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Effect of tobacco use on disease activity and DMT discontinuation in multiple sclerosis patients treated with dimethyl fumarate or fingolimod

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Abstract

Background: Tobacco exposure is a modifiable risk factor for multiple sclerosis (MS). Studies evaluating the relationship between tobacco, disease activity, and disease modifying therapy (DMT) persistence yielded conflicting results. We sought to address this issue with data from clinical practice.

Objective: To compare 24-month disease outcomes in tobacco versus non-tobacco users treated with dimethyl fumarate (DMF) or fingolimod (FTY) in clinical practice.

Methods: We retrospectively identified 659 MS patients treated with DMF or FTY, stratified by patient-reported tobacco use. DMT discontinuation and measures of disease activity at 24 months were assessed using propensity score (PS) weighting. Outcome estimates were calculated as tobacco vs non-tobacco use.

Results: 164 tobacco users (DMF n = 101; FTY n = 63) and 495 non-tobacco users (DMF n = 294; FTY n = 201) were identified. Tobacco (39.4%) and non-tobacco (34.4%) users were equally likely to discontinue DMT (OR = 1.17, 95% CI 0.79, 1.75), but tobacco users discontinued therapy earlier (HR = 1.53, 95% CI 1.06, 2.43). There were no differences in ARR (rate ratio = 1.39, 95% CI 0.97, 1.96). However, tobacco users had decreased odds of NEDA-2 (OR = 0.61, 95% CI 0.44, 0.83).

Conclusion: Our findings suggest that tobacco is a negative risk factor for inflammatory disease activity and earlier DMF and FTY discontinuation.

Keywords: Tobacco, dimethyl fumarate, fingolimod, comparative effectiveness, discontinuation, multiple sclerosis

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Introduction

Growing scientific evidence has identified numerous, modifiable environmental risk factors for multiple sclerosis (MS), including low vitamin D levels, certain viruses such as Epstein-Barr virus, and importantly, tobacco use. At least 98 chemicals in tobacco have an established health risk. In addition to carcinogenic effects, many of these chemicals affect the immune system.[1] Epidemiological studies since the mid-twentieth century demonstrated tobacco use as a key environmental risk factor for MS with a dose-dependent increased susceptibility.[2] There is also mounting evidence that tobacco use increases the risk of conversion from clinically isolated syndrome to MS and similarly conversion from relapsing-remitting to secondary progressive MS.[3–5]

Numerous studies demonstrated that tobacco exposure is a risk factor for early disability.[6–10] However, studies evaluating the relationship between tobacco, MS disease activity, and disease modifying therapy (DMT) persistence have yielded conflicting results. In our clinical experience, we recognized a potentially higher rate of relapses among tobacco users, specifically individuals on oral DMTs, dimethyl

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fumarate (DMF) and fingolimod (FTY). We sought to clarify this relationship using real-world data in a population of MS patients treated with either DMF or FTY. Our objective was to compare markers of inflammatory disease such as annualized relapse rates (ARR) and MRI activity via new T2 and/or gadolinium-enhancing (GdE) lesions; and determine if there is higher propensity for DMF/FTY discontinuation in tobacco vs. non-tobacco users. We hypothesized DMF- and FTY-treated tobacco users would be at higher risk of breakthrough disease.

Materials and methods

Patient population

We previously conducted a retrospective observational cohort study of patients with MS at the Cleveland Clinic Mellen Center who were either treated with DMF or FTY.[11] In the current study, this population was stratified by patient-reported tobacco use to explore the effects of tobacco on disease outcomes. We included all patients who started FTY between October 2010 and August 2011 who had 24-month follow-up data available. All patients starting DMF between March and July 2013 with 24-month follow-up were included to ensure a sample size similar to that of FTY. Tobacco status- defined as cigarette and/or cigar use (there were no reported pipe users)- was patient-reported and entered into the electronic medical record (EMR) at the index visit of DMF/FTY initiation. A tobacco user at baseline was considered a tobacco user for the duration of the study and the same for non-tobacco users. Longitudinal data on tobacco users who quit during the study were unavailable for the current analysis. Former tobacco users (3.8%) were classified as "non-tobacco users" at the time of study inclusion to simplify comparisons. Reliable quantitative tobacco data (e.g. "pack-years") were unavailable.

