Original Article

Efficacy and tolerability of oral versus injectable disease-modifying therapies for multiple sclerosis in clinical practice

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Abstract

Background: The advent of oral disease-modifying therapies fundamentally changed the treatment of multiple sclerosis. Nevertheless, impressions of their relative efficacy and tolerability are primarily founded on expert opinion.

Objective: The purpose of this study was to determine whether oral disease-modifying therapies were better tolerated and/or more effective for controlling multiple sclerosis compared to injectable therapies in clinical practice.

Methods: Single-center, retrospective cohort study. 480 patients initiated oral (fingolimod, teriflunomide, or dimethyl fumarate) or injectable therapy between March 2013–March 2015 and follow-up data was collected for 5–31 months. Outcomes included on-drug multiple sclerosis activity and drug discontinuation. Cox proportional hazards models were used to control for baseline differences and sensitivity analyses using propensity-weighted matching were performed.

Results: A higher proportion of teriflunomide-treated patients experienced multiple sclerosis activity compared to those treated with injectable therapies ($p = 0.0053$) in the adjusted model. Breakthrough multiple sclerosis was equally prevalent among fingolimod and dimethyl fumarate-treated compared to injectable therapy-treated patients. Of patients initiating a disease-modifying therapy, 32–46% discontinued or switched treatments during the study. After controlling for baseline differences, discontinuation rates were comparable across treatment groups.

Conclusions: In this cohort, oral and injectable disease-modifying therapies were equally well tolerated, but teriflunomide appeared less effective for controlling multiple sclerosis activity than injectable therapies. Further study is needed.

Introduction

Disease modifying therapies (DMTs) became available to treat multiple sclerosis (MS) in the mid-1990s, but for years the only options were injectable (INJ) beta-interferons or glatiramer acetate. More recently, three oral DMTs have become available to treat relapsing MS: fingolimod (FGD, released in the USA in 2010), teriflunomide (TER, released in 2012), and dimethyl fumarate (DMF, released in 2013). Stable treatment with DMT improves the clinical course of MS and reduces long-term disability,[1–3] and patients who adhere to DMT incur lower medical costs and are less likely to require hospitalization.[4] Nevertheless, the expansion of treatment options for MS has been paralleled by uncertainties regarding the best prescribing practice for these medications.

Many MS clinicians now strive for a benchmark of ''no evidence of disease activity'' (NEDA) and recommend switching DMT whenever MS activity occurs during treatment,[5–7] which has led to increased switching between medications.[8] In most

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cases, the decision to change medications is based on clinical acumen, as little data is available to guide recommendations. This is especially true of the oral agents. These have never been directly compared to one another in clinical trials, and little empirical evidence exists to differentiate them.

Several groups have utilized Phase 3 clinical trial data to indirectly compare the oral DMTs with varying results. When individual level data for FGD were re-analyzed using the same methodologies used in trials for TER and DMF, patients taking FGD were more likely to achieve NEDA than patients taking TER or DMF.[9] Others found DMF to be superior to INJ therapy and TER, equivalent to FGD, and inferior to natalizumab for reducing the annualized relapse rate by performing a systematic review and data synthesis of published randomized controlled trials.[10] These data were derived from Phase 3 trials, which have stringent inclusion and exclusion criteria and do not represent the full spectrum of MS. The relative efficacy of oral and INJ DMTs may differ in clinical practice.

Observational data gleaned from clinical registries represent a broader spectrum of MS patients. Researchers using the NeuroTransData network, a cohort of patients who switched DMTs due to INJ therapy failure, concluded that patients switching to FGD were more likely to become relapse and progression free than those who initiated a second INJ therapy.[11] Data obtained from MS Base, a multi-national registry, suggested that both treatment-naïve patients starting FGD and patients switching to FGD because of breakthrough MS had improved clinical outcomes and were less likely to discontinue treatment than comparable patients prescribed INJ therapy.[12,13] Insurance claims analyses also found that MS patients were less likely to discontinue FGD compared to INJ therapy.[14,15] These studies did not assess the performance of the other oral agents.

Comparative data to guide DMT selection is lacking. It is therefore important to simultaneously study all three oral DMTs in conjunction with first-line INJ treatments. We evaluated a cohort of 480 patients who initiated treatment with an oral or INJ DMT in order to compare drug effectiveness and persistence with therapy in a real world clinical setting.

