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Clinical trial

Discontinuation of disease-modifying therapy for patients with relapsing-remitting multiple sclerosis: Effect on clinical and MRI outcomes

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ABSTRACT

Background: Disease-modifying therapy (DMT) for patients with relapsing-remitting multiple sclerosis (RRMS) have been shown to reduce relapses and new MRI lesions. However, few studies have assessed the impact of discontinuing DMT after a period of disease inactivity.

Objective: To investigate the impact of DMT discontinuation on clinical and radiological outcomes in RRMS patients.

Methods: 69 RRMS patients who discontinued DMT after a period of disease inactivity were identified from the Comprehensive Longitudinal Investigation of MS study at the Brigham and Women's Hospital, based on the following inclusion criteria: age 18 or older; treated with DMT ≥2 years; no clinical and radiological relapse ≥2 years until the discontinuation; not restarting DMT for ≥6 months after discontinuation. Patients matched by age, gender, treatment, treatment duration, disease duration and Expanded Disability Status Scale score who remained on DMT were identified. Univariate and multivariable Cox proportional hazard models with robust standard errors to account for the paired data were used to test the differences based on DMT discontinuation with the outcome measures: time to clinical relapse, MRI event, disability progression, and disease activity (either clinical relapse or MRI event).

Results: Based on the 69 pairs of patients, discontinuation was not associated with time to clinical relapse (HR = 0.87, 95% CI = 0.44–1.72, $p = 0.69$), MRI event (HR = 0.95, 95% CI = 0.57 to 1.59, $p = 0.84$), disability progression (HR = 1.24, 95% CI = 0.61 to 2.53, $p = 0.55$) and disease activity (HR = 0.89, 95% CI = 0.56 to 1.42, $p = 0.62$). When we performed subgroup analysis to compare the impact of DMT discontinuation between older (age > 45) and younger (age ≤ 45) patients, we found a significant difference in the association between young and old for time to MRI event ($p = 0.012$) and time to new disease activity ($p = 0.0005$).

Conclusions: This study found that patients who discontinued treatment after a period of disease inactivity had a similar time to next event compared to subjects who remained on first-generation DMTs. In our cohort, we found that discontinuation after age 45 was associated with a stable disease course, while patients younger than age 45 who discontinued treatment were more likely to experience a new clinical relapse or MRI event.

1. Introduction

MS is a chronic autoimmune, inflammatory neurological disease of the CNS (Poser et al., 1983; Reich et al., 2018). Among the four clinical forms of MS, relapsing remitting (RRMS) is the most common. As of September 2018, 15 disease-modifying therapies (DMTs) are FDA approved to control MS activity by targeting different components of the immune system.

DMTs in RRMS patients have been extensively investigated and these treatments have been shown to reduce relapse rate and occurrence of new MRI lesions (Calabresi et al., 2014; Cohen et al., 2012; Gold et al., 2012; Goodin et al., 2012; Group, 1995; Kappos et al., 2016, 2010; Mikol et al., 2008; Polman et al., 2006; Shirani et al., 2012). However, DMT can also result in adverse events (AEs), varying from non-life-threatening events such as flu-like symptoms, injection site-reaction to severe events like progressive multifocal leukoencephalopathy (Bloomgren et al., 2012; Hauser et al., 2008; Rosenkranz et al., 2015; Tobin and Weinshenker, 2015). Also, even mild AEs can

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negatively impact a patient's quality of life and can reduce adherence to treatment (Beer et al., 2011). Therefore, considering discontinuation of DMT may be an important option for patients who have experienced AEs. In addition, the natural history of MS is that relapses and new MRI scan changes diminish substantially with age (Tremlett et al., 2008). Furthermore, subgroup analyses, when performed, of the Phase III trials of approved DMTs uniformly show greater measured impact of DMT in younger participants (Kappos et al., 2016; Mikol et al., 2008). Thus, it is not surprising that physicians are frequently asked about DMT discontinuation, especially from patients who have remained in a stable state for a prolonged period of time (Devonshire et al., 2011; Melesse et al., 2017; O'Rourke and Hutchinson, 2005). Studies assessing new disease activity in patients who discontinued DMT after a period without disease activity compared to those who continued DMT are limited, and there are no published randomized controlled trials (RCT) directly comparing clinical outcomes between patients who stopped their DMT and patients who continued DMT. Prior studies have assessed the impact of DMT discontinuation on subsequent relapse risk (Kister et al., 2016, 2018). However, MRI measures are a more sensitive outcome of inflammatory disease activity and have not been assessed as an outcome in this scenario.

We sought to evaluate the clinical course of RRMS patients who discontinued DMT after ≥2 years of no clinical relapse and no MRI activity by comparing these subjects to pair-matched patients who continued DMT. We also investigated the predictors of new clinical relapse, MRI event and disability progression among patients who discontinued DMT.