Data collection

Following institutional review board approval, all patients prescribed DMF or FTY during the study period were identified and stratified by patient-reported tobacco use. Similar to a previous study, the EMR was reviewed to collect baseline and outcome data 24 months after treatment exposure.[11] We collected baseline covariates from the EMR in the 12 months prior to DMT start, which were reviewed and approved by an MS specialist.

Clinical, radiographic, and patient reported outcome (PRO) measures were collected from the EMR. Post-baseline follow-up assessments (e.g. visit/MRI frequency and protocols) were comparable between groups. Comorbidities were assessed as a composite measure of diabetes mellitus (DM II), hypertension (HTN), and/or hyperlipidemia. Clinical relapses, defined as new or worsening MS symptoms lasting greater than 24 hours without co-existent infection or fever, were reported by treating clinicians. Relapses were captured from either telephone or office visit encounters in the EMR. The timed 25-foot walk (T25FW) and 9-hole peg test (9-HPT) were assessed as part of routine clinical practice. Number of new T2 lesions and semi-quantitative assessment of overall lesion burden (defined as mild, <10 lesions; moderate, 10-20 lesions; or severe, >20 lesions) were manually determined by the author (CH) and interpreting neuroradiologist. MRI data collected by 24 months were comprised of MRIs completed at both 12- and 24-month time points, reflective of routine Cleveland Clinic practice. MRIs were compared to the immediate preceding scan. MRIs completed within 3 months of the pre-specified time frames were included for analysis. Since this investigation was a real-world, retrospective observational study, patients performed their routine MRIs on different commercial scanners- both 1.5 T and 3.0 T magnet strength- at the Cleveland Clinic and outside of the institution. Therefore, uniform MRI parameters were neither available nor a requirement. PRO measures including Patient Health Questionnaire-9 (PHQ-9),[12] Performance Scales (MSPS),[13] and European Quality of Life-5 Dimensions (EQ5D)[14] were collected.

Statistical analysis

Data were analyzed using R version 3.5.0©. Descriptive statistics (categorical data: number/% of patients meeting pre-specified endpoints; continuous data: mean, median, standard deviation) were calculated for baseline and 24-month endpoints. Propensity score (PS) analysis was used to reduce indication bias by balancing covariate distributions between tobacco and non-tobacco users. Covariates determined to affect treatment decisions were included in the PS-weighted model. We used the same approach to account for missingness as in a previous study.[11] Covariates with missingness $>10\%$ were excluded.

Outcome analyses were conducted for the entire cohort, comparing all tobacco users vs. all non-tobacco users. An interaction term, "DMF/FTY*Tobacco" was included in the PS-weighted model to determine if either DMT drove the observed endpoints. As a sensitivity analysis, separate subgroup

comparisons of tobacco users vs. non-tobacco users stratified by DMT, were also conducted to identify any treatment effect differences amongst DMF- and FTY-treated patients. A sensitivity analysis investigating the RRMS subgroup was also completed.

Analyses were conducted "on-treatment." The primary outcome was the ARR ratio (tobacco vs. non-tobacco use). Secondary outcomes included: time to first relapse; time to discontinuation; proportion of patients with new T2 lesions and/or GdE lesions; proportion discontinuing therapy, also stratified by discontinuation due to intolerance and disease activity; and proportion with 20% worsening on the T25FW or 9-HPT.[15] We also evaluated the proportion of patients with no evidence of disease activity (NEDA-2), defined as absence of clinical relapses and brain MRI activity (composite measure of new T2 and/or GdE lesions).

The PS, defined as propensity for tobacco use at DMF/FTY initiation, was built as a logistic regression model, using *a priori* demographics and baseline disease characteristics (Table 1). A PS was derived for each patient and subsequently used in Average Treatment effect on the Treated (ATT) weighting to identify otherwise similar samples of tobacco and non-tobacco users (PS model point estimates are summarized in Supplementary Table 1). This approach reduced indication bias while retaining information from all patients. We selected the weighting approach on the basis of excellent covariate balance (defined as standardized difference $<10\%$ between groups). Before and after PS-weighting, groups were compared, respectively, using simple and conditional logistic regression to obtain odds ratio (OR) estimates for binary outcomes, linear regression to obtain difference estimates for continuous outcomes, and survival analysis to obtain estimates for time-to-event outcomes at 24 month follow-up. On-treatment ARRs were analyzed using Poisson regression. Unadjusted and PS-weighted outcomes were compared. ORs and hazard ratios (HRs) were calculated as tobacco vs. non-tobacco users. Assuming 80% power with a total sample size = 659 patients, the minimum detectable effect size (MDES) was 0.28. ARR ratio was based on a two-tailed test of statistical significance with $\alpha = 0.05$.