Methods

Design
This was a retrospective, observational cohort study at an MS center comprised of five board-certified

neurologists subspecializing in MS. All patients who initiated therapy with oral (DMF, TER, FGD) or INJ DMT between March 2013−March 2015 were included. All patients had a relapsing form of MS (relapsing−remitting or secondary progressive with relapses) and could be either treatment-naïve or switching between DMTs. For this study, interferon β (IFN-β) medications and glatiramer acetate were pooled as INJ medications. No significant differences in efficacy were observed when subcutaneous IFN-β1a and glatiramer acetate were compared in a randomized trial,[16] and pooling INJ medications is a common technique for large observational studies.[8,11] Data were collected for an additional six months to ensure a minimum follow-up duration. This study was approved by the Human Research Protection Office at Washington University in St Louis, USA.

Chart reviews
Medical records were reviewed by a board-certified MS neurologist (EEL). Demographic and clinical data were extracted. Demographic data included age, sex, and race. Clinical data included time since diagnosis, number of previous DMTs, expanded disability status scale (EDSS), relapses within the last 12 months (0 vs ≥1) and prescribing neurologist. EDSSs were estimated based on physical examination at the time of DMT initiation, then categorized as mild (EDSS 0−3), moderate (EDSS 3.5−5.5), or severe disability (EDSS ≥ 6). All patients taking TER were prescribed 14 mg daily. Outcomes included on-treatment MS activity, treatment discontinuation, and reasons for discontinuation. MS activity was defined as a clinical relapse (based on the treating physician's documented impression and/or decision to treat with corticosteroids) or new radiological evidence of disease activity (new T2-weighted or gadolinium-enhancing lesion on follow-up magnetic resonance imaging (MRI) compared to baseline) after treatment for three months or longer. Clinical relapse or MRI activity within the first two months of starting a medication was not considered as MS activity, since most DMTs require several months to reach efficacy. Persistence was defined as the length of time a patient remained on a DMT. When assessing drug discontinuation, relapses, MRI progression, and slow disability accumulation were judged to be MS activity-related reasons for discontinuing. Skin/hair side effects included rash, flushing, injection site reactions, and hair loss. Cardiovascular side effects included chest pain and bradycardia. Neurologic side effects included paresthesia, neuropathy, and headache. ''Other'' side effects included flu-like symptoms

and generalized complaints. Laboratory abnormalities included lymphopenia and transaminitis.

Statistical analysis

Demographic and clinical characteristics were summarized using descriptive statistics. One-way analysis of variance (ANOVA) was used to compare age, disease duration, and follow-up duration. Pearson chi-square tests were used to compare sex, race, number of relapses in the past 12 months, EDSS category, and number of prior medications. Only the first observation for each patient was used for baseline comparisons. A Cox proportional hazards model accounting for recurrent events was used to evaluate the time to discontinuation and MS disease activity to control for differences in baseline covariates.

Sensitivity analysis

Propensity score matching was used as a sensitivity analysis to evaluate the robustness of the adjusted model results in a sample which is more homogeneous at baseline. Patients initiating FGD, TER, or DMF were matched to patients initiating INJ therapy using propensity scores. These were estimated using three separate logistic regression models with FGD/INJ, TER/INJ and DMF/INJ as the dependent variable and age, sex, race, prescribing physician, disease duration, categorized EDSS, presence of relapses in last 12 months, and number of prior DMTs as potential confounders. The matching process used the nearest neighbor method within specified caliper widths (caliper $= 0.20 \times$ standard deviation (logit of the propensity score)) without replacement.[17] Patients who initiated multiple types of medication during the study used only the first observed treatment for matching.

