Effect of smoking on disease activity in multiple sclerosis patients treated with dimethyl fumarate or fingolimod

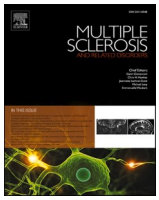
田中, 栄蔵

Multiple Sclerosis and Related Disorders 70 (2023) 104513

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Original article

Effect of smoking on disease activity in multiple sclerosis patients treated with dimethyl fumarate or fingolimod

Eizo Tanaka, Mitsuru Watanabe, Shoko Fukumoto, Katsuhisa Masaki, Ryo Yamasaki, Takuya Matsushita, Noriko Isobe *

Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

ARTICLE INFO

Keywords:
Multiple sclerosis
Oral disease-modifying drug
Fingolimod
Dimethyl fumarate
Smoking
Relapse

ABSTRACT

Background: In relapsing-remitting multiple sclerosis (RRMS), smoking is a known risk factor for disease susceptibility and disability progression. However, its impact on the efficacy of oral disease-modifying drugs (DMDs) is unclear. Therefore, we initiated a single-center, retrospective, observational study to investigate the relationship between smoking and disease activity in RRMS patients under oral DMDs.

Methods: We retrospectively enrolled RRMS patients who initiated oral DMDs (fingolimod or dimethyl fumarate) at our hospital between January 2012 and December 2019. Clinical data and smoking status at oral DMD initiation were collected up to December 2020. We conducted survival analyses for relapse and any disease activity, defined as relapse or MRI disease activity, among patients with distinct smoking statuses.

Results: We enrolled 103 RRMS patients under oral DMDs including 19 (18.4%) current smokers at baseline. Proportions of relapses and any disease activity during follow-up were higher in current smokers (relapse: $p = 0.040$, any disease activity: $p = 0.004$) and time from initiating oral DMDs to relapse was shorter in current smokers (log-rank test: $p = 0.011$; Cox proportional hazard analysis: hazard ratio (HR) 2.72 [95% confidence interval (CI) 1.22–6.09], $p = 0.015$) than in non-smokers. Time from initiating oral DMDs to any disease activity was also shorter in current smokers (log-rank test: $p = 0.016$; Cox proportional hazard analysis: HR 2.18 [95% CI 1.14–4.19], $p = 0.019$) than in non-smokers. The survival curves for relapse and any disease activity were not different between the former smoker and never-smoker groups. Multivariate survival analysis showed current smoking was an independent risk factor for relapse or any disease activity after adjusting for covariates (relapse: HR 2.54 [95% CI 1.06–6.10], $p = 0.037$; any disease activity: HR 3.47 [95% CI 1.27–9.50], $p = 0.015$).

Conclusion: Smoking was a risk factor for disease activity in RRMS patients under oral DMD treatment. RRMS patients should be advised to stop smoking even after the initiation of DMDs.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system. Most MS patients have recurrent attacks without progressive deterioration during remission in the early course of disease, termed relapsing-remitting MS (RRMS); however, some RRMS patients proceed to secondary progressive MS (SPMS), in which neurological disability progresses independently from relapse episodes. Several disease modifying drugs (DMDs) have been developed to suppress relapses and disability progression. Currently, more effective and tolerable oral DMDs, including fingolimod (FTY) and dimethyl fumarate (DMF), complement traditional injectable DMDs, such as interferon-β and glatiramer acetate. MS is a complex disease in which genetic and environmental factors contribute to its onset (Sadovnick et al., 1993). Among these environmental factors, smoking is a widely known risk factor, along with low sun exposure, low vitamin D intake, and Epstein–Barr virus infection (Olsson et al., 2017), but these observations were based mainly on populations of European descent in which

Abbreviations: ARR, annualized relapse rates; CI, confidence intervals; CSF, cerebrospinal fluid; DMD, disease modifying drug; DMF, dimethyl fumarate; EDSS, Kurtzke's expanded disability status scale; FTY, fingolimod; GA, glatiramer acetate; HR, hazard ratio; IFN-β, interferon-beta; IQR, interquartile range; MS, multiple sclerosis; MSSS, multiple sclerosis severity score; NEDA, no evidence of disease activity; NOx, nitrogen oxide; OCBs, oligoclonal IgG bands; PSL, prednisolone; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

* Corresponding author.
E-mail address: isobe.noriko.342@m.kyushu-u.ac.jp (N. Isobe).

https://doi.org/10.1016/j.msard.2023.104513
Received 15 June 2022; Received in revised form 22 November 2022; Accepted 9 January 2023
Available online 10 January 2023

MS is prevalent. Our recent study of environmental factors in Japanese patients with MS showed that smoking or passive smoking was more predominant in MS patients than in healthy controls, and that disability and its progression were more prominent in smokers than in non-smokers (Sakoda et al., 2020). These findings indicate the harmful effects of smoking on MS etiology across populations. Smoking contributes to MS susceptibility as well as SPMS conversion (Hernán et al., 2005; Degelman and Herman, 2017; Barzegar et al., 2021). Some studies suggested that smoking had no effect on disease activity (Kvistad et al., 2016; Messina et al., 2021), but whether smoking is a risk for relapse in patients with RRMS, especially when patients are treated with non-injectable DMDs, is controversial. Only one study has reported the impact of smoking on the effectiveness of oral DMDs (FTY or DMF). They showed that the proportions of patients with no clinical relapse and MRI activity were lower in smokers than in non-smokers, and that smokers discontinued DMD earlier because of disease activity and intolerance. There was no difference in the annualized relapse rates between the two groups (Hersh et al., 2020). However, this study was based on a cohort composed mainly of Caucasians and there is no data related to the impact of smoking on disease activity in Asians, including Japanese, especially when treated with oral DMDs. Therefore, we conducted a single-center, retrospective, observational study to investigate whether smoking affected the disease-modifying efficacy of oral DMDs in Japanese MS patients.

