag. Care Spec. Pharm. 21 (8), 650–660 Aug.

Spelman, T., Kalincik, T., Trojano, M., Grand'Maison, F., Izquierdo, G., Havrdova, E., Horakova, D., Lugaresi, A., Duquette, P., Grammond, P., Hupperts, R., Lechner-Scott, J., Granella, F., Petersen, T., Terzi, M., Pucci, E., Sola, P., Van Pesch, V., Iuliano, G., Oreja-Guevara, C., Boz, C., Bergamaschi, R., Slee, M., Butzkueven, H., 2016. Comparative analysis of MS outcomes in dimethyl fumarate-treated patients relative to propensity matched fingolimod, interferon, glatiramer acetate, or teriflunomide. In: Proceedings of the Poster session presented at: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis. London, United Kingdom. Sept 14–17.

Stokes, M.E., Davis, C.S., Koch, G.G., 2012. Categorical Data Analysis Using the SAS System, Third ed. SAS Institute Inc, Cary, NC.

Torkildsen, Ø., Myhr, K.M., Bø, L., 2016. Disease-modifying treatments for multiple sclerosis – a review of approved medications. Eur. J. Neurol. 23 (Suppl 1), 18–27 Jan.

Vollmer, B., Nair, K.V., Sillau, S.H., Corboy, J., Vollmer, T., Alvarez, E., 2017. Comparison of FTY and DMF in the treatment of multiple sclerosis: two-year experience. Mult. Scler. J. Exp. Transl. Clin. 3 (3), 2055217317725102 Aug 17.