After matching, the balance of covariates was evaluated. The absolute standardized differences of the covariates for the unmatched and matched cohorts were compared between the INJ and matched FGD, TER, and DMF samples. Standardized differences greater than 0.1 have been shown to indicate some covariate imbalance between matched groups.[18] After propensity matching, time to event outcomes between matched groups were tested using Cox proportional hazards model with robust standard errors to account for the within-pair homogeneity in matched sample models.[19]

Results

We identified 480 unique patients who initiated treatment with 579 oral or INJ DMTs during the predefined study period. Eighty-seven patients discontinued and restarted another DMT at least once during the study. There were significant differences between the treatment groups at baseline, reflecting clinical prescribing practice. Patients who initiated INJ therapy had more recent MS diagnoses, milder disability, increased relapse frequency, and fewer prior DMT exposures when compared to patients initiating oral DMTs (Table 1). Patients taking TER tended to be older than those in the other treatment groups. Differences in prescriber practice were also observed. Within the INJ group, interferons ($n = 72$, 48%) and glatiramer acetate ($n = 78$, 52%) were equally prescribed. Notably, a third or more (33–46%) of patients taking any given DMT opted to discontinue or switch treatments during the 2.5 years of study observation (Table 1).

MS activity

Younger age (hazard ratio (HR) 0.70, 95% confidence interval (CI) 0.58–0.85 per 10-year age increase), severe disability (HR 2.52, 95% CI 1.41–4.50 versus mild disability), and relapses within the last year (HR 1.96, 95% CI 1.33–2.89) were statistically significant predictors of on-treatment MS activity (Figure 1(a)). After controlling for all covariates, treatment with TER (HR 2.63, 95% CI 1.33–5.19 compared to INJ) was associated with an independent risk of MS activity. There were no differences in breakthrough MS activity for patients treated with DMF and FGD compared to those treated with INJ therapy. Given the heterogeneity of the patient population, we then excluded treatment-naïve patients and evaluated only patients switching between DMTs. TER treatment remained a significant risk factor for on-treatment MS activity (HR 2.49, 95% CI 1.14–5.4) (Supplementary Material, Figure 1).

Discontinuation

Since oral therapies are considered more convenient than INJ therapies, we hypothesized that discontinuation rates would be lower for oral compared to INJ DMTs. After controlling for baseline differences, younger age (HR 0.80, 95% CI 0.70–0.92 per 10-year age increase) was associated with an increased risk of discontinuing medication. Patients previously treated with one DMT were less likely to discontinue medication than those who were DMT-naïve (HR 0.57, 95% CI 0.35–0.92). However, there were no differences in discontinuation rate between oral and INJ treatments. (Figure 1(b)).

Sensitivity analysis with propensity matched patients

To validate our findings, we employed propensity matching as an alternative statistical tool. After matching, most variables were balanced although

Table 1. Uncorrected cohort characteristics.

	INJ (n = 150)	DMF (n = 254)	TER (n = 83)	FGD (n = 92)	p-Value
Females, n (%)	118 (78.7)	183 (72.0)	68 (81.9)	67 (72.8)	0.113
Age, mean (SD)	41.6 (13.1)	44.7 (12.2)	49.4 (10.4)	39.8 (9.3)	<0.001
Caucasian, n (%)	120 (80.0)	216 (85.0)	70 (84.3)	71 (77.2)	0.020
MS duration, years, mean (SD)	5.4 (8.2)	10.6 (9.4)	12.2 (9.8)	7.1 (6.9)	<0.001
Follow-up duration, months, mean (SD)	18.2 (7.7)	20.4 (6.5)	20.3 (7.2)	17.2 (7.2)	0.015
Number of previous meds, n (%)					
0	77 (51.3)	33 (13.0)	4 (4.8)	11 (12.0)	<0.001
1	33 (22.0)	75 (30.0)	40 (48.2)	34 (37.0)	
2	25 (16.7)	73 (28.7)	23 (27.7)	25 (27.2)	
3+	15 (10.0)	73 (28.7)	16 (19.3)	22 (23.9)	
Physician, n (%)					
1	27 (18.0)	24 (9.5)	6 (7.2)	14 (15.2)	<0.001
2	38 (25.3)	58 (22.8)	17 (20.5)	7 (7.6)	
3	19 (12.7)	33 (13.0)	38 (45.8)	33 (26.8)	
4	19 (12.7)	23 (9.1)	3 (3.6)	7 (7.6)	
5	47 (31.3)	116 (45.7)	19 (22.9)	31 (33.7)	
Disability					
Mild (EDSS 0-3)	110 (73.3)	143 (56.3)	43 (51.8)	52 (56.5)	<0.001
Moderate (EDSS 3.5-5.5)	29 (19.3)	46 (18.11)	19 (22.9)	30 (32.6)	
Severe (EDSS ≥ 6.0)	11 (7.3)	65 (25.6)	21 (25.3)	10 (10.9)	
Relapses in last 12 months, n (%)	92 (61.3)	112 (44.1)	27 (32.5)	46 (50.0)	<0.001
On-drug MS activity, n (%)	28 (18.7)	54 (21.3)	25 (30.1)	24 (26.1)	0.144
Discontinued DMT, n (%)	58 (38.7)	90 (35.4)	38 (45.8)	30 (32.6)	0.167
Switched to a different DMT	46 (79.3)	74 (82.2)	31 (81.6)	24 (80.0)	
Permanently discontinued	12 (20.7)	15 (16.7)	6 (15.8)	6 (20.0)	
Death	0	1 (1.1)	1 (2.6)	0	