2. Materials and methods

2.1. Patient population

This single-center, retrospective, observational study consecutively enrolled all patients with RRMS who were initiated with FTY or DMF at Kyushu University Hospital between January 2012 and December 2019. All enrolled patients were retrospectively confirmed to fulfill the 2017 McDonald criteria (Thompson et al., 2018) and were thoroughly examined and regularly followed-up at Kyushu University Hospital. The study protocol was approved by the ethics committee of Kyushu University.

2.2. Data collection

Clinical information, laboratory data, and MRI findings were collected from the medical records of our hospital. Collected information and data at the time of initiating FTY or DMF (defined as baseline) included smoking status, age at examination, age at onset, sex, Kurtzke's Expanded Disability Status Scale (EDSS) (Kurtzke, 1983), Multiple Sclerosis Severity Score (MSSS) (Roxburgh et al., 2005), oligoclonal IgG bands (OCB), and IgG index. Annualized relapse rates (ARR) under the previous treatment status during 2 years prior to baseline were also calculated. If the disease duration at baseline or the duration under prior DMD status was less than 2 years, the maximum period in those situations was applied. The endpoints of this study were clinical relapse, and any disease activity confirmed as clinical relapse or MRI disease activity, detected by December 31, 2020. Clinical relapses were defined as novel MS symptoms persisting for more than 24 h that were not caused by infection, fever, or other diseases. MRI disease activity was defined as positive when new T2 lesions or gadolinium-enhanced lesions were observed. We defined any disease activity as relapse or MRI disease activity. We stratified the study participants into two groups, current smokers and non-smokers, on the basis of their smoking status at baseline. Additionally, non-smokers at baseline were further categorized as former or never smokers on the basis of whether they had smoked and quit before the baseline or never smoked at all, respectively. The observation period was defined as the time from oral DMD initiation to the earlier event, either oral DMD termination or the end of December 2020. If patients were administered FTY and DMF during the observation period, observations during FTY treatment were used, because DMD switching from FTY to other DMDs, including DMF, sometimes causes severe relapses termed "rebound"; (Barry et al., 2019) however, most of these cases used FTY prior to DMF because of the order of the timing of drug release.

2.3. Statistical analysis

Categorical variables were described using counts and percentages, and continuous and ordinal variables were demonstrated using median and interquartile ranges (IQRs). To compare baseline demographic data, Fisher's exact probability test was performed for categorical variables and the Mann–Whitney *U test* for continuous variables. Kaplan–Meier curves were generated for time from baseline to clinical relapse or any disease activity. Log-rank tests and Cox proportional hazard analyses were performed to evaluate the risk of smoking on relapse or any disease activity. Hazard ratio (HR) and 95% confidence intervals (CI) were also calculated. In multivariate analysis, sex, age of onset, disease duration, EDSS score at baseline, ARR during the prior treatment status up to 2 years before baseline, and DMD type (FTY or DMF) were included as covariates. Multivariate analyses included the interaction between smoking status and DMD type toward endpoints to assess the impact of DMD type on the effect of smoking. All analyses were performed using JMP Pro 15.1.0 software (SAS Institute, Cary, NC, USA). The significance level was set at $p < 0.05$.

3. Results

3.1. Baseline characteristics

We enrolled 103 patients with RRMS who were initiated with FTY or DMF between January 2012 and December 2019. Of these, 19 patients (18.4%) were current smokers at baseline. Smoking status during the observation period was available for all the current smokers, and of these, 15 (78.9%) continued smoking until their endpoint. Out of 84 non-smokers at baseline, 23 were former smokers (smoked before baseline) and 61 were never-smokers. Based on a previous report (Hersh et al., 2020), we estimated the statistical power of the sample size in our cohort. It had 80% power with a total sample size of 650, and approximately 30% power with the sample size of our cohort, which allowed us to detect a difference between the groups if the HR exceeded 1.8. Baseline demographic data are shown in Table 1. Current smokers had a smaller proportion of females than males compared with non-smokers (52.6% vs 83.3%, $p = 0.012$), but other clinical and laboratory data were similar between the two groups. There was no significant difference in the proportion of DMD type between the two groups ($p = 0.786$). In the non-smoker group, never-smokers had a younger age at onset (24.0 [19.0–33.0] years vs 31.0 [24.0–34.0] years, $p = 0.010$) and lower EDSS score (1.5 [1.0–2.0] vs 2.0 [1.5–3.0], $p = 0.021$) than former smokers. Never-smokers were more likely to be female (90.2% vs 65.2%, $p = 0.017$), OCB positive (78.6% vs 50.0%, $p = 0.025$), and treated with FTY (75.4% vs 43.5%, $p = 0.009$) compared with former smokers. When never-smokers were compared with current smokers, the proportion of females was higher in never-smokers than in current smokers (90.2% vs 52.6%, $p = 0.001$).

