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RESEARCH ARTICLE

Natalizumab versus fingolimod and dimethyl fumarate in multiple sclerosis treatment

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Abstract

Objective: To compare 2-year effectiveness and discontinuation of natalizumab (NTZ) versus fingolimod (FTY) and dimethyl fumarate (DMF) in the treatment of multiple sclerosis (MS). **Methods**: Patients prescribed NTZ, FTY, or DMF at the Rocky Mountain MS Center at University of Colorado were identified. Clinician-reported data were retrospectively collected. Outcomes include a composite effectiveness measure consisting of new T2 lesion, gadolinium-enhancing lesion, and/or clinical relapse, individual effectiveness outcomes and discontinuation over 2 years. Logistic regression was used for data analysis on patients matched by propensity scores and using ATT doubly robust weighting estimator. **Results**: A total of 451, 271, and 342 patients were evaluated on NTZ, FTY, and DMF over 2 years, respectively. Patients had a mean age of 39.8 (NTZ), 42.5(FTY), and 45.8 (DMF) years; were predominantly female (76.7% NTZ; 72.0% FTY; 69.6% DMF); and had a mean MS disease duration of 11–12 years for all groups. At ≤24 months, 22.2%, 34.7%, and 33.6% experienced a new T2 lesion, gadolinium-enhancing lesion, and/or clinical relapse on NTZ, FTY, and DMF, respectively. Using ATT doubly robust weighting estimator, FTY versus NTZ and DMF versus NTZ had an odds ratio of 2.00 (95%CI:[1.41–2.85], $P < 0.001$) and 2.38 [95% CI: 1.68–3.37], $P < 0.001$) respectively, for experiencing a new T2 lesion, gadolinium enhancing lesion, and/or clinical relapse. At ≤24 months, 32.6%, 34.3%, and 47.1% discontinued NTZ, FTY, and DMF, respectively. The majority of discontinuations were due to becoming JCV positive(12.6%) for NTZ and due to adverse events for both FTY(17%) and DMF (24.0%). **Interpretation**: NTZ appears to be more effective and tolerable than FTY and DMF.

Introduction

There are now over a dozen disease modifying therapies (DMTs), with varied mechanisms of action, side effects, and efficacy, available to treat patients with multiple sclerosis (MS). While injectable DMTs, including interferons and glatiramer acetate, have been used for the treatment of MS as early as 1993, more recently approved drugs such as natalizumab (NTZ), fingolimod (FTY), dimethyl fumarate (DMF), alemtuzumab, and ocrelizumab have been shown to be more efficacious.[1–7]

While NTZ, FTY, and DMF are all considered highly effective, previous systematic reviews suggest improved outcomes for NTZ over FTY and DMF.[4,7] However, when investigating real-world data, there are limited data for NTZ versus DMF and conflicting results exist when comparing NTZ to FTY.[8–10] Two studies demonstrate no significant difference in clinical efficacy between NTZ and FTY, while a third study does, particularly during the second year of treatment.[8–10] Importantly, these three studies do not include follow-up MRI data which would be useful when assessing

superiority in effectiveness, as lesion load has been demonstrated to predict disability.[11]

Additionally, there are substantial differences in adverse events (AEs) and tolerability profiles that may affect discontinuation rates for NTZ, FTY, and DMF. NTZ treatment is most notably associated with the risk of progressive multifocal leukoencephalopathy (PML), a rare, but potentially life-threatening neurological infection resulting from viral reactivation after prior exposure to the JC virus (JCV).[12] While cases of PML have also been documented in those taking FTY and DMF, the frequency is substantially lower compared to NTZ.[13,14] FTY is most commonly associated with nasopharyngitis, headaches, and fatigue in addition to the risk of rare cardiovascular events during treatment initiation of FTY.[15,16] In comparison, DMF has proved challenging due to flushing and gastrointestinal (GI)-related issues associated with the first few weeks of treatment.[2,17]

While clinical trials, systematic reviews, and meta-analyses have established tolerability and efficacy profiles, limited and conflicting comparative effectiveness data exist for the increasing number of DMTs for the treatment of MS. As a result, it has become challenging for patients and providers to select and establish consistent long-term care with an appropriate DMT. Our retrospective study addresses this gap in knowledge through investigating the real-world experience of patients on NTZ compared to FTY and DMF in regards to effectiveness and discontinuation, with the inclusion of MRI outcomes. No comparison of FTY to DMF is shown here due to its inclusion in our previous study.[18]

Methods

Patient population

A list of potential study participants was generated from patients who completed enrollment forms and initiated the approval process through their insurance companies for NTZ, FTY, or DMF at the Rocky Mountain Multiple Sclerosis Center at the University of Colorado (RMMSC at CU). All potential participants were included in this study if they (1) were diagnosed with any form of MS; (2) began taking NTZ, FTY, or DMF between 1 January 2010 and 1 October 2013; and (3) for only NTZ patients had a negative JCV serology test at baseline. It is common practice at our clinic to treat JCV antibody-positive patients with NTZ while they transit to another DMT. These patients initiate NTZ with the plan of short-term use. We believed these patients would obscure our results, particularly when assessing reasons for discontinuations and achieving long-term care; therefore, we did not include them in this study.

Study design

Data were collected through retrospective chart reviews of patient electronic medical records. The index date was defined as the date of first administration of NTZ, FTY, or DMF. All RMMSC at CU encounters following each study participant's index date was reviewed by BV for up to 24 months after index date or until study drug discontinuation to collect clinician-reported data including patient characteristics, relapse history, MRI outcomes, medication history, AEs, and MS disease history. Baseline characteristics were at the time of DMT index date and baseline MRIs were the closest MRI within 2 years of DMT initiation. Quality checks were completed by conducting a second review of a subgroup of charts to confirm accuracy of outliers and consistency of data collection.