Results

Baseline characteristics

A total of 164 tobacco users (DMF = 101; FTY = 63) and 495 non-tobacco users (DMF = 294, FTY = 201) were available for 24-month follow-up (Figure 1). Baseline demographic and disease characteristics are presented in Table 1. Tobacco users were younger (mean age, tobacco users: 44.4 years; non-tobacco users: 46.2 years) with a lower proportion of women (tobacco users: 60.6%; non-tobacco users: 73.9%). Tobacco users were also more likely to be depressed with poorer overall perception of MS health and quality of life compared to non-tobacco users at baseline.

Propensity score model

The covariates listed in Table 1 were incorporated into the PS-weighted model. Missing data did not meaningfully change covariate balance following PS-weighting. The model demonstrated suitable overlap of the linear PS between the tobacco and non-tobacco groups (Supplementary Figure 1). Before ATT weighting, the groups were unbalanced with a 68.4% standardized difference of the linear PS, substantially over the 50% standard.[16] We, therefore, favored utilizing PS-weighting to account for observed indication bias prior to calculating treatment effect differences. PS-weighting provided effective balancing with no covariates having absolute standardized differences $\geq 10\%$ (Supplementary Figures 2 to 5). PS-weighting also yielded a favorable linear PS distribution with a standardized difference of 0.4%.

Outcome estimates for the entire cohort

Unadjusted and PS-weighted outcome estimates are presented in Tables 2 and 3.

By 24 months, 21.8% of tobacco users and 15.9% of non-tobacco users experienced a clinical relapse. Tobacco users experienced 36 relapses over 330 patient-years of treatment with ARR = 0.11 (95% CI 0.25, 0.41). Non-tobacco users experienced 78 relapses over 988 patient-years of treatment with ARR = 0.08 (95% CI 0.23, 0.39). After PS-weighting, there was no significant difference in ARR (rate ratio = 1.39, 95% CI 0.97, 1.96; p = 0.061). Median time to first relapse was 8.5 months for tobacco users vs. 9.7 months for non-tobacco users, but this difference was not significant (HR = 1.37, 95% CI 0.78, 2.42; p = 0.271). Clinical disability measures were comparable between tobacco and non-tobacco users after PS-weighting (Table 3).

By the end of 24 months, 65 tobacco users discontinued oral DMT (39.4%), and 170 non-tobacco uses discontinued treatment (34.4%), mostly driven by

Table 1. Baseline characteristics of DMF- and FTY-treated patients stratified by tobacco use.[a]

	Tobacco use n = 165		No tobacco use n = 494	
	n or mean	% or SD	n or mean	% or SD
Age (years, SD)	44.35	9.6	46.22	10.6
Female	100	60.6%	365	73.9%
Race				
White	151	91.5%	425	86.0%
Black	9	5.5%	53	10.7%
Other	5	3.0%	16	3.2%
Comorbidities[b]	55	33.3%	124	25.1%
Disease duration (years, SD)	14.3	8.1	15.5	8.8
Relapsing-remitting MS	129	78.2%	379	76.7%
Prior relapse	109	65.0%	295	59.4%
DMT used as first-line agent	15	6.2%	36	6.5%
Direct switch from prior DMT	147	89.1%	435	88.1%
Reason for switch from prior DMT				
Clinical relapse	21	13.1%	81	16.5%
MRI activity	18	11.2%	64	13.1%
Disability progression	28	17.5%	114	23.3%
Intolerance	76	46.1%	234	47.4%
Cost/insurance coverage	6	3.8%	14	2.9%
Last therapy prior to DMF or FTY				
Interferon-beta	47	28.4%	159	32.2%
Glatiramer acetate	48	29.0%	153	31.0%
Natalizumab	28	17.0%	62	12.6%
Immunosuppression[c]	20	12.1%	56	11.3%
None[d]	22	13.3%	64	13.0%
# Prior DMTs (mean, SD)	2.2	1.2	2.0	1.9
Interferon-beta	114	70.8%	349	71.2%
Glatiramer acetate	82	50.9%	259	52.9%
Natalizumab	40	24.8%	101	20.6%
Immunosuppression[c]	31	19.3%	97	19.8%
Laboratory values				
Mean WBC (x 10^9/L)	8.1	3.1	6.9	2.8
Mean ALC (x 10^9/L)	2.3	1.0	2.9	17.8
MRI available for review	164	99.4%	481	97.4%
Disease burden on MRI[e]				
Mild	68	41.5%	229	47.6%
Moderate	80	48.8%	205	42.6%
Severe	16	9.8%	47	9.8%
GdE lesions on MRI	35	21.5%	112	23.4%
New T2 Lesions on MRI	35	21.5%	119	24.9%
Objective measures				
T25FW (sec, SD)	8.1	12.7	7.6	7.5
Ambulation assistance				
None	128	84.2%	370	79.1%
Unilateral	11	7.2%	43	9.2%
Bilateral	13	8.6%	54	11.5%
9 HPT (sec, SD)	27.8	15.0	25.5	12.4