3.2. Baseline demographic features associated with clinical disease activity

We stratified all participants into two groups based on the presence of relapse or any disease activity during the observation period (Table 2). Clinical relapse was noted for 27 patients (26.2%) and any disease activity was noted for 49 (47.6%) patients. The frequency of current smokers was higher in patients with clinical relapse or any disease activity than in patients in the other groups (33.3% vs 13.2%, $p = 0.04$ and 30.6% vs 7.4%, $p = 0.004$, respectively). Except for the ratio of current smokers at baseline, there was no significant difference in

Table 1
Demographic features of patients with RRMS stratified by distinct smoking status.

	Current smokers ($n = 19$)	Non-smokers ($n = 84$)	p-value	Non-smokers ($n = 84$) Former smokers ($n = 23$)	Never-smokers ($n = 61$)	p-value	p-value Current smokers vs Former smokers	Current smokers vs Never-smokers
Age[a] (years)	35.0 [32.0 – 41.0]	35.0 [29.0 – 45.8]	0.756	38.0 [33.0 – 48.0]	34.0 [27.0 – 45.0]	0.055	0.105	0.760
Female, n (%)	10/19 (52.6)	70/84 (83.3)	0.012	15/23 (65.2)	55/61 (90.2)	0.017	0.531	0.001
Disease duration[a] (years)	4.7 [2.4 – 10.4]	6.7 [2.2 – 14.4]	0.284	6.6 [2.9 – 14.2]	6.8 [1.9 – 14.8]	0.936	0.343	0.320
OCBs positivity, n (%)	11/18 (61.1)	55/78 (70.5)	0.573	11/22 (50.0)	44/56 (78.6)	0.025	0.537	0.213
IgG index[a]	0.73 [0.59 – 0.96]	0.66 [0.54 – 0.98]	0.623	0.60 [0.52 – 0.86]	0.76 [0.56 – 1.05]	0.146	0.174	0.960
EDSS[a]	2.0 [1.0 – 2.5]	1.8 [1.0 – 2.4]	0.641	2.0 [1.5 – 3.0]	1.5 [1.0 – 2.0]	0.021	0.393	0.437
MSSS[a]	2.91 [1.77 – 5.87]	2.44 [0.89 – 4.82]	0.552	3.17 [1.70 – 5.87]	2.29 [0.67 – 4.30]	0.103	0.667	0.322
FTY:DMF (%FTY)	14:5 (73.7)	56:28 (66.7)	0.786	10:13 (43.5)	46:15 (75.4)	0.009	0.065	1.000
Observation period[a] (years)	1.8 [0.8 – 4.7]	2.9 [1.6 – 5.7]	0.222	2.4 [1.6 – 3.6]	3.3 [1.5 – 5.9]	0.192	0.456	0.199
ARR of prior treatment status up to 2 years before oral DMD initiation[a]	1.0 [0.5 – 1.5]	0.5 [0 – 1.5]	0.247	0.5 [0 – 1.7]	0.5 [0 – 1.5]	0.475	0.226	0.323
DMD naïve: usage history (+) (%naive)	10:9 (52.6)	45:39 (53.6)	1.000	12:11 (52.2)	33:28 (54.1)	1.000	1.000	1.000
DMD used just before oral DMD initiation	IFN-β: 7 (75.0%) GA: 1 (12.5%) DMF: 1 (12.5%)	IFN-β: 25 (64.1%) GA: 5 (12.8%) DMF: 3 (7.7%) PSL: 3 (7.7%) Natalizumab: 3 (7.7%)	0.941	IFN-β: 6 (54.5%) GA: 2 (18.2%) DMF: 2 (18.2%) PSL: 1 (9.1%)	IFN-β: 19 (67.9%) GA: 3 (10.7%) DMF: 1 (3.6%) PSL: 2 (7.1%) Natalizumab: 3 (10.7%)	0.456	0.761	0.867

ARR: annualized relapse rate; DMD: disease modifying drug; DMF: dimethyl fumarate; EDSS: Extended Disability Status Scale; FTY: fingolimod; GA: glatiramer acetate; IFN-β: interferon-beta; IQR: interquartile range; MSSS: Multiple Sclerosis Severity Score; OCBs: oligoclonal IgG bands; PSL: prednisolone; RRMS: relapsing-remitting multiple sclerosis.
[a] Median [IQR].

Table 2
Demographic data of patients with RRMS stratified by distinct disease activity.