DMF: dimethyl fumarate; DMT: disease-modifying therapy; EDSS: estimated disability status score; FGD: fingolimod; INJ: injectable; MS: multiple sclerosis; SD: standard deviation; TER: teriflunomide.
A total of 480 unique patients contributed 579 observations to this cohort. Repeated observations were not considered for the statistics reported. One-way analysis of variance (ANOVA) was used to compare age, disease duration, and follow-up duration between groups. Pearson chi-square tests were used to compare sex, race, MS activity, discontinued DMT, and number of prior medications between groups. One patient in the DMF group and one in the TER group died due to comorbid medical conditions; deaths were unrelated to MS treatment.

some residual imbalance remained (Table 2, Supplementary Material, Figure 2). Remaining imbalances varied depending on the drug being studied (Supplementary Material, Figure 2), and may be attributable to small numbers within some of these subcategories. Unmatched patients differed from matched patients primarily in number of prior DMTs, disease severity/duration, and age, with unmatched patients being older and having longer disease durations with more DMT exposure compared to matched patients (Supplementary Material, Figure 2).

We compared breakthrough MS activity between propensity-matched patients taking oral and INJ DMTs using Cox proportional hazard analyses and controlling for time in study. As with the prior models, there were no differences in MS activity between DMF-treated (HR 0.985, 95% CI 0.47−2.08) or FGD-treated (HR 1.79, 95% CI 0.75−4.26) when compared to INJ-treated patients (Figure 2(a) and (c)). However, patients taking TER were more likely to experience breakthrough MS activity than matched INJ patients (HR 3.9, 95% CI 1.43−10.64) (Figure 2(b)). Once again, patients taking oral and INJ DMTs were equally likely to discontinue or switch treatments (Figure 2(d)−(f)).