(continued)

Table 1. Continued.

	Tobacco use n = 165		No tobacco use n = 494	
	n or mean	% or SD	n or mean	% or SD
Patient reported outcomes				
MSPS score (mean, SD)	13.3	8.0	11.0	7.2
EQ5D score (mean, SD)	666.7	215.6	744.5	190.0
PHQ-9 score (mean, SD)	8.6	6.6	6.1	5.3

[a]Baseline data collected from the EMR in the 12 months prior to treatment exposure.
[b]Comorbidities = composite measure of diabetes mellitus (DM II), HTN, and/or hyperlipidemia (patients were included if they had at least 1 of the 3 comorbidities).
[c]Immunosuppression = mycophenolate mofetil, azathioprine, monthly IVIG/IVMP.
[d]None = no prior DMT or remote switch (defined as last DMT > 3 months prior to DMF or FTY).
[e]MRI [T2-weighted] lesion burden defined as: Mild, <10 lesions; Moderate, 10–20 lesions; Severe, >20 lesions.
9-HPT: 9-hole peg test; ALC: absolute lymphocyte cell; DMF: dimethyl fumarate; DMT: disease modifying therapy; GdE: gad-enhancing lesions; EQ5D: European Quality of Life 5 Dimensions; FTY: fingolimod; MSPS: Multiple Sclerosis Performance Scale; PHQ-9, Patient Health Questionnaire-9; SD: standard deviation; T25FW: timed 25' walk; WBC: white blood cell.

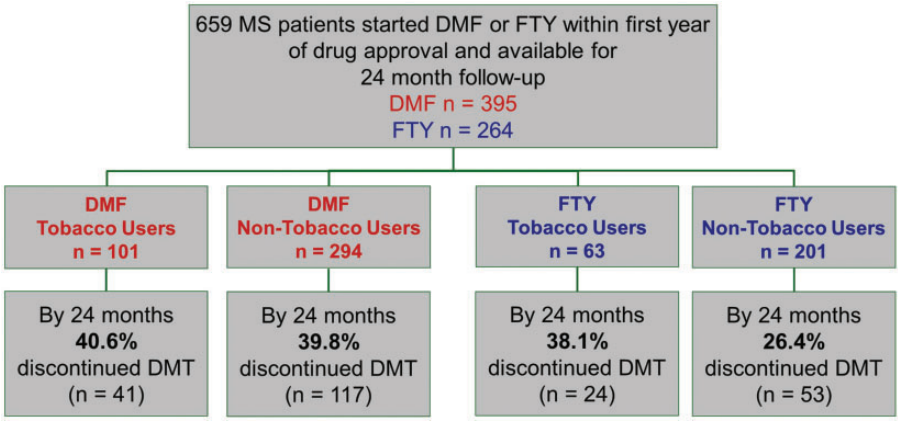

Figure 1. Study flow diagram summarizing the breakdown of DMF- (n = 395) and FTY-treated patients (n = 264) in our cohort, stratified by tobacco use (DMF n = 101; FTY n = 63). Discontinuation was sizeable among tobacco and non-tobacco cohorts.

intolerance (tobacco users = 25.7%; non-tobacco users = 26.1%). There was no significant difference in the proportion of patients who discontinued either DMT (OR = 1.17, 95% CI 0.79, 1.75; p = 0.405), nor were there significant differences in the proportion discontinuing due to intolerance or breakthrough disease activity. However, tobacco users discontinued DMF/FTY earlier (3.8 months) than non-tobacco users (5.3 months) (HR = 1.53, 95% CI 1.06, 2.43; p = 0.045) (Figure 2).