	Relapsed ($n = 27$)	Relapse-free ($n = 76$)	p-value	Any disease activity[b] ($n = 49$)	No disease activity ($n = 54$)	p-value
Age at onset[a] (years)	29.0 [21.0 – 33.0]	27.5 [22.0 – 34.0]	1.000	29.0 [21.0 – 33.0]	26.5 [21.8 – 34.3]	0.861
Female, n (%)	22/27 (81.5)	58/76 (76.3)	0.789	38/49 (77.6)	42/54 (77.8)	1.000
Disease duration[a] (years)	5.6 [3.1 – 14.4]	6.7 [1.8 – 11.9]	0.967	5.0 [2.7 – 14.1]	7.5 [1.8 – 13.9]	0.304
OCBs positivity, n (%)	20/25 (80.0)	46/71 (64.8)	0.212	33/44 (75.0)	33/52 (63.5)	0.272
IgG index[a]	0.77 [0.56 – 1.25]	0.66 [0.54 – 0.89]	0.183	0.75 [0.57 – 1.17]	0.63 [0.53 – 0.86]	0.066
EDSS[a]	2.0 [1.0 – 3.0]	1.5 [1.0 – 2.0]	0.120	2.0 [1.0 – 3.0]	1.5 [1.0 – 2.0]	0.135
MSSS[a]	2.44 [1.70 – 5.38]	2.50 [0.80 – 4.82]	0.476	2.91 [1.58 – 5.63]	2.39 [0.67 – 4.43]	0.155
FTY:DMF (%FTY)	17:10 (63.0)	53:23 (69.7)	0.632	33:16 (67.4)	37:17 (68.5)	1.000
Current smokers: non-smokers (%smokers)	9:18 (33.3)	10:66 (13.2)	0.040	15:34 (30.6)	4:50 (7.4)	0.004
Current smokers: former smokers: never-smokers (%)	9:3:15 (33.3:11.1:55.6)	10:20:46 (13.2:26.3:60.5)	0.038	15:7:27 (30.6:14.3:55.1)	4:16:34 (7.4:29.6:63.0)	0.005
Observation period[a]	3.3 [1.1 – 5.8]	2.8 [1.3 – 5.4]	0.569	3.0 [1.1 – 4.9]	2.8 [1.6 – 5.9]	0.976
ARR of prior treatment status up to 2 years before oral DMD initiation[a]	0.5 [0 – 2.0]	0.6 [0 – 1.5]	0.828	1.0 [0.5 – 1.9]	0.5 [0 – 1.5]	0.205

ARR: annualized relapse rate; DMF: dimethyl fumarate; EDSS: Extended Disability Status Scale; FTY: fingolimod; IQR: interquartile range; MSSS: Multiple Sclerosis Severity Score; OCBs: oligoclonal IgG bands.
[a] Median [IQR].
[b] Any disease activity: any event of clinical relapse or MRI disease activity.

clinical features according to the two disease activity measurement statuses.

3.3. Effect of smoking on disease activity during DMD treatment in a univariate model

We analyzed whether smoking status affected the disease course of MS patients. Nine (47.4%) out of 19 current smokers and 18 (21.4%) out of 84 non-smokers experienced clinical relapse during the observation period, indicating a higher incidence of clinical relapse in current smokers than in non-smokers ($p = 0.040$). In addition, a higher incidence of any disease activity was observed in current smokers than in non-smokers (15/19 (79.0%) vs 34/84 (40.5%), $p = 0.004$). Relapse-free survival curves using the Kaplan–Meier method demonstrated that time from DMD initiation to relapse was significantly shorter in current smokers than in non-smokers (log-rank test: $p = 0.011$; Cox proportional hazard analysis: HR 2.72 [95% CI 1.22–6.09], $p = 0.015$) (Fig. 1A). Current smoking was also associated with any disease activity (Fig. 1B; log-rank test: $p = 0.016$; Cox proportional hazard analysis: HR 2.18 [1.14–4.19], $p = 0.019$).

Next, we stratified the non-smoker group into former smokers and never-smokers and compared the survival curves among three groups