Reasons for stopping DMT
The most common reasons for stopping any given DMT were side effects (30−52%) and breakthrough
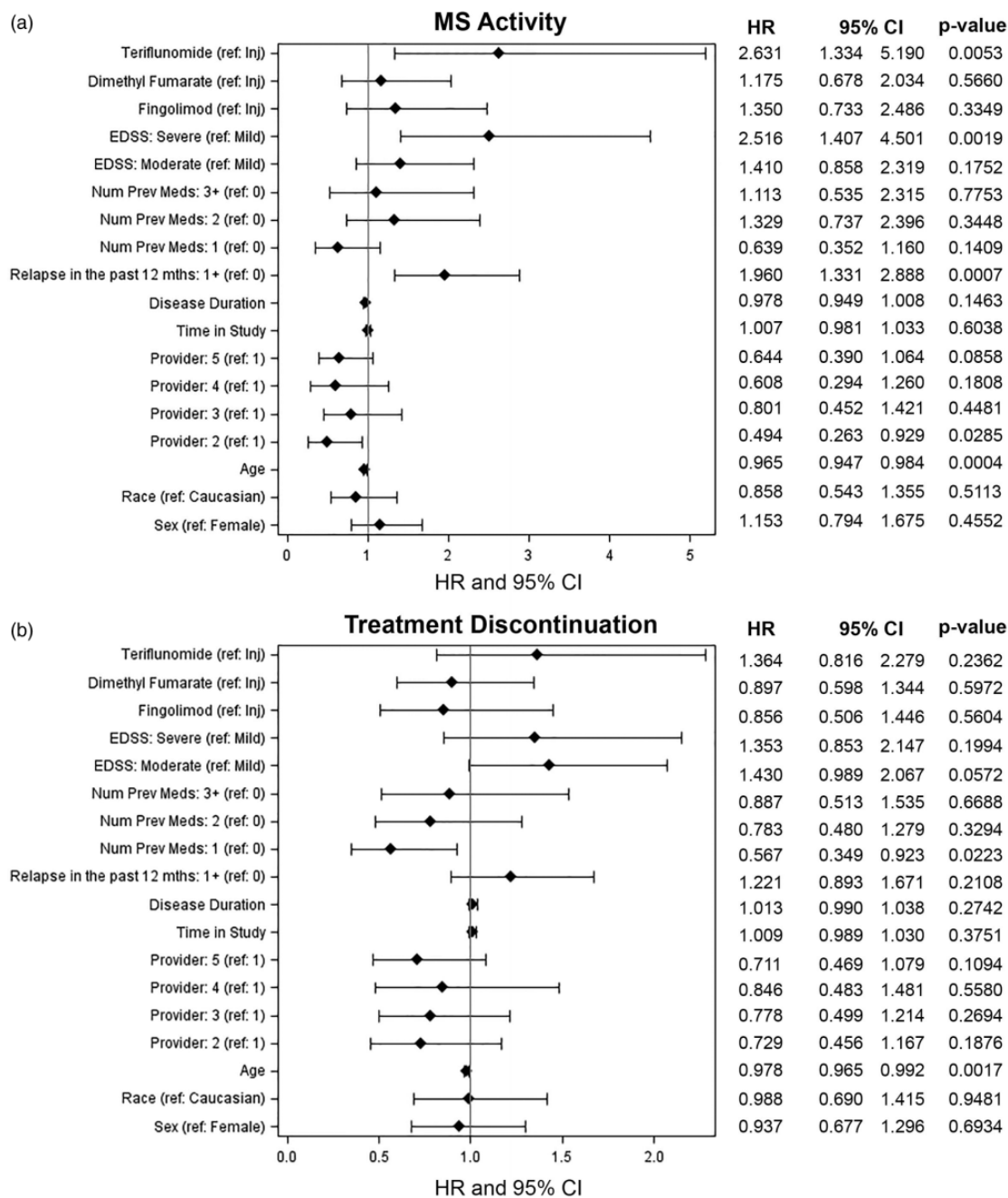
Figure 1. Forest plots of hazard ratios (HRs) for multiple sclerosis (MS) activity (a) and treatment discontinuation (b) after controlling for measured baseline variables.
CI: confidence interval; EDSS: estimated disability status score.

MS activity (17–42%) (Figure 3). As expected, the type of side effects leading to drug discontinuation differed between medications. Injection reactions and flu-like symptoms commonly led to discontinuation among patients taking INJ therapies, and GI side effects were notable among patients taking both DMF and TER (Figure 3). Side effects were less common among patients taking FGD, but included headache and macular edema.

Discussion

Randomized, placebo-controlled trials have demonstrated that both oral and INJ DMTs are effective in relapsing MS, yet many questions remain about their

Table 2. Patient characteristics for propensity-matched groups for each oral DMT.