Among patients undergoing brain MRI while on DMT by 24-month follow-up, which included available MRI data between 0-12 months and 12-24 months (tobacco n = 116; non-tobacco n = 386), 28.4% of tobacco users demonstrated MRI activity (25.0% new T2 lesions), compared to 21.7% of non-tobacco users (16.8% new T2 lesions), but this difference was not significant (p = 0.275). A sensitivity analysis comparing only patients with incomplete MRI data (e.g. lack of MRI data between 0-12 months or 12-24 months; tobacco n = 48; non-tobacco n = 109) showed similar findings (data not shown). Cumulatively, there was equivalent risk of new GdE lesions between tobacco and non-tobacco users (OR = 1.34, 95%

Table 2. Summary of pooled unadjusted outcomes for tobacco vs. no tobacco use by 24 months.

	Tobacco use n = 164		No tobacco use n = 495	
	n or mean	% or SD	n or mean	% or SD
Discontinued drug by 24 months	65	39.4%	170	34.4%
Disease activity	22	13.7%	41	8.3%
Intolerance/adverse effects	43	25.7%	129	26.1%
Median time to discontinuation (months, SD)	3.8	4.0	5.3	4.1
Clinical relapse by 24 months	36	21.8%	78	15.9%
Relapses per patient (mean, SD)	0.22	0.4	0.17	0.4
Median time to first relapse (months, SD)	8.5	4.5	9.7	4.1
MRI available for review by 24 months on DMT	116	70.7%	386	77.9%
Disease activity on MRI by 24 months on DMT	33	28.4%	84	21.7%
Gadolinium enhancement	13	13.0%	47	12.1%
New T2 lesions	29	25.0%	65	16.8%
Adverse effects (number of patients)				
Mean WBC (x 10^9/L)	6.6	2.7	5.5	2.4
Mean ALC (x 10^9/L)	1.4	0.9	1.1	0.7
Measures of neurologic disability at 24 months				
T25FW (mean sec, SD)	7.9	12.3	7.9	6.4
20% worsening of T25FW	43/139	30.9%	125/428	29.2%
9-HPT (mean, SD)	27.3	20.2	25.7	14.4
20% worsening of 9 HPT- dominant	7/75	9.3%	23/227	10.1%
Absence of disease activity				
NEDA-2[a]	112	54.3%	370	67.9%
Patient reported outcomes – PHQ-9				
PHQ-9 score (mean, SD)	7.9	5.8	5.9	5.4
PHQ-9 score $\geq$ 10	44	31.0%	80	18.7%

[a]NEDA-2 is defined as the absence of clinical relapses and MRI activity (new T2-weighted and/or new GdE lesions) by 24 months.
9-HPT: 9-hole peg test; ALC: absolute lymphocyte cell; PHQ-9: Patient Health Questionnaire-9; NEDA-2: no evidence of disease activity 2; SD: standard deviation; T25FW: timed 25' walk; WBC: white blood cell.

CI 0.80, 2.60; p = 0.111). Tobacco users had significantly lower likelihood of achieving absence of disease activity than non-tobacco users (54.3% vs. 67.9%) (OR = 0.61, 95% CI 0.44, 0.83; p = 0.008). In a sensitivity analysis, there were no significant differences in the RRMS subgroup compared to the overall cohort (Supplementary Tables 2 to 4).

Outcome estimates stratified by DMT use

As a primary analysis to demonstrate if the observed tobacco effects were driven by either DMF or FTY, an interaction term, "DMF/FTY*Tobacco" was included in the PS-weighted model. Since this term was not significant (p = 0.216), it was determined that neither oral DMT was the primary driver of the observed relationships. As a sensitivity analysis, a stratification model by DMT was included to confirm that neither treatment individually influenced the observed tobacco effects. Table 4 shows PS-weighted outcomes for tobacco vs. no tobacco use, stratified by DMT. Individual baseline and unadjusted outcomes of DMF- and FTY-treated patients are summarized in Supplementary Tables 5 to 8.