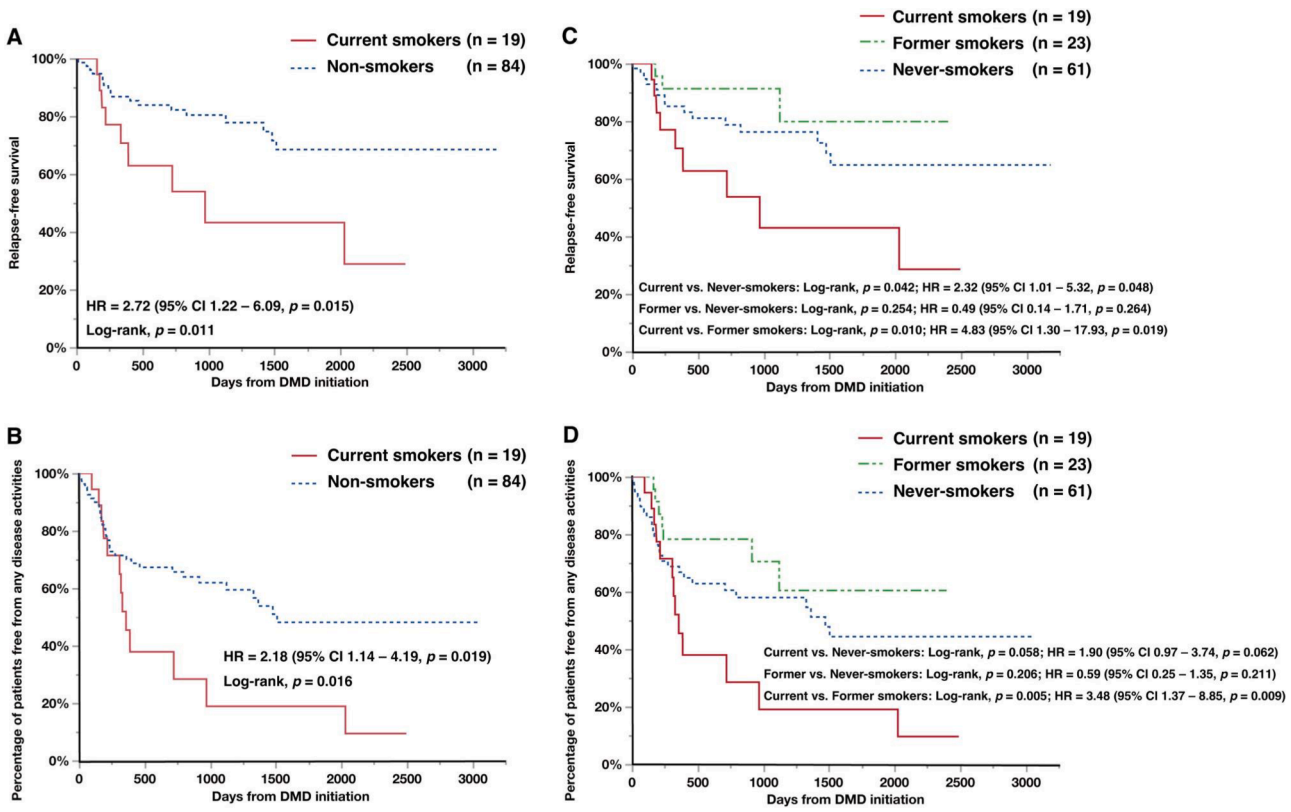


Fig. 1. Comparison of Kaplan–Meier survival curves stratified by smoking status at baseline.
(A, B) Relapse-free survival curves (A) and survival curves for any disease activity (B) between current smokers and non-smokers.
(C, D) Relapse-free survival curves (C) and survival curves for any disease activity (D) among current smokers, former smokers, and never-smokers.
The *p*-values of the log-rank tests and hazard ratios (HRs) and 95% confidence intervals (CIs) of Cox proportional hazard analysis are shown.

including current smokers. The survival curves for relapse were not different between the former smoker and never-smoker groups (log-rank test: $p = 0.254$; Cox proportional hazard analysis: HR 0.49 [0.14–1.71], $p = 0.264$) (Fig. 1C) as well as the curves for any disease activity (log-rank test: $p = 0.206$; Cox proportional hazard analysis: HR 0.59 [0.25–1.35], $p = 0.211$) (Fig. 1D). Notably, the HR for relapse and any disease activity in current smokers versus former smokers (HR 4.83 [1.30–17.93], $p = 0.019$ for relapse; HR 3.48 [1.37–8.85], $p = 0.009$ for any disease activities) was higher than between current smokers and never-smokers (HR 2.32 [1.01–5.32], $p = 0.048$ for relapse; HR 1.90 [0.97–3.74], $p = 0.062$ for any disease activity). When we extended our analysis to the achievement of no evidence of disease activity-3 (Kappos et al., 2016) by adding EDSS progression to the current definition of any disease activity, the patients' classification remained exactly the same and the survival curves and the obtained statistical analysis results were comparable with the results for any disease activity (Supplementary Figure).

3.4. Risk factors of disease activity in a multivariate model

We performed multivariate analysis to identify risk factors related to disease activity. Current smoking was an independent risk factor for clinical relapse in a model adjusted for the ARR under prior treatment status before baseline, sex, EDSS score at baseline, age at disease onset, disease duration, and DMD type (DMF or FTY) against never-smokers and former smokers (current smokers vs never-smokers: HR 2.54 [1.06–6.10], $p = 0.037$; current smokers vs former smokers: HR 8.05 [1.92–33.68], $p = 0.004$). For any disease activity, current smokers demonstrated an independent risk versus former smokers (HR 3.47 [1.27–9.50], $p = 0.015$) (Table 3). Additionally, DMF treatment showed a trend towards an increased rate of clinical relapse compared with FTY (2.30 [0.94–5.65], $p = 0.069$). No interaction with statistical significance was detected between smoking status and DMD type for clinical relapse or any disease activity ($p = 0.596$ and 0.446, respectively).

Table 3
Multivariate analysis for factors contributing to clinical relapse or any disease activity.

	Clinical relapse		Any disease activity[a]	
	HR [95% CI]	*p*-value	HR [95% CI]	*p*-value
Current smokers [vs never-smokers]	2.54 [1.06 – 6.10]	0.037	1.63 [0.79 – 3.39]	0.187
Current smokers [vs former smokers]	8.05 [1.92 – 33.68]	0.004	3.47 [1.27 – 9.50]	0.015
Former smokers [vs never-smokers]	0.32 [0.08 – 1.18]	0.086	0.47 [0.19 – 1.17]	0.104
ARR of prior treatment status up to 2 years before oral DMD initiation	0.94 [0.71 – 1.17]	0.596	1.08 [0.90 – 1.27]	0.385
Female [vs male]	1.36 [0.48 – 3.83]	0.557	1.33 [0.60 – 2.94]	0.478
EDSS	1.21 [0.91 – 1.54]	0.159	1.17 [0.94 – 1.43]	0.131
Age at onset (years)	1.01 [0.96 – 1.05]	0.710	1.00 [0.96 – 1.03]	0.907
Disease duration (years)	0.98 [0.91 – 1.04]	0.455	0.96 [0.92 – 1.01]	0.181
DMF [vs FTY]	2.30 [0.94 – 5.65]	0.069	1.55 [0.78 – 3.07]	0.212

95% CI: 95% confidence interval; ARR: Annualized relapse rate; DMD: disease modifying drug; DMF: dimethyl fumarate; FTY: fingolimod; HR: hazard ratio.
[a]Any disease activity: any event of clinical relapse or MRI disease activity.

4. Discussion

This single center, retrospective, observational study revealed that smoking at oral DMD initiation was associated with clinical relapse or any disease activity, detected as relapse or MRI activity, in patients with RRMS. Multivariate analysis demonstrated that smoking was an independent risk factor for clinical relapse.