Outcomes

The primary outcome of this study was a composite effectiveness measure defined as the patient experiencing a clinical relapse, gadolinium enhancing (GdE) lesion, and/or new T2 lesion. For the purpose of this study, clinical relapses were defined as clinician-reported per patient chart notes as new or worsening neurological symptoms lasting $\geq$24 h. No consistent measure of disability was available due to the retrospective nature of this study; therefore, disability was not included in the composite effectiveness measure. All effectiveness outcomes were on treatment measures.

Secondary outcomes include (1) individual effectiveness measures including clinical relapse, GdE lesions, and new T2 lesions, (2) discontinuation and time to discontinuation of NTZ, FTY, or DMF, and (3) primary reason for discontinuation, categorized as disease activity, being JCV positive, AE/tolerability, issues with insurance, loss to follow-up or any other reason. Discontinuation was defined as no longer taking the study drug at 24 months after index date and/or initiation of any other DMT for the treatment of MS during the 24-month follow-up period. Patients were not considered a discontinuation if they withheld medication for a period of time, for example to alleviate AEs or due to travel, and reinitiated the medication without interruption by any other MS DMT.

Statistical analysis

Statistical analyses were conducted using SAS Version 9.4 and STATA Version 13.1. Cohen's D effect size plots were created using R Version 3.1.0. All two-tailed $P < 0.05$ were considered significant. When assessing baseline characteristics and secondary outcomes, differences were

assessed using *T*-tests or Wilcoxon ranks sum tests for continuous variables, and Chi-squared tests for categorical data. Odds ratios (ORs) were obtained for the primary outcome (composite effectiveness measure at <24 months) and select secondary outcomes (discontinuation due to any reason and discontinuation due to AEs) using multiple methods to account for imbalances between groups. Methods used include simple logistic regression, adjusted logistic regression, logistic regression on sample group 1:1 nearest neighbor matched by propensity scores with replacement, and Average Treatment Effect on Treated (ATT) doubly robust weighting estimator, which uses a combination of regression and propensity scores with DMF and FTY matched to NTZ. Additional analyses include investigating outcomes for the relapsing-remitting cohort and disease activity during 6–24 months.

Propensity scores were created with a logistic regression model for probability of receiving NTZ. Adjusting covariates used to create propensity scores were pre-determined and included age, gender (female/male), disease duration, diagnosis (relapsing-remitting MS/secondary progressive MS/primary progressive MS), GdE lesion (yes/no/no MRI available), and disease burden on baseline MRI (mild/moderate/severe/no MRI available). The adjusted logistic regression model assessing the primary outcome and select secondary outcomes of our study employed the same adjusting covariates as used in the creation of propensity scores.

Results

Baseline characteristics

Figure 1 demonstrates the identification process for each cohort. A total of 1064 participants met the inclusion criteria for our study, consisting of 451 NTZ, 271 FTY, and 342 DMF. Table 1 presents baseline characteristics for each cohort.

Propensity model

Figure S1 in supplementary material demonstrates the Cohen's D values for effect sizes comparing baseline covariates between NTZ and FTY/DMF before and after adjustment. Prior to propensity adjustment, the treatment groups were not well-balanced (absolute value of the standardized difference of the linear PS, comparing FTY to NTZ = 55%, comparing DMF to NTZ = 71%). Through ATT doubly robust weighting, we effectively achieved well-balanced groups with no covariates having an absolute standardized difference <10% for both FTY to NTZ and DMF to NTZ. Although PS 1:1 nearest neighbor matching resulted in some covariates having a standardized difference >10%, the linear PS distribution had standardized difference of 1.5% for FTY to NTZ and 1.0% for DMF to NTZ, well within the 50% standard proposed by Rubin.[19]

Effectiveness outcomes

There was a significant difference between NTZ and FTY for our unadjusted composite effectiveness measure ($P < 0.001$) as seen in Figure 2A. After adjustment, results were consistent, (Table 2) demonstrating increased odds of FTY patients experiencing a clinical relapse, GdE lesion, and/or new T2 lesion [OR = 2.00 (95% CI [1.41–2.85], $P < 0.001$ using ATT doubly robust weighting). Significant differences were observed between NTZ and FTY in the unadjusted individual measures of GdE lesions ($P = 0.004$) and new T2 lesions ($P = 0.017$); however, no difference was seen for clinical relapses ($P = 0.145$) (Fig. 2A). There was a significant difference between NTZ and DMF for our unadjusted composite effectiveness measure ($P < 0.001$) as seen in Figure 2A. After adjustment, results are consistent (Table 3) demonstrating increased odds of DMF patients experiencing a clinical relapse, GdE lesion, and/or new T2 lesion (OR = 2.38, 95% CI [1.68–3.37], $P < 0.001$ using ATT doubly robust weighting). Significant differences were observed between NTZ and DMF in the unadjusted individual measure of clinical relapses ($P = 0.001$); however, no difference was seen for GdE lesions ($P = 0.066$) and new T2 lesions ($P = 0.101$) (Fig. 2A). Figure 3A shows the Kaplan–Meier failure curve demonstrating cumulative probability of experiencing a clinical relapse, GdE lesion and/or new T2 lesion. Time to event analyses demonstrate consistent results for the composite effectiveness measure (Table S7). RRMS-only patients demonstrated results consistent with the overall cohort as seen in Table S2–S4. When investigating disease activity between months 6 and 24, adjusted results for the composite effectiveness measure were consistently significant (Fig. S5) and the individual measure of clinical relapses was significantly different for both DMF versus NTZ and FTY versus NTZ after adjustment (Table S6).