By 24 months, there were no significant differences in ARR between DMF-treated patients who were tobacco vs. non-tobacco users (OR = 1.08, 95% CI 0.75, 1.54) nor between FTY-treated patients who were tobacco vs. non-tobacco users (OR = 1.12, 95% CI 0.62, 2.04). As summarized in Table 4, there were no differences in time to first relapse, 20% T25FW worsening, 20% 9-HPT worsening, MRI activity, or NEDA-2. However, DMF-treated tobacco users had higher likelihood of DMT discontinuation due to intolerance (OR = 1.46, 95% CI

Table 3. Pooled unadjusted and PS-weighted outcomes for tobacco vs. no tobacco use by 24 months.

	Unadjusted			PS-Weighted		
Study endpoints	Odds or hazards ratio	95% CI	p-value[a]	Odds or hazards ratio	95% CI	p-value[a]
DMT discontinuation	1.24	0.86–1.78	0.261	1.17	0.79–1.75	0.405
Disease activity	1.63	0.94–3.01	0.064	1.31	0.69–2.47	0.412
Intolerance	1.43	0.96–1.79	0.068	1.51	0.95–2.24	0.058
Time to discontinuation	1.31	0.92–1.87	0.139	**1.53**	**1.06–2.43**	**0.045**[a]
Relapse (ARR)	1.38	0.97–1.96	0.071	1.39	0.97–1.96	0.061
Time to first relapse	1.48	0.94–2.34	0.087	1.37	0.78–2.42	0.271
T25FW 20% worsening	1.09	0.72–1.65	0.337	1.08	0.69–1.70	0.817
9–HPT 20% worsening	0.92	0.38–2.23	0.147	0.69	0.27–1.75	0.472
MRI activity by 24 months	1.43	0.90–2.30	0.087	1.27	0.76–2.12	0.275
GdE lesions	1.21	0.83–1.75	0.123	1.34	0.80–2.60	0.111
New T2 lesions	**1.65**	**1.00–2.72**	**0.047**[a]	1.62	0.94–2.79	0.072
NEDA-2[a]	**0.56**	**0.43–0.87**	**0.011**[a]	**0.61**	**0.44–0.83**	**0.008**[a]

[a]NEDA-2 is defined as the absence of clinical relapses and MRI activity (new T2-weighted and/or new GdE lesions) by 24 months.
Unadjusted analysis used simple logistic regression. PS-weighted methods used conditional logistic regression after average treatment effect on the treated (ATT) weighting for propensity scores.
Statistical significance considered $p < 0.05$.
9-HPT: 9-hole peg test; ARR: annualized relapse rate; DMT: disease modifying therapy; GdE: gad-enhancing lesions; NEDA-2: no evidence of disease activity 2; PS: propensity score; T25FW: timed 25' walk.

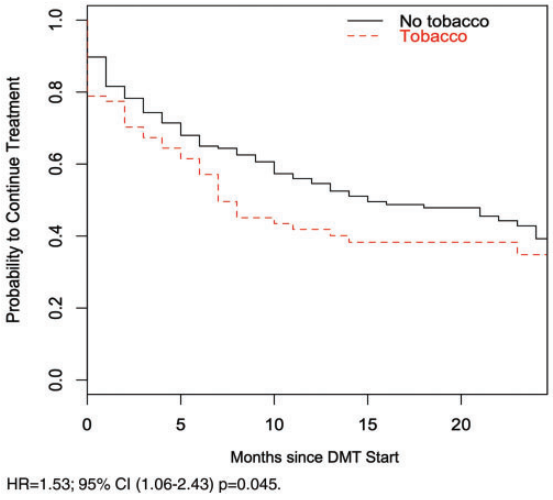

Figure 2. Kaplan-Meier survival plot demonstrating that tobacco users discontinued oral DMTs earlier compared to non-tobacco users ($p = 0.045$) by 24-month follow-up.

1.15, 2.74). Following PS-weighting, there were no differences in the odds of overall FTY discontinuation between tobacco vs. non-tobacco users (OR = 0.88, 95% CI 0.43, 1.32) nor due to disease activity (OR = 1.00, 95% CI 0.50, 2.27) or intolerance (OR = 0.98, 95% CI 0.53, 1.64).