Smoking is an environmental risk factor for MS susceptibility (Degelman and Herman, 2017; Handel et al., 2011). Additionally, smoking increases the risk of conversion from a relapsing-remitting to progressive disease course (Hernán et al., 2005; Degelman and Herman, 2017; Barzegar et al., 2021), and smokers progress from RRMS to SPMS earlier compared with non-smokers (Hernán et al., 2005; Healy et al., 2009).

Smoking also modulates the immune system by reducing the numbers of Foxp3-positive regulatory T cells (Correale and Farez, 2015), activating and reprogramming myelin-autoreactive T cells in the lungs (Odoardi et al., 2012), altering innate and adaptive immunity, and increasing the production of proinflammatory cytokines (Qiu et al., 2017). The effect of tobacco smoke on these factors skews the immune balance towards a proinflammatory state and might negatively influence the clinical course of MS by reducing the anti-inflammatory effects of DMDs, as demonstrated in the current study.

A variety of chemicals are contained in tobacco smoke including nitrogen oxide (NOx). Rejdak et al. reported elevated levels of cerebrospinal fluid (CSF) NOx (nitrite and nitrate) in MS patients, and a correlation between CSF NOx levels and disability progression (Rejdak et al., 2004). Serum nitric oxide and glutamate levels were also elevated in RRMS patients during relapse (abdel Naseer et al., 2020). The neuroprotective effect of FTY is partially mediated by inhibiting astrocytic nitric oxide; (Colombo et al., 2014) thus, nitric oxide in tobacco smoke may cancel the beneficial effect of FTY in MS patients who smoke.

When we stratified non-smokers at baseline into former smokers and never-smokers, there was no significant difference in the survival curves of relapse or any disease activity between the two groups, suggesting that smoking history before initiating oral DMDs in former smokers did not affect the subsequent disease course or effect of DMDs. Additionally, most smokers at baseline continued smoking up to the end of the observation period. These results indicate that continued smoking exacerbates the disease course of MS, even after the onset of the disease, but that quitting smoking might reduce the proinflammatory immune status to normal and restore the beneficial effects of DMDs. This is a novel finding because a previous study used current smoking status only and did not estimate the effect of smoking history (Hersh et al., 2020). We also assessed the impact of previous smoking including smoking history information before DMD initiation. Although the small sample size in this study might have resulted in the lack of statistical difference for disease activity observed between former smokers and never-smokers, these results suggest the advantage of smoking cessation on the efficacy of oral DMDs to prevent future disease activity. Therefore, it is recommended to quit smoking, even after the onset of MS.

Our findings were consistent with several previous studies on the association between smoking and the disease-modifying effects of DMDs. Relapses were reported to be more frequent in smokers than non-smokers in patients treated with interferon-β (Petersen et al., 2018) and natalizumab (Petersen et al., 2019). Neutralizing antibodies to DMDs were reported to be more likely to develop in smokers (Sena et al., 2010; AK Hedström et al., 2014; AK Hedström et al., 2014). These reports and our data suggest that smoking might alter the host immune status even after initiating DMDs, which are used to normalize immunological alterations and reduce MS clinical relapses. A previous study of patients treated with DMF or FTY reported that the discontinuation rate related to intolerance was higher in smokers than in non-smokers, and that the proportion of patients who showed no signs of any disease activity was lower in smokers than in non-smokers. However, the time to clinical relapse was comparable between smokers and non-smokers (Hersh et al., 2020). The current study is the first to show that smoking might disturb the effect of FTY or DMF on lowering the risk of clinical relapse. We previously clarified that in a Japanese population, smoking and passive smoking after the age of 16 years were risks for susceptibility to MS, and that smokers had higher EDSS scores and MSSS than non-smokers (Sakoda et al., 2020). Therefore, in accordance with previous studies of MS patients of European descent, smoking is a risk for relapse, even under treatment with DMDs, and for susceptibility to MS, independent of ethnicity. Smoking is ubiquitously hazardous to MS beyond its heterogeneity in clinical features, which are derived from the background differences in genetics and environmental factors (Yoshimura et al., 2012; Piccolo et al., 2015; Ishizu et al., 2009).

Our multivariate analysis revealed no significant interaction between smoking status and oral DMD type on clinical relapses. These findings imply that the unfavorable proinflammatory effects of smoking on the clinical course of MS were not DMD-specific and were not related to the pharmacological mechanisms of DMDs. Our results demonstrate the importance of smoking cessation in all patients with MS in various clinical settings including those under oral DMDs. Furthermore, multivariate analysis showed that smoking was an independent risk factor only for clinical relapse, and that the HR for any disease activity detected as clinical or radiological relapses did not reach statistical significance. We speculate that the effect of oral DMDs might be detectable for the parameters with clinically definite disease activity rather than more subtle or subclinical activity, especially considering the small sample size setting of our study. Intriguingly, the impact of current smoking on disease activity was more prominent in former smokers than never-smokers according to multivariate analysis and survival analysis. This might be explained as follows: even though past smoking might partially contribute to the onset of MS in former smokers, their subsequent disease activity after smoking cessation might be lower than that in never-smokers whose disease susceptibility was derived from factors other than smoking.