Discontinuation outcomes

Figure 2B demonstrates the unadjusted discontinuation outcomes. For NTZ, FTY, and DMF, respectively, 32.6, 34.3, and 47.1% discontinued at ≤2 years. NTZ and FTY did not differ significantly in overall discontinuations ($P = 0.634$). FTY patients were more likely to discontinue due to disease activity ($P < 0.001$) and AEs ($P < 0.001$), while NTZ patients were more likely to discontinue due

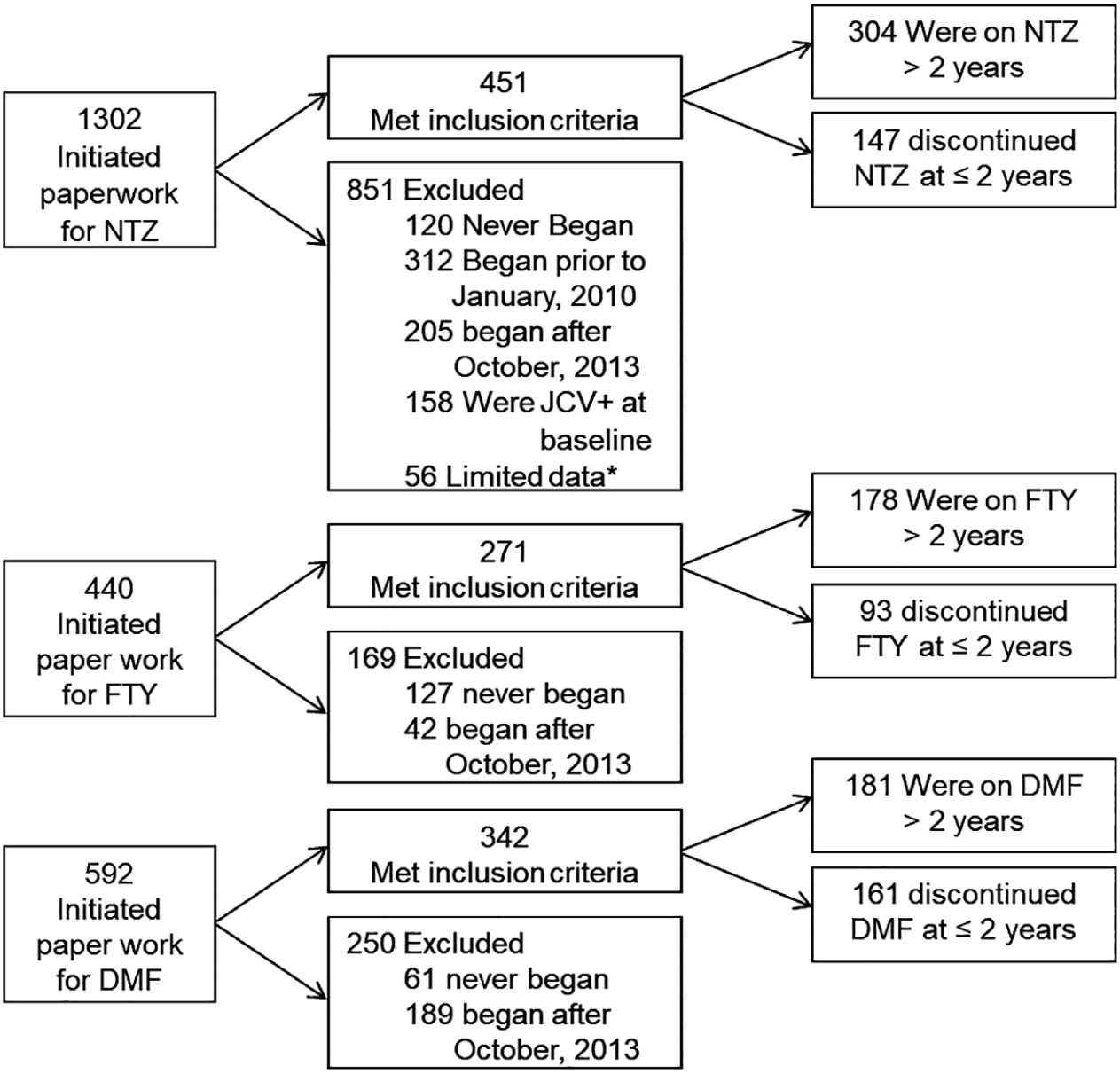


Figure 1. Sample identification. *Limited data refer to patients who transferred to our center after already initiating study drug with no medical records documenting the first 2 years of treatment and patients who participated in research studies resulting in limited access to data for this study. NTZ, natalizumab; FTY, fingolimod; DMF, dimethyl fumarate.

to becoming JCV positive ($P < 0.001$). NTZ compared to DMF demonstrated a significant difference in overall discontinuations ($P < 0.001$). DMF patients were more likely to discontinue due to disease activity ($P < 0.001$) and AEs ($P < 0.001$). No significant differences were seen for discontinuation due to insurance or loss to follow up for both FTY versus NTZ and DMF versus NTZ. The most commonly cited reasons for discontinuation that were classified as "other" included attempting pregnancy and preference for a more convenient DMT for NTZ patients and nonadherence and attempting pregnancy for both FTY and DMF patients. Of those who discontinued, the mean time to discontinuation was 13.0, 10.3, and 10.0 months for NTZ, FTY, and DMF, respectively. No comparison of FTY to DMF is shown here due to its inclusion in our previous study.[18]

Tables 2 and 3 exhibit the unadjusted and adjusted ORs of FTY compared to NTZ and DMF compared to NTZ, respectively, for discontinuation due to any reason and discontinuation due to AEs. All methods of

Table 1. Baseline characteristics for study cohort.