	Matched for dimethyl fumarate			Matched for teriflunomide			Matched for fingolimod		
	INJ (n = 82)	DMF (n = 82)	SD	INJ (n = 48)	TER (n = 48)	SD	INJ (n = 57)	FGD (n = 57)	SD
Females, n (%)	61 (74.4)	60 (73.2)	0.028	40 (83.3)	41 (85.4)	0.057	45 (79.0)	46 (80.7)	0.044
Age, mean (SD)	43.7 (12.6)	44.1 (12.8)	0.032	47.9 (11.8)	49.4 (11.0)	0.128	41.1 (11.7)	39.4 (9.5)	0.160
Caucasian, n (%)	68 (82.9)	70 (85.4)	0.067	42 (87.5)	41 (85.4)	0.061	42 (73.7)	44 (77.2)	0.081
MS duration, years, mean (SD)	7.8 (8.8)	8.3 (9.3)	0.053	11.0 (9.5)	11.5 (11.0)	0.053	6.8 (6.6)	7.7 (7.7)	0.118
Number of previous meds, n (%)									
0	26 (31.7)	30 (36.6)	0.103	3 (6.3)	4 (8.3)	0.080	10 (17.5)	11 (19.3)	0.045
1	31 (37.8)	25 (30.5)	0.154	21 (43.8)	19 (39.6)	0.085	22 (38.6)	17 (29.8)	0.186
2	17 (20.7)	15 (18.3)	0.062	14 (29.2)	15 (31.3)	0.045	16 (28.1)	16 (28.1)	0.000
3+	8 (9.8)	12 (14.6)	0.149	10 (20.8)	10 (20.8)	0.000	9 (15.8)	13 (22.8)	0.179
Physician, n (%)									
1	7 (8.5)	10 (12.2)	0.12	6 (12.5)	6 (12.5)	0.000	9 (15.8)	8 (14.0)	0.049
2	21 (25.6)	19 (23.2)	0.057	16 (33.3)	14 (29.2)	0.089	6 (10.5)	7 (12.3)	0.055
3	9 (11.0)	8 (9.8)	0.04	6 (12.5)	6 (12.5)	0.000	13 (22.8)	11 (19.3)	0.086
4	9 (11.0)	7 (8.5)	0.082	3 (6.3)	3 (6.3)	0.000	4 (7.0)	4 (7.0)	0.000
5	36 (43.9)	38 (46.3)	0.049	17 (35.4)	19 (39.6)	0.086	25 (43.9)	27 (47.4)	0.070
Disability									
Mild (EDSS 0–3)	57 (69.5)	58 (70.7)	0.027	29 (60.4)	26 (54.2)	0.127	40 (70.2)	40 (70.2)	0.000
Moderate (EDSS 3.5–5.5)	16 (19.5)	12 (14.6)	0.130	11 (22.9)	14 (29.2)	0.143	13 (22.8)	11 (19.3)	0.086
Severe (EDSS ≥ 6.0)	9 (11.0)	12 (14.6)	0.110	8 (16.7)	8 (16.7)	0.000	4 (7.0)	6 (10.5)	0.124
Relapses in last 12 months, n (%)	43 (52.4)	43(52.4)	0.000	17 (35.4)	19 (39.6)	0.087	26 (45.6)	27 (47.4)	0.035