There were several limitations in our study. First, this was a single-center, observational study with a small number of patients. It will be necessary to conduct prospective, multicenter studies including a large number of patients to confirm these results. Second, this was a retrospective study, and a prospective interventional study should be initiated to confirm the effect of cessation of smoking on relapses under DMD treatment. Third, we were unable to obtain data on the history of passive smoking, the duration on smoking, and the amount of smoking (e.g., pack years). Therefore, a dose-dependent effect estimation of smoking on disease activity should be determined in the future.

5. Conclusions

We investigated an association between smoking and relapse or any disease activity in Japanese patients with RRMS taking oral DMDs. Smoking at the initiation of oral DMD attenuated the disease-modifying effects of DMDs. Education about smoking cessation is necessary for patients with RRMS under FTY or DMF treatment who smoke.

Funding

The authors disclose the receipt of the following financial support for the research, authorship, and/or publication of this article. This work was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI [grant numbers JP19K07995, JP20K07869, JP21K07464, JP22K07351], a Health and Labour Sciences Research Grant on Intractable Diseases (Neuroimmunological Diseases) from the Ministry of Health, Labour and Welfare of Japan (20FC1030), and Japan Agency for Medical Research and Development (AMED) Grant Number JP21zf0127004.

Data availability statement

The datasets generated and/or analyzed during the present study will be available from the corresponding author based on the guidelines of the Ethics Committee of Kyushu University upon reasonable request from any qualified investigator.

CRediT authorship contribution statement

Eizo Tanaka: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Mitsuru Watanabe:** Conceptualization, Methodology, Resources, Writing – review & editing, Funding acquisition. **Shoko Fukumoto:** Investigation, Resources, Data curation, Writing – review & editing. **Katsuhisa Masaki:** Resources, Writing – review & editing. **Ryo Yamasaki:** Conceptualization, Writing – review & editing. **Takuya Matsushita:** Conceptualization, Methodology, Resources, Writing – review & editing, Funding acquisition. **Noriko Isobe:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

E.T. and S.F. declare that there is no conflict of interest. M.W. was supported by grants from JSPS KAKENHI (Grant Numbers JP19K07995, JP22K07351) and received honoraria for lecturing and interviewing from Novartis Pharma, Chugai Pharmaceutical Co. Ltd., Biogen Japan, and Alexion. M.K. received honoraria for lecturing from Novartis Pharma, Chugai Pharmaceutical Co. Ltd., Alexion, and Nihon Pharmaceutical. R.Y. received honoraria from Teijin Pharma, Ono Pharmaceutical, Takeda Pharmaceutical, Eisai, Novartis, Nihon Pharmaceutical, and CSL Behring. T.M. was supported by grants from JSPS KAKENHI (Gant Number JP20K07869) and received speaker honoraria from Novartis Pharma, Biogen Japan, Alexion, and Chugai Pharmaceutical Co. Ltd. N.I. was supported by grants from JSPS KAKENHI (Grant Number JP21K07464) and AMED Grant Number JP21zf0127004, and received speaker honoraria from Alexion, Novartis Pharma, Biogen Japan, Mitsubishi Tanabe Pharma, Chugai Pharmaceutical Co. Ltd., Teijin Pharma, Takeda Pharmaceutical, CSL Behring, and Eisai.

Acknowledgements

We thank J. Ludovic Croxford, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2023.104513.

References

Sadovnick, A.D., Armstrong, H., Rice, G.P.A., et al., 1993. A population-based study of multiple sclerosis in twins: update. Ann. Neurol. 33, 281–285. https://doi.org/10.1002/ana.410330309.

Olsson, T., Barcellos, L.F., Alfredsson, L., 2017. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nat. Rev. Neurol. 13, 25–36. https://doi.org/10.1038/nrneurol.2016.187.

Sakoda, A., Matsushita, T., Nakamura, Y., et al., 2020. Environmental risk factors for multiple sclerosis in Japanese people. Mult. Scler. Relat. Disord. 38, 101872 https://doi.org/10.1016/j.msard.2019.101872.

Hernán, M.A., Jick, S.S., Logroscino, G., et al., 2005. Cigarette smoking and the progression of multiple sclerosis. Brain 128, 1461–1465. https://doi.org/10.1093/brain/awh471.

Degelman, M.L., Herman, K.M., 2017. Smoking and multiple sclerosis: a systematic review and meta-analysis using the Bradford Hill criteria for causation. Mult. Scler. Relat. Disord. 17, 207–216. https://doi.org/10.1016/j.msard.2017.07.020.

Barzegar, M., Najdaghi, S., Afshari-Safavi, A., et al., 2021. Early predictors of conversion to secondary progressive multiple sclerosis. Mult. Scler. Relat. Disord. 54, 103115 https://doi.org/10.1016/j.msard.2021.103115.

Kvistad, S., Myhr, K.M., Holmøy, T., et al., 2016. No association of tobacco use and disease activity in multiple sclerosis. Neurol. Neuroimmunol. NeuroInflammation 3, e260. https://doi.org/10.1212/NXI.0000000000000260.

Messina, S., Mariano, R., Geraldes, R., et al., 2021. The influence of smoking on the pattern of disability and relapse risk in AQP4-positive Neuromyelitis Optica Spectrum Disorder, MOG-Ab Disease and Multiple Sclerosis. Mult. Scler. Relat. Disord. 49, 102773 https://doi.org/10.1016/j.msard.2021.102773.