	Natalizumab (*N* = 451)	Fingolimod (*N* = 271)		Dimethyl fumarate (*N* = 342)	
	N or Mean (% or SD)	*N* or Mean (% or SD)	*P*-value	*N* or Mean (% or SD)	*P*-value
Disease duration (Years, SD)	11.4 (7.5)	11.5 (7.5)	0.666	11.1 (7.4)	0.303 [3]
Age (Years, SD)	39.8 (12.1)	42.5 (11.4)	**0.003**	45.8 (12.2)	**<0.001** [3]
Gender-female	346 (76.7%)	195 (72.0%)	0.153	238 (69.6%)	**0.024** [4]
Type of multiple sclerosis			0.129		**0.005** [4]
Relapsing-remitting	382 (84.7%)	244 (90.0%)		265 (77.5%)	
Secondary progressive	58 (12.9%)	23 (8.5%)		54 (15.8%)	
Primary progressive	11 (2.4%)	4 (1.5%)		23 (6.7%)	
Previous DMT[1]			**<0.001**		**<0.001** [4]
Interferons	107 (23.7%)	36 (13.3%)		49 (14.3%)	
Glatiramer acetate	152 (33.7%)	49 (18.1%)		106 (31.0%)	
Natalizumab	0 (0.0%)	115 (42.4%)		65 (19.0%)	
Rituximab	1 (0.2%)	1 (0.4%)		9 (2.6%)	
Fingolimod	8 (1.8%)	0 (0.0%)		24 (7.0%)	
Dimethyl fumarate	2 (0.4%)	1 (0.4%)		0 (0.0%)	
None	170 (37.7%)	66 (24.4%)		84 (24.6%)	
Other	11 (2.4%)	3 (1.1%)		5 (1.5%)	
GdE lesion on baseline MRI[2]	123 (33.1%)	57 (24.6%)	**0.026**	44 (14.6%)	**<0.001** [4]

Bold indicates a *P*-value < 0.05 when compared to natalizumab.

N, number; SD, Standard deviation; DMT, Disease modifying therapy; GdE, Gadolinium enhancing.

[1]Within 6 months prior to starting study drug.

[2]Percentage calculated using denominator as those who had baseline MRI data available (Natalizumab *N* = 372; Fingolimod = 232; Dimethyl fumarate *N* = 302)

[3]*T*-test.

[4]Chi-Squared test.

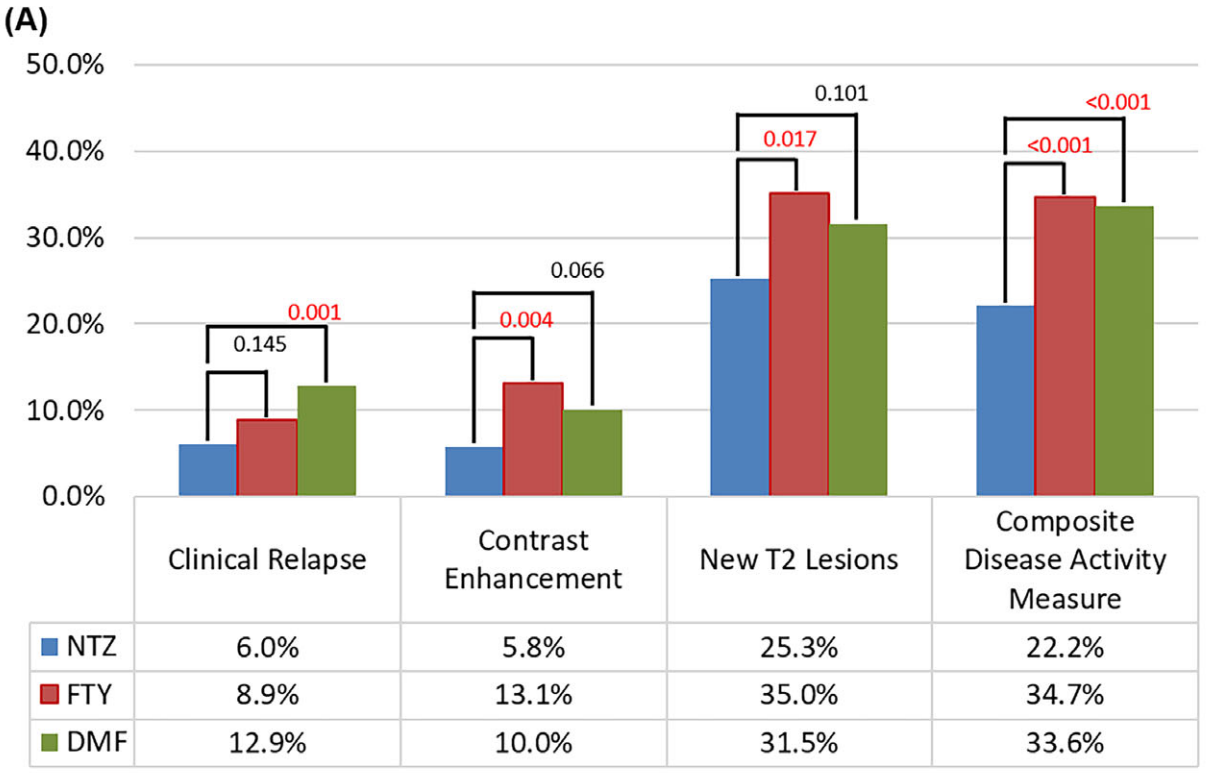
adjustment demonstrated consistent results. No significant difference was observed between odds of discontinuing FTY or NTZ for any reason (OR = 1.19, 95% CI [0.84–1.67], $P = 0.332$ using ATT doubly robust weighting). However, there was significantly increased odds of discontinuing FTY compared to NTZ due to AEs only (OR = 2.65, 95% CI [1.59–4.43], $P < 0.001$). DMF compared to NTZ demonstrated a significant increase in odds of discontinuing due to any reason (OR = 2.13, 95% CI [1.53–2.96], $P < 0.001$), as well as due to AEs only (OR = 4.53, 95% CI [2.82–7.26], $P < 0.001$). Figure 3B–C demonstrates Kaplan–Meier failure curves demonstrating cumulative probability of discontinuation overall and due to AEs over time.