DMF: dimethyl fumarate; EDSS: estimated disability status score;INJ: injectable; MS: multiple sclerosis; SD: standard difference; TER: teriflunomide; FGD: fingolimod. SD ≤ 0.1 indicates covariate balance between matched groups.
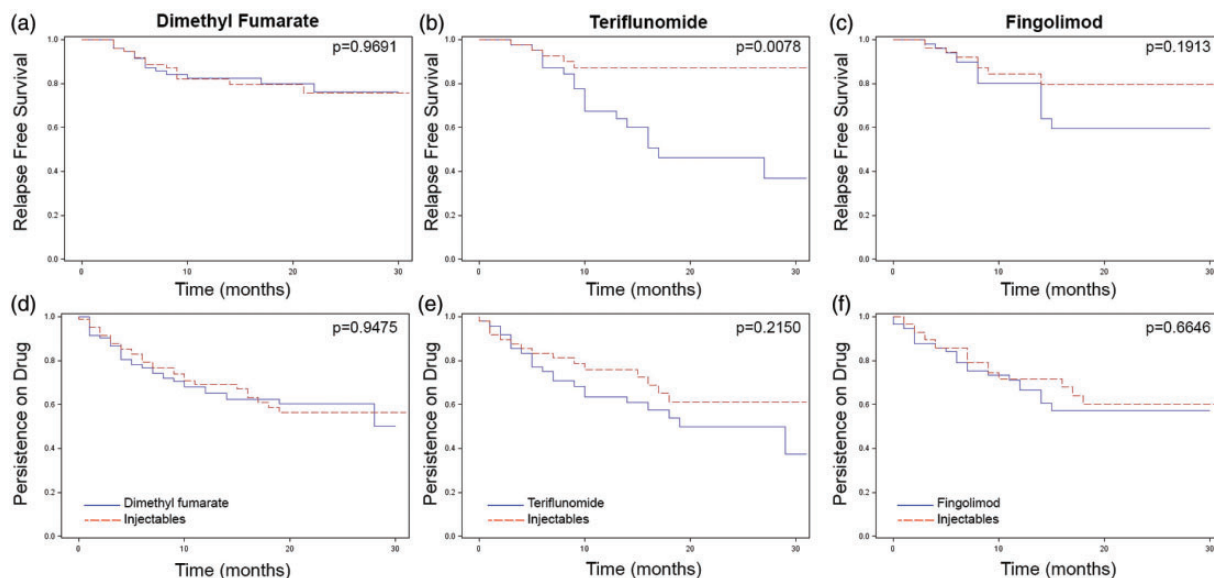
Figure 2. Multiple sclerosis (MS) activity and persistence on therapy for oral (blue lines) versus injectable (red lines) disease modifying therapies (DMTs). After propensity weighted matching, 82 dimethyl fumarate (DMF)-treated patients, 48 teriflunomide (TER)-treated patients and 57 fingolimod (FGD)-treated patients were matched with comparable injectable (INJ)-treated patients. On-drug MS activity (a)–(c) and persistence on drug (d)–(f) were evaluated. Kaplan-Meier time to event analyses are shown.
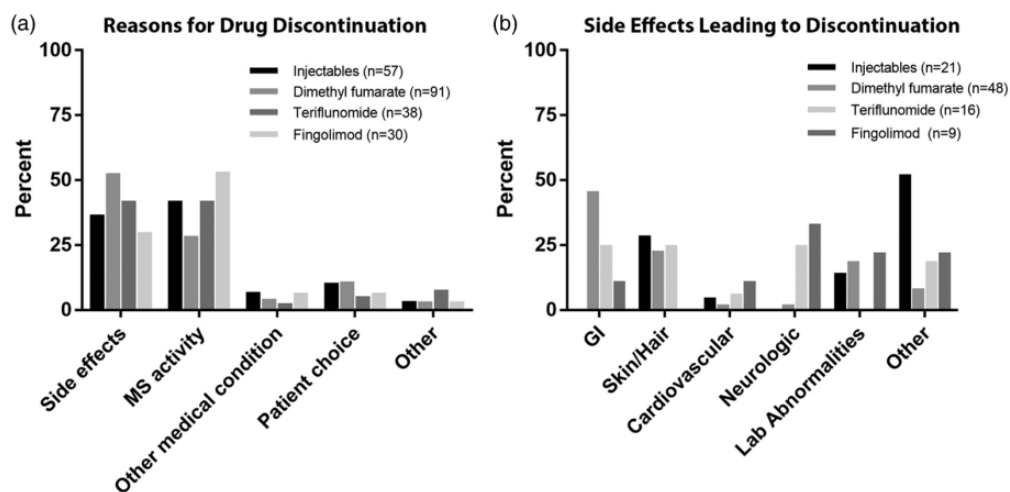
Figure 3. Factors contributing to multiple sclerosis (MS) disease-modifying therapy discontinuation. Primary reasons for drug discontinuation (a). Side effects precipitating discontinuation (b). Number (*n*) of discontinuation events (a) or discontinuations due to drug side effects (b).

relative efficacy. We retrospectively assessed the use and performance of these medications in a real world cohort. As expected, there was variability among the patients chosen to receive each drug. INJ therapies were commonly prescribed for patients who were early in their disease course and had not previously been exposed to immunomodulators. In contrast, oral medications were prescribed for individuals later in their disease course who had failed or could not tolerate other forms of DMT. There was also variability among patients initiating oral DMTs, with FGD-treated patients tending to be younger and having a more recent diagnosis than those starting the other oral medications. Physician prescribing practice varied widely, illustrating the current lack of evidence available to guide treatment decisions.

After controlling for baseline differences, we found that DMF and FGD were comparable to INJ therapies for controlling breakthrough MS activity. This is

in line with Phase 3 trials, where DMF performed similarly to glatiramer acetate.[20] FGD out-performed low dose IFN-β in its Phase 3 trial,[21] but that interferon formulation was previously found to be less effective than a higher dose formulation.[22] We considered all INJ therapies together, which may contribute to the lack of an observed difference in efficacy between FGD and INJ therapies. The sample size in this study may also have been too small to detect differences between these groups. In contrast, while TER performed similarly to high dose IFN-β in a Phase 3 clinical trial,[23] cohort patients treated with TER experienced significantly more breakthrough MS activity than patients treated with INJ therapies. This finding was reproduced when data were re-analyzed using propensity score matching. The observation is likely driven by patients switching to TER from a different DMT, as few treatment-naïve patients initiated TER. Subgroup analyses of data from patients who were not treatment-naive support this hypothesis. Other significant predictors of MS activity included neurologic disability (based on EDSS) and relapse frequency, both of which are consistent with the published literature.