Discussion

While tobacco has been linked to an increased risk of MS, data are conflicting on the relationship between tobacco exposure, MS inflammatory activity, and disease progression. For example, a prospective cohort study by Kvistad et al. reported no influence of tobacco exposure, as measured by cotinine levels, on relapses or MRI activity (OR = 0.81; 95% CI 0.43–1.53; $p = 0.51$).[17] With respect to disability progression, a large UK cohort study of 895 patients demonstrated that the risk of reaching an Expanded Disability Status Scale (EDSS) score of 4.0 or 6.0 in ever-smokers (RR = 1.34, 95% CI 1.12, 1.60) was higher compared to never-smokers (RR = 1.25, 95% CI 1.02, 1.51). Further, ever-smokers had higher MS disease severity scores (RR = 0.68, 95% CI 0.36, 1.01).[9] Similarly, a cross-sectional study of 1372 patients found an association between smoking and increased risk of reaching EDSS 6.0,[18] and a large cross-sectional study of patients who smoked at the time of MS diagnosis (n = 728) demonstrated an accelerated time to transitioning to secondary progressive MS with each additional year of smoking (acceleration factor = 1.047, 95% CI 1.023, 1.072; $p < 0.001$).[5] However, a prospective, longitudinal study did not

Table 4. Outcomes for tobacco vs. no tobacco use by 24 months stratified by DMT.

	DMF Tobacco (n = 101) vs. No Tobacco (n = 294)		FTY Tobacco (n = 63) vs. No Tobacco (n = 201)	
PS-weighted study endpoints	Odds or hazards ratio	95% CI	Odds or hazards ratio	95% CI
DMT discontinuation	1.36	0.88–2.10	0.88	0.43–1.32
Disease activity	0.63	0.33–1.19	1.00	0.50–2.27
Intolerance	**1.46**	**1.15–2.74**	0.98	0.53–1.64
Time to discontinuation	1.19	0.96–1.46	1.49	0.94–2.35
Relapse (ARR)	1.08	0.75–1.54	1.12	0.62–2.04
Time to first relapse	1.43	0.98–2.09	1.44	0.81–2.54
T25FW 20% worsening	1.27	0.65–2.50	1.24	0.54–2.87
9–HPT 20% worsening	1.71	0.54–5.42	1.19	0.72–4.30
MRI activity by 24 months	1.26	0.51–1.48	1.64	0.62–4.33
GdE lesions	1.44	0.80–2.60	1.39	0.32–5.96
New T2 lesions	1.00	0.56–1.79	2.15	0.89–5.16
NEDA–2[a]	0.97	0.62–1.07	0.72	0.60–3.18

9-HPT: 9-hole peg test; ARR: annualized relapse rate; DMT: disease modifying therapy; GdE: gad-enhancing lesions; NEDA-2: no evidence of disease activity 2; PS: propensity score; T25FW: timed 25' walk.
[a]NEDA-2 is defined as the absence of clinical relapses and MRI activity (new T2-weighted and/or new GdE lesions) by 24 months.
Unadjusted analysis used simple logistic regression. PS-weighted methods used conditional logistic regression after average treatment effect on the treated (ATT) weighting for propensity scores.

observe any association between tobacco use and MS disease activity or progression over a 5-year period.[19]

To better understand the role of tobacco use on various MS outcomes, we conducted a retrospective observational study investigating the effects of tobacco vs. no tobacco use on disease activity and DMT discontinuation in an early population of DMF- and FTY-treated patients. We selected this population based on previous experience suggesting tobacco users are more prone to inflammatory disease and earlier DMT discontinuation. We chose to address this important knowledge gap to better inform decision-making in clinical practice because DMF and FTY remain the most commonly prescribed oral DMTs for relapsing MS to date and have potential safety risks, especially among tobacco users. Specifically, tobacco use among FTY-treated patients has been discouraged due to potential respiratory and cardiovascular risks. In our study, tobacco users: 1) were more likely to experience disease activity, 2) demonstrated non-statistically significant tendencies towards higher ARR and MRI disease activity, for which disease activity endpoints were not driven by either DMT alone, 3) showed no significant differences in disability outcomes, and 4) discontinued DMF/FTY earlier than non-tobacco users.

Similar to other reports,[17] our study demonstrated that individual relapse and MRI activity outcome measures were not significantly different between tobacco and non-tobacco users, though they appeared to favor the latter cohort. Although the current study nullified our initial hypothesis of increased relapse rates among DMF/FTY-treated tobacco vs. non-tobacco users, we demonstrated that tobacco users in both the entire cohort and RRMS subgroup were at increased risk of overall disease activity, as evaluated by a composite measure of NEDA-2 (defined as freedom from clinical relapses and new MRI activity). This finding could at least partly be explained by the relative restrictive nature of the NEDA-2 definition, for which significantly fewer tobacco users met this criterion compared to non-tobacco users. These results perhaps underscore a pathophysiological mechanism in

which the pro-inflammatory effects of tobacco increase MS disease activity. Similar to Munger et al.,[19] we did not appreciate significant differences in disability progression, possibly obscured by a relatively shorter follow-up period.