Adverse events/tolerability

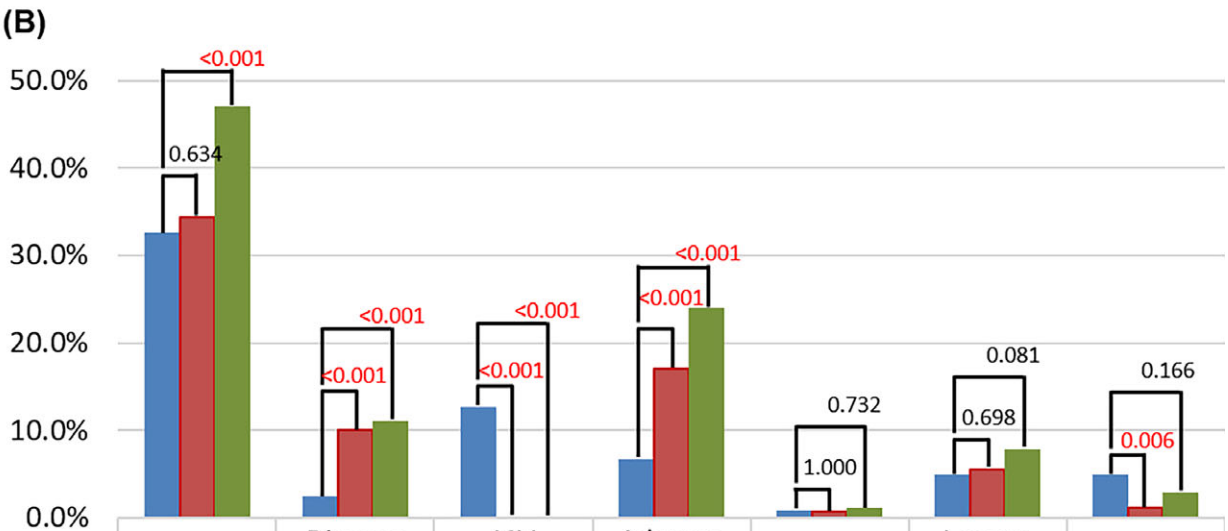
Table 4 shows the AEs that led to discontinuation of NTZ, FTY, and DMF. Twelve of the 30 NTZ patients who discontinued due to AEs tested positive for NTZ neutralizing antibodies. Flushing, rashes, or hot flashes were the most common AE cited as a reason for discontinuation of NTZ, accounting for 46.7% of discontinuations due to AEs and included all 12 of the patients who tested positive for NTZ neutralizing antibodies. The most common AE leading to discontinuation of FTY and DMF were GI-related issues (FTY: 23.9%; DMF: 80.5%), followed by headaches for FTY (17.4%) and flushing, rashes, or hot flashes for DMF (30.5%).

Discussion

While there have been relatively few head-to-head clinical trials of MS DMTs, comparative effectiveness data in a real-world setting can provide valuable insight for clinicians to establish consistent long-term care with an appropriate DMT. Our study shows NTZ was not only more efficacious than FTY and DMF, but also was better tolerated. Previous systematic reviews of clinical trial data have consistently demonstrated NTZ to be more efficacious than FTY and DMF.[4,7] To our knowledge, there are no previous large real-world studies investigating NTZ versus DMF; however, studies investigating NTZ versus FTY have demonstrated conflicting results. Two studies conducted by Koch-Henriksen et al. and Braune et al. demonstrated no significant differences in clinical outcomes in RRMS patients, whereas a Kalincik et al. demonstrated NTZ to be superior to FTY in active-RRMS patients switching from injectable therapies. Koch-Henricksen et al. had a mean follow-up time of 1.8 year and Braune et al. followed patients for 12 months and only included patients who remained on therapy for the study



	Clinical Relapse	Contrast Enhancement	New T2 Lesions	Composite Disease Activity Measure
NTZ	6.0%	5.8%	25.3%	22.2%
FTY	8.9%	13.1%	35.0%	34.7%
DMF	12.9%	10.0%	31.5%	33.6%



	Overall	Disease Activity	JCV Positive	Adverse Event	Insurance	Loss to Follow-Up	Other
NTZ	32.6%	2.4%	12.6%	6.7%	0.9%	4.9%	4.9%
FTY	34.3%	10.0%	0.0%	17.0%	0.7%	5.5%	1.1%
DMF	47.1%	11.1%	0.0%	24.0%	1.2%	7.9%	2.9%

Note: Values above bars are p-values

Figure 2. (A) Unadjusted effectiveness outcomes for natalizumab (NTZ), fingolimod (FTY), and dimethyl fumarate(DMF). (B) Unadjusted discontinuation outcomes for NTZ, FTY, and DMF for overall discontinuations and discontinuations by reason. NTZ, Natalizumab; FTY, fingolimod; DMF, dimethyl fumarate.

Table 2. Unadjusted & adjusted odds ratios for FTY vs NTZ for disease activity, discontinuation due to any reason at ≤24 months and discontinuation due to adverse events only.