Hersh, C.M., Harris, H., Ayers, M., et al., 2020. Effect of tobacco use on disease activity and DMT discontinuation in multiple sclerosis patients treated with dimethyl fumarate or fingolimod. Mult. Scler. J. Exp. Transl. Clin. 6, 2055217320959815 https://doi.org/10.1177/2055217320959815.

Thompson, A.J., Banwell, B.L., Barkhof, F., et al., 2018. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 17, 162–173. https://doi.org/10.1016/S1474-4422(17)30470-2.

Kurtzke, J.F., 1983. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33, 1444–1452. https://doi.org/10.1212/wnl.33.11.1444.

Roxburgh, R.H.S.R., Seaman, S.R., Masterman, T., et al., 2005. Multiple sclerosis severity score: using disability and disease duration to rate disease severity. Neurology 64, 1144–1151. https://doi.org/10.1212/01.WNL.0000156155.19270.F8.

Barry, B., Erwin, A.A., Stevens, J., et al., 2019. Fingolimod rebound: a review of the clinical experience and management considerations. Neurol. Ther. 8, 241–250. https://doi.org/10.1007/s40120-019-00160-9.

Kappos, L., De Stefano, N., Freedman, M.S., et al., 2016. Inclusion of brain volume loss in a revised measure of 'no evidence of disease activity' (NEDA-4) in relapsing-remitting multiple sclerosis. Mult. Scler. 22, 1297–1305. https://doi.org/10.1177/1352458515616701.

Handel, A.E., Williamson, A.J., Disanto, G., et al., 2011. Smoking and multiple sclerosis: an updated meta- analysis. PLoS One 6, e16149. https://doi.org/10.1371/journal.pone.0016149.

Healy, B.C., Ali, E.N., Guttmann, C.R.G., et al., 2009. Smoking and disease progression in multiple sclerosis. Arch. Neurol. 66, 858–864. https://doi.org/10.1001/archneurol.2009.122.

Correale, J., Farez, M.F., 2015. Smoking worsens multiple sclerosis prognosis: two different pathways are involved. J. Neuroimmunol. 281, 23–34. https://doi.org/10.1016/j.jneuroim.2015.03.006.

Odoardi, F., Sie, C., Streyl, K., et al., 2012. T cells become licensed in the lung to enter the central nervous system. Nature 488, 675–679. https://doi.org/10.1038/nature11337.

Qiu, F., Liang, C.L., Liu, H., et al., 2017. Impacts of cigarette smoking on immune responsiveness: up and down or upside down? OncoTargets Ther. 8, 268–284. https://doi.org/10.18632/oncotarget.13613.

Rejdak, K., Eikelenboom, M.J., Petzold, A., et al., 2004. CSF nitric oxide metabolites are associated with activity and progression of multiple sclerosis. Neurology 63, 1439–1445. https://doi.org/10.1212/01.wnl.0000142043.32578.5d.

abdel Naseer, M., Rabah, A.M., Rashed, L.A., et al., 2020. Glutamate and Nitric Oxide as biomarkers for disease activity in patients with multiple sclerosis. Mult. Scler. Relat. Disord. 38, 101873 https://doi.org/10.1016/j.msard.2019.101873.

Colombo, E., Di Dario, M., Capitolo, E., et al., 2014. Fingolimod may support neuroprotection via blockade of astrocyte nitric oxide. Ann. Neurol. 76, 325–337. https://doi.org/10.1002/ana.24217.

Petersen, E.R., Oturai, A.B., Koch-Henriksen, N., et al., 2018. Smoking affects the interferon beta treatment response in multiple sclerosis. Neurology 90, e593–e600. https://doi.org/10.1212/WNL.0000000000004949.

Petersen, E.R., Søndergaard, H.B., Laursen, J.H., et al., 2019. Smoking is associated with increased disease activity during natalizumab treatment in multiple sclerosis. Mult. Scler. 25, 1298–1305. https://doi.org/10.1177/1352458518791753.

Sena, A., Bendtzen, K., Cascais, M.J., et al., 2010. Influence of apolipoprotein E plasma levels and tobacco smoking on the induction of neutralising antibodies to interferon-beta. J. Neurol. 257, 1703–1707. https://doi.org/10.1007/s00415-010-5606-4.

Hedström, A.K., Ryner, M., Fink, K., et al., 2014a. Smoking and risk of treatment-induced neutralizing antibodies to interferon β-1a. Mult. Scler. 20, 445–450. https://doi.org/10.1177/1352458513498635.

Hedström, A.K., Alfredsson, L., Lundkvist Ryner, M.,., et al., 2014b. Smokers run increased risk of developing anti-natalizumab antibodies. Mult. Scler. 20, 1081–1085. https://doi.org/10.1177/1352458513515086.

Yoshimura, S., Isobe, N., Yonekawa, T., et al., 2012. Genetic and Infectious Profiles of Japanese Multiple Sclerosis Patients. PLoS One 7, e48592. https://doi.org/10.1371/journal.pone.0048592.

Piccolo, L., Kumar, G., Nakashima, I., et al., 2015. Multiple sclerosis in Japan appears to be a milder disease compared to the UK. J. Neurol. 262, 831–836. https://doi.org/10.1007/s00415-015-7637-3.

Ishizu, T., Kira, J., Osoegawa, M., et al., 2009. Heterogeneity and continuum of multiple sclerosis phenotypes in Japanese according to the results of the fourth nationwide survey. J. Neurol. Sci. 280, 22–28. https://doi.org/10.1016/j.jns.2009.01.008.