The baseline patient heterogeneity makes evaluating the comparative effectiveness of DMTs challenging, but statistical methods can account for measured differences in factors known to affect disease course.[24] The consistency of the adjusted models with the propensity matched models support our results. Nevertheless, Cox models and propensity score matching are not perfect substitutes for randomization and only control for measured variables. Unmeasured variables may account for some of the observed difference in efficacy between TER and INJ therapies. For example, prior MRI activity often plays a role in treatment decisions, but because these data were not consistently captured in the clinical record, they were not statistically accounted for. Moreover, although propensity score matching markedly reduced the measured differences between the treatment groups, residual bias remained for several variables (Table 2, Supplementary Material, Figure 2).

It is worth noting that the patients prescribed TER in this clinical cohort differed markedly from those studied in Phase 3 trials. For example, the average age for TER-treated patients in this real-world sample was 49 years, with patients as old as 76 years initiating the drug. In contrast, the upper age limit for patients entering the Phase 3 trials was 55 years, and the average age was 38 years.[25,26]

Real-world patients also included a larger proportion of African-Americans, increased prior DMT exposure, and a longer duration of MS compared to clinical trial patients.[25,26] Overall, these data suggest that as it is being used in clinical practice, TER may be less effective than INJ DMTs for controlling inflammatory MS activity.

A surprisingly high proportion of patients discontinued DMT during the study period; within a 2.5 year window, 33—46% of patients newly prescribed any given DMT subsequently discontinued or switched therapies. These proportions are higher than those previously reported for observational studies. One systematic review reported that 22—43% of patients taking INJ therapy long-term (>24 months) ultimately discontinued or switched medications, but only 10—15% discontinued within the first year.[27] Another large observational study found annual discontinuation rates of 20—25%[24]. These numbers largely reflect the pre-oral DMT epoch. Since the advent of oral options, patients are more likely to discontinue other DMTs in favor of an oral medication.[8,12] Previous work suggested that MS patients were more adherent with oral DMTs and were less likely to discontinue treatment when compared with INJ or infused medications.[14,15] Despite this, we were unable to confirm improved efficacy or tolerability for oral therapies in this cohort. This may be due in part to our limited sample size; a larger cohort would increase the power for detecting differences between the treatment groups. Nevertheless, when combined with a well-established safety record, our data suggest that INJ therapies will continue to play an important role in MS treatment for the foreseeable future.

Drug persistence may depend partly on the geo-political situation. The published literature is primarily based on data from countries with nationalized healthcare, and the unique healthcare situation in the USA may contribute to high rates of switching between medications. Increased ease of switching likely has both positive and negative effects. DMT adherence improves MS outcomes and helps manage healthcare costs.[4] When physicians have access to many DMTs, this increases the likelihood that an effective and tolerable treatment can be found. On the other hand, since DMTs are expensive and come with a substantial administrative burden, rapidly switching between therapies can strain the resources of clinical practices.

The expanding armamentarium of therapies against relapsing MS has encouraged physicians to strive for NEDA. This may result in multiple medication

changes. Notably, the cumulative health effects of multiple immunomodulatory therapies are not known. Past exposure to immunosuppressants increases the likelihood of developing progressive multifocal leukoencephalopahy during natalizumab therapy.[28] Serial exposure to multiple DMTs may change the immune systems of patients and affect risk of future complications. The immunologic effects of sequential DMT exposures deserves more study.

These data should be generalized with caution, given the limited size of the patient cohort and potential for bias among the patients selected to initiate each therapy, which may remain despite statistical corrections. This study was relatively short, with an average follow-up period of around 18 months. Additional differences between groups may emerge with longer follow up. Additionally, our cohort consisted of patients treated at a single Midwestern US center and thus may not be representative of larger regions. Further evaluation of the comparative effectiveness of the oral DMTs is needed.

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