		Effectiveness		Discontinuation			
		Composite measure[2]		Due to any reason		Due to adverse events	
	N	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Simple logistic regression	722	1.86 (1.32, 2.58)	<0.001	1.08 (0.79, 1.49)	0.634	2.87 (1.76, 4.67)	<0.001
Adjusted logistic regression[1]	722	1.96 (1.37, 2.80)	<0.001	1.16 (0.83, 1.62)	0.387	2.78 (1.68, 4.61)	<0.001
Propensity matching with 1:1 nearest neighbor matching with replacement[1]	902 (632 unique)	2.90 (1.80, 4.67)	<0.001	1.18 (0.75, 1.86)	0.472	2.93 (1.57, 5.50)	0.001
ATT doubly robust weighting estimator[1]	722	2.00 (1.41, 2.85)	<0.001	1.19 (0.84, 1.67)	0.332	2.65 (1.59, 4.43)	0.001

All methods use NTZ as reference group. FTY, fingolimod; NTZ, natalizumab.
[1]Controlling for age, disease duration, type of MS, gender, contrast enhancement on baseline MRI, and disease burden on baseline MRI
[2]Includes clinical relapse, new T2 lesion on follow-up MRI, or contrast enhancement on follow-up MRI regardless of the event leading to discontinuation of drug

Table 3. Unadjusted and adjusted odds ratios for DMF versus NTZ for disease activity, discontinuation due to any reason at ≤24 months and discontinuation due to adverse events only.

		Effectiveness		Discontinuation			
		Composite measure[2]		Due to any reason		Due to adverse events	
	N	Odds Ratio (95% CI)	*P*-value	Odds Ratio (95% CI)	*P*-value	Odds Ratio (95% CI)	*P*-value
Simple logistic regression	793	1.78 (1.28, 2.41)	<0.001	1.84 (1.38, 2.46)	<0.001	4.43 (2.83, 6.91)	<0.001
Adjusted logistic regression[1]	793	2.22 (1.57, 3.15)	<0.001	2.10 (1.53, 2.89)	<0.001	5.11 (3.14, 8.31)	<0.001
Propensity matching with 1:1 nearest neighbor matching with replacement[1]	902 (635 unique)	2.23 (1.44, 3.46)	<0.001	2.17 (1.43, 3.29)	<0.001	4.10 (2.38, 7.08)	<0.001
ATT doubly robust weighting estimator[1]	793	2.38 (1.68, 3.37)	<0.001	2.13 (1.53, 2.96)	<0.001	4.53 (2.82, 7.26)	<0.001

All methods use NTZ as reference group. DMF: dimethyl fumarate; NTZ: natalizumab.
[1]Controlling for age, disease duration, type of MS, gender, contrast enhancement on baseline MRI, and disease burden on baseline MRI.
[2]Includes clinical relapse, new T2 lesion on follow-up MRI, or contrast enhancement on follow-up MRI regardless of the event leading to discontinuation of drug.

period, potentially introducing a bias toward less active disease. Kalincik et al. followed patients for up to 24 months with a median follow-up time of 21 months and demonstrated a significant difference in clinical efficacy particularly in the second year of treatment, suggesting longer follow-up time may be necessary to detect differences. To further support this, our study demonstrated no significant difference in clinical relapses for NTZ versus FTY over 2 years; however, a significant difference was seen in clinical relapses between 6 and 24 months. This may be suggestive that clinical relapses occur earlier on NTZ and may be dependent on previous DMT or prior washout periods.

Additionally, while only Kalincik had baseline MRIs for a small subset of patients, none of these studies include follow-up MRI outcomes when assessing efficacy. MRIs may be required when determining superior efficacy among highly effective DMTs, allowing for observation of more events to increase power needed to detect smaller differences. This is further supported by the fluctuating significance among our individual effectiveness outcomes, as clinical relapses alone were not significantly different when comparing NTZ and FTY while MRI outcomes were. Differences observed in the composite effectiveness measure for FTY versus NTZ appear to be primarily driven by MRI activity. Conversely, when comparing NTZ and DMF, a significant difference was observed among clinical relapses, but was not for MRI outcomes. Although the composite effectiveness measure is more robust with the inclusion of both clinical and MRI outcomes, it is important to note the limitations that come with MRI data availability. As a retrospective observational study, all