As previously demonstrated,[11]DMF-treated patients had a higher likelihood of earlier DMT discontinuation, primarily driven by intolerance, compared to FTY-treated patients by 24 months. However, there are limited published data reporting the effects of tobacco use on DMT persistence. In our study, tobacco users in the overall cohort had a higher hazard for earlier discontinuation. In a sensitivity analysis, this relationship was primarily driven by DMF-treated tobacco users who discontinued treatment due to AEs. One possibility is that a synergistic effect of tobacco use and eosinophilia yields a higher proclivity for DMF intolerance, for which a previous study showed a negative predictive value of eosinophilia on DMF persistence.[20] Although eosinophil counts were unavailable in our retrospective study, DMF-treated tobacco users had higher WBC counts than non-tobacco users, a biological marker of inflammation. In contrast, a prospective study evaluating gastrointestinal tolerability of DMF ($n = 233$) found no differences in AE severity between tobacco and non-tobacco users. Interestingly, a recent study demonstrated that smoking was associated with an 80% increased hazard of natalizumab cessation due to intolerance ($HR = 1.80$, 95% CI 1.17, 2.78; $p = 0.008$).[21] Additional reports on other DMTs also suggest an increased risk of relapses among smokers treated with natalizumab.[22] Further, data showed increased neutralizing antibodies among smokers treated with interferon-beta and natalizumab,[23] which may negatively affect DMT tolerance and effectiveness. These findings suggest a putative mechanism for increased DMT intolerance across a wide spectrum of therapies in tobacco users, which deserves further examination. Ultimately, if tobacco use decreases tolerance across immunomodulatory and newer immunosuppressive treatments, this could partially explain increased disease activity and disability progression in tobacco users with MS.

In a PS-weighted sensitivity analysis, we did not observe any significant relationships in terms of inflammatory disease activity nor discontinuation rates as they applied to FTY-treated patients alone. The small sample size of FTY-treated tobacco users in our study- likely driven by early skepticism about S1P modulator safety in smokers - may have influenced these non-significant treatment effects. Perhaps tobacco users who started FTY in our cohort had fewer pack-years, thereby nullifying any significant tendencies compared to non-tobacco users.

Despite the use of PS-weighting to minimize the effects of confounding by indication, there are several limitations of the current study that deserve consideration. First, PS-weighting can only mitigate measured biases. To this point, we believe we included a comprehensive list of baseline covariates in the PS-weighted model to minimize hidden bias. Further, a sensitivity analysis exploring RRMS patients and individual effects of tobacco use on patients treated with DMF and FTY complemented our primary conclusions that tobacco leads to higher inflammatory disease and earlier DMF/FTY discontinuation. The authors also recognize that the primary analysis in this study may be underpowered. To this effect, a larger, multi-center study investigating the effects of tobacco use on DMF and FTY-treated patients should be conducted to confirm the current findings. Other limitations include missing data (e.g. MRI, PROs), which is an inherent shortcoming of retrospective observational studies, and potential recall/reporting bias of clinical relapses. To the latter point, frequent follow-up visits and confirmation by the treating MS clinician should partially mitigate these effects. While there were no significant differences in disability outcomes in our investigation, lack of consistent EDSS measurements and long-term assessments are limitations. Self-reporting of tobacco use, the inability to account for the amount of tobacco used, a simple definition of "yes/no" tobacco status, leaving out "former tobacco users" from the tobacco cohort, and lack of longitudinal tobacco assessments with the assumption of stable tobacco use throughout the duration of the study may have also skewed the results toward non-significant trends. Given the retrospective study design, this investigation was unable to test serum cotinine to confirm tobacco status. Lastly, single-center reporting from a large tertiary referral MS center may reduce external validity.

In conclusion, our findings suggest that tobacco is a negative modifiable risk factor for inflammatory disease activity and DMT persistence in a population of MS patients treated with DMF and FTY. These

data warrant further exploration using a larger, multi-center, heterogeneous population. Further, evaluation of tobacco effects in other DMTs will substantiate appropriate treatment recommendations and tobacco cessation counseling on a more individualized level.

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Supplemental Material

Supplemental material for this article is available online.

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