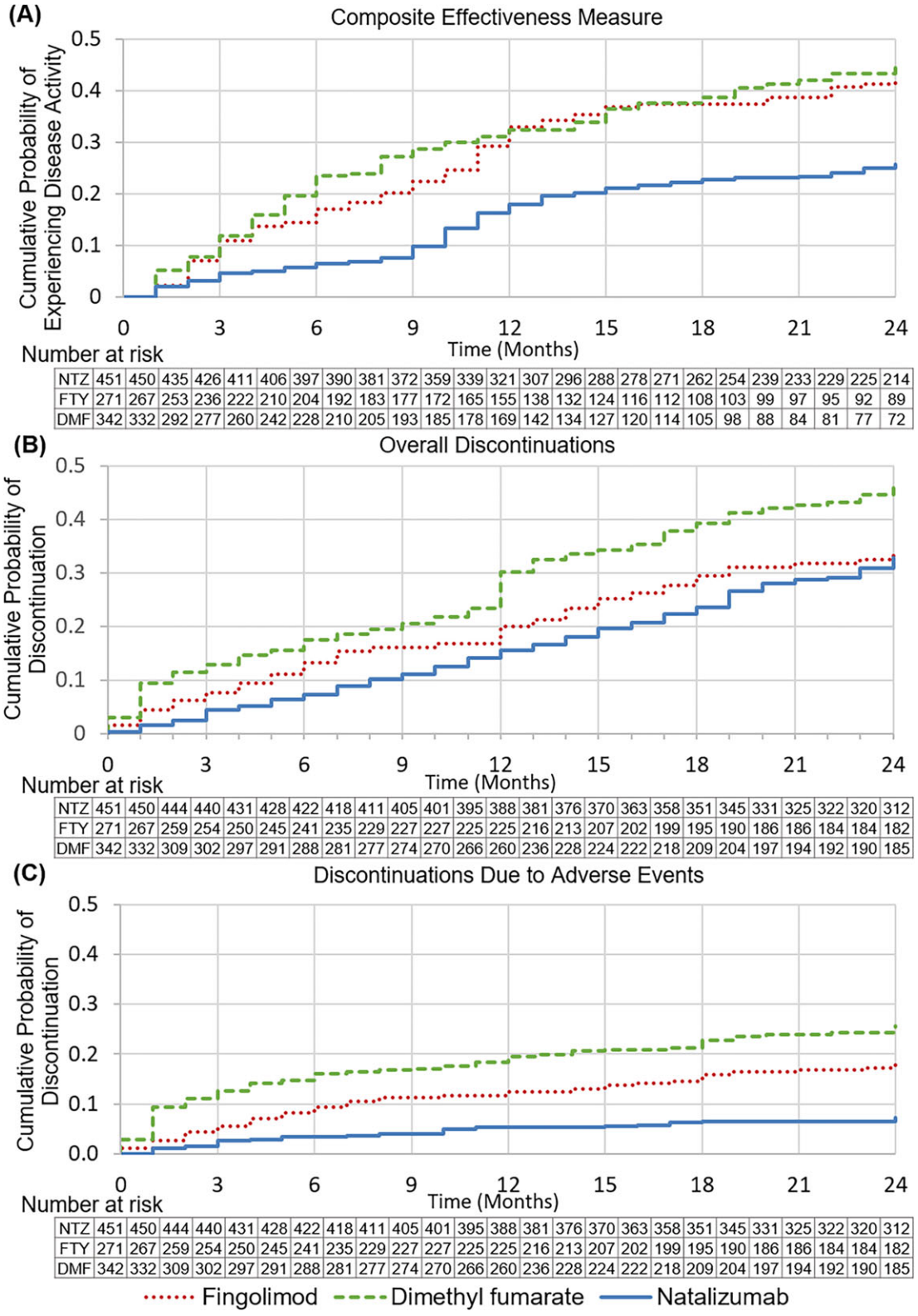


Figure 3. (A) Kaplan–Meier failure curve demonstrating cumulative probability of experiencing disease activity over time, including clinical relapse, contrast enhancing lesion and/or new T2 lesion. (B) Kaplan–Meier failure curve demonstrating cumulative probability of discontinuation for any reason over time. (C) Kaplan-Meier failure curve demonstrating cumulative probability of discontinuation due to adverse events.

Table 4. Adverse events (AEs) leading to discontinuation.

	Natalizumab (*N* = 30)		Fingolimod (*N* = 46)		Dimethyl fumarate (*N* = 82)	
Adverse event	*N*	%	*N*	%	*N*	%
GI Issues	4	13.3%	11	23.9%	66	80.5%
Flushing/rash/hot flashes (NAb+)	14 12	46.7% (40.0%)	–	–	25	30.5%
Headaches	5	16.7%	8	17.4%	1	1.2%
Infections	3	10.0%	7	15.2%	4	4.9%
Fatigue	6	20.0%	–	–	–	–
Lymphopenia	–	–	7	15.2%	6	7.3%
Elevated LFTs	3	10.0%	6	13.0%	1	1.2%
Psychiatric disorders	4	13.3%	2	4.3%	1	1.2%
Weight gain	1	3.3%	1	2.2%	1	1.2%
Hypotension	1	3.3%	–	–	–	–
Ovarian cyst	1	3.3%	–	–	–	–
Arrhythmia	–	–	4	8.7%	–	–
Hair loss	–	–	2	4.3%	2	2.4%
Bradycardia	–	–	3	6.5%	–	–
Hypertension	–	–	3	6.5%	–	–
Shortness of breath (NAb+)	2 (2)	6.7% (6.7%)	3	6.5%	–	–
Tachycardia	–	–	3	6.5%	–	–
Muscle spasms/ weakness	1	3.3%	1	2.2%	3	3.7%
Taste and vision changes	–	–	2	4.3%	1	1.2%
Reported pain (Other than abdominal)	–	–	1	2.2%	2	2.4%
Alveolar hemorrhage	–	–	1	2.2%	–	–
Palpitations	–	–	1	2.2%	–	–
Pancytopenia	–	–	1	2.2%	–	–
Seizures	–	–	1	2.2%	–	–

NAb+, neutralizing antibody positive; GI, gastrointestinal; LFTs, liver function test.

Percentages may equal >100% as a result of multiple AEs cited as reason for discontinuation. Percentages are calculated from those who discontinued drug due to AEs.

MRIs were standard of care, and the number and timing of MRIs varied by patient. Unlike our clinical outcomes, not all patients have MRI data available. Potentially, those with more active disease may have more MRI data. Despite this, we believe the inclusion of MRI outcomes provides important insight into the efficacy of highly effective therapies.

Our results show NTZ to have similar odds of discontinuation due to any reason compared to FTY. A large study using MSBase data for active-RRMS patients demonstrated similar results with no difference observed in discontinuation at 24 months for NTZ versus FTY, at 27% and 31%, respectively.[10] Although slightly lower, this is similar to 32.6% NTZ and 34.3% FTY demonstrated in our study. When comparing NTZ to DMF, there was a significant difference in odds of discontinuation with DMF patients being twice as likely to discontinue due to any reason compared to NTZ patients. While limited comparative effectiveness data exist comparing NTZ to DMF, previous research has demonstrated high proportions of discontinuation for DMF.[18,20] A population-based cohort study conducted in Sweden investigating DMF persistence demonstrated 57% of DMF patients discontinuing at 2 years or less.[21] However, other real-world observational studies demonstrate fairly lower percentages ranging from 31% to 41% of DMF patients discontinuing at 2 years or less.[18,20,22] For NTZ, FTY, and DMF, the proportions of overall discontinuations are higher in our study than clinical trials, exemplifying the importance of real-world observational studies.[1,2,15–17,23]

While the proportions of those who discontinued NTZ, FTY, and DMF have varied among studies, the leading causes for discontinuations were consistent with previous research. For our NTZ participants, the leading cause for discontinuation at 2 years or less was a change to JCV positive status at 12.6%. Although 12.6% over 2 years is lower than initially expected due to a demonstrated seroconversion for second-generation JCV ELISA testing at 1 year to be 8.5–11.7%, it is understandable given the number who discontinues due to being JCV positive is not indicative of seroconversion rates as some prescribers and patients may choose to remain on treatment for a period of time while monitoring through index values and MRIs.[24,25]

FTY participants in our study discontinued this drug due to a wide range of AEs. Similarly, the leading cause for discontinuation for DMF patients was due to AEs; however, primarily GI-related issues and flushing. This is consistent with previous literature demonstrating GI-related issues to be associated with DMF treatment, particularly in the first few months of treatment. Interestingly, while there was a sharp jump in discontinuations due to AEs for DMF in months 0–3 of treatment, the probability of discontinuation continues to steadily increase up to 24 months after drug initiation, as seen in Figure 3, suggesting tolerability issues may persist in some patients longer than initially thought.

In distinction, AEs leading to discontinuation of NTZ occurred in only 6.7% of patients. Consistent with previous literature, infusion-related reactions (flushing and rashes) were the most common, accounting for 46.7% of discontinuations of NTZ due to AEs.[1,23] As a limitation to our study design, we were unable to distinguish between flushing and rashes as individual AEs. No serious AEs or cases of PML occurred in our NTZ participants. Although previous research shows patients report a preference for convenient oral DMTs versus infusion DMTs, this preference may be counteracted by issues with tolerability and

AEs associated with oral DMTs.[26] AEs may not only affect persistence/discontinuation, but potentially also disease activity, as a result of noncompliance.

Our study does have limitations. As a retrospective observational study, we are restricted to already existing data extracted from electronic medical records. Although adjustment methods are used to achieve balanced groups, there may be hidden bias as a result of unmeasured covariates. However, we believe our adjustment methods are adequate as selected covariates are representative of baseline characteristics used in DMT decision-making and are consistent with previous literature. We demonstrated consistent results with multiple methods and achieved well-balanced groups, particularly with ATT doubly robust weighting. Furthermore, this is a single academic center study, affecting generalizability. For example, clinicians at RMMSC at CU may differ in amount and type of counseling for tolerability or AEs compared to other centers. Adherence was not assessed and may have affected outcomes. Finally, compared to RCTs in relapsing-only MS patients, our study included relatively older patients and some with progressive forms of MS. While this is representative of those treated in clinical practice, the low inflammatory profile of these patients may limit interpretability of treatment effects. However, our inclusion of the RRMS subgroup analysis allows for treatment effects demonstrated in a cohort similar to those in phase 3 RCTs and other observational studies for RRMS.

In conclusion, our study demonstrates similar odds of discontinuation for FTY compared to NTZ, and increased odds of discontinuation for DMF compared to NTZ over 2 years. Discontinuations for FTY and particularly DMF appear to be driven by AEs, while JCV-positive status resulted in a majority of the NTZ discontinuations. Our results showed improved effectiveness outcomes for NTZ compared to FTY and DMF in clinical practice. The inclusion of MRI data may be necessary to adequately assess differences in effectiveness in highly effective DMTs.

Author Contributions

B. L. Vollmer drafted and revised the manuscript, and contributed to the study design, acquisition, and interpretation of the data. K. V. Nair and E. Alvarez contributed to the study concept and design, data interpretation, and revision of the manuscript. S. Sillau contributed to the analysis and interpretation of the data. J. R. Corboy and T. Vollmer contributed to the study concept and revision of the manuscript.
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Conflicts of Interest

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Additional analyses including Cohen's D plots, individual effectiveness outcomes, subgroup analyses and time to event analyses.
Figure S2. Comparison of dose distributions calculated on planning CT (left) and repeat CT (right).
Figure S3. Unadjusted effectiveness outcomes occurring between 6 and 24 months for natalizumab (NTZ), fingolimod (FTY), and dimethyl fumarate (DMF)
Table S1. Individual effectiveness outcomes for entire cohort.
Table S2.Baseline characteristics for relapsing-remitting multiple sclerosis cohort.
Table S3. Unadjusted and adjusted odds ratios for FTY vs NTZ for discontinuation due to any reason at ≤24 months, discontinuation due to adverse events only and disease activity for RRMS cohort.
Table S4. Unadjusted and adjusted odds ratio for DMF vs NTZ for discontinuation due to any reason at ≤24 months, discontinuation due to adverse events only and disease activity for RRMS cohort.
Table S5. Effectiveness outcomes for events between 6 and 24 months for treatment.
Table S6. Individual effectiveness outcomes occurring between 6 and 24 month.
Table S7. Time to event analyses for composite disease measure.