2. Methods

2.1. Subjects

Subjects included in this study were originally from the Comprehensive Longitudinal Investigation of MS at the Brigham and Women's Hospital (CLIMB) study, which was initiated in the year 2000 and has enrolled 2406 patients from the Partners MS Center (Gauthier et al., 2006). We identified patients who fulfilled the following inclusion criteria at the time of data lock (11/01/2017): (1) 18 years or older, (2) relapsing-remitting MS (RRMS) at first CLIMB visit, (3) treated with FDA-approved DMT for at least 2 year, (4) relapse-free at least 2 year until the discontinuation of DMT, (5) no radiological Gadolinium-enhancing (Gd+) or T2 lesions, or T2 lesion enlargement for at least 2 years, and (6) no DMT was restarted within 6 months after discontinuation. Relapse date, symptoms, and Expanded Disability Status Scale (EDSS) scores were evaluated at 6-month intervals for each patient during the time of clinic visits by the treating neurologist. Additionally, brain MRI (1.5T or 3T) was performed annually. Patients were excluded from our study if they received monthly IV steroid or documented pregnancy during the follow-up period (Fig. 1). The final sample size for the DMT discontinuation group was 69 subjects, and the reasons for discontinuation were classified as: (1) adverse events, (2) patient's preference (including financial issue, desire of pregnancy); the patient discontinued DMT without physician's agreement, and (3) planned discontinuation (both physician and patient agreed with the discontinuation in advance).

The comparison group was composed of patients who continued DMT and were matched according to the following criteria: (1) sex, (2) DMT, (3) ± 2 years difference in DMT duration, (4) ± 3 years difference in disease duration, and (5) ± 5 years difference in age. Subjects from the comparison group were randomly selected for 1:1 match with the 69 subjects who discontinued DMT. All study participants provided written informed consent for their study participation and the Partners Human Research Committee provided Institutional Review Board (IRB) approval.

2.2. Outcomes

Our primary outcome was time to clinical relapse. A clinical relapse was defined as the appearance of new MS symptoms or signs that lasted more than 24 h without concurrent fever or illness (Poser et al., 1983). Clinical relapses were recorded by the treating neurologist at face-to-face biannual visits.

The secondary outcomes were time to MRI event, disability progression and time to disease activity. An MRI event was defined as new or enlarging T2 hyperintense lesions or T1 Gd+ lesions on the brain or spinal cord MRI. Disability progression was defined as an increase on the EDSS that was sustained for at least 6 months. Increase in EDSS was defined using the definition commonly used in clinical trials and was dependent on the baseline EDSS: an increase of 1.5 units for baseline EDSS scores of zero, an increase of 1 point for baseline EDSS of 1.5–5, and half point increase for baseline EDSS 5.5 or more. Time to disease activity was defined as time to either clinical relapse or MRI event.

2.3. Statistical analysis

Baseline demographic and clinical characteristics were compared between the subjects who discontinued and subjects who continued treatment. The primary analysis compared the time to clinical relapse, time to MRI event, time to disability progression, and time to disease activity between the groups using a Cox proportional hazards model with robust standard errors to account for the within pair clustering. Since differences between the pairs were observed for age and treatment duration, all Cox proportional hazards models were also adjusted for these features as the fixed effects and robust standard errors were used to calculate standard errors. We also separately performed survival analysis among patients who received Glatiramer acetate (GA) and Interferons (IFNs). In addition to the primary analysis, we performed subgroup analysis to compare the impact of DMT discontinuation between older group (age > 45) and younger group (age ≤ 45) of patients.

In addition to the group comparison, we investigated whether baseline demographic and clinical characteristics were associated with the time to clinical relapse, time to MRI event, time to disability progression, and time to disease activity in the discontinuation group. The candidate predictors were age at onset, age at DMT discontinuation, sex, EDSS at discontinuation, disease duration, treatment duration and reason for discontinuation. Statistical analysis was conducted using R version 3.5.0 (www.r-project.org) and for all analyses, $p < 0.05$ was considered significant.

3. Results

3.1. Demographics

The demographic and baseline characteristics of the discontinued and continued DMT groups are provided in Table 1. All demographic characteristics were well-balanced between the two groups even though statistically significant differences in age and treatment duration were observed (p-value < 0.05). Most of our patients received glatiramer acetate (GA) (N(%) = 31 (44.9)) and interferons (IFNs) (N(%) = 31 (44.9), (IFN-β1a; 29 (42.0) and IFN-β1b; 2 (2.9)). The other DMTs used were Natalizumab (N(%) = 6 (8.7)), Fingolimod (N(%) = 1 (1.4)). Reason for discontinuation were due to either (1) adverse events 50.7% (n = 35), (2) patient's preference 40.6% (n = 28), and (3) planned discontinuation 8.7% (n = 6). Among patients who discontinued DMT, 40 patients (58.0%) ended up restarting their DMT treatment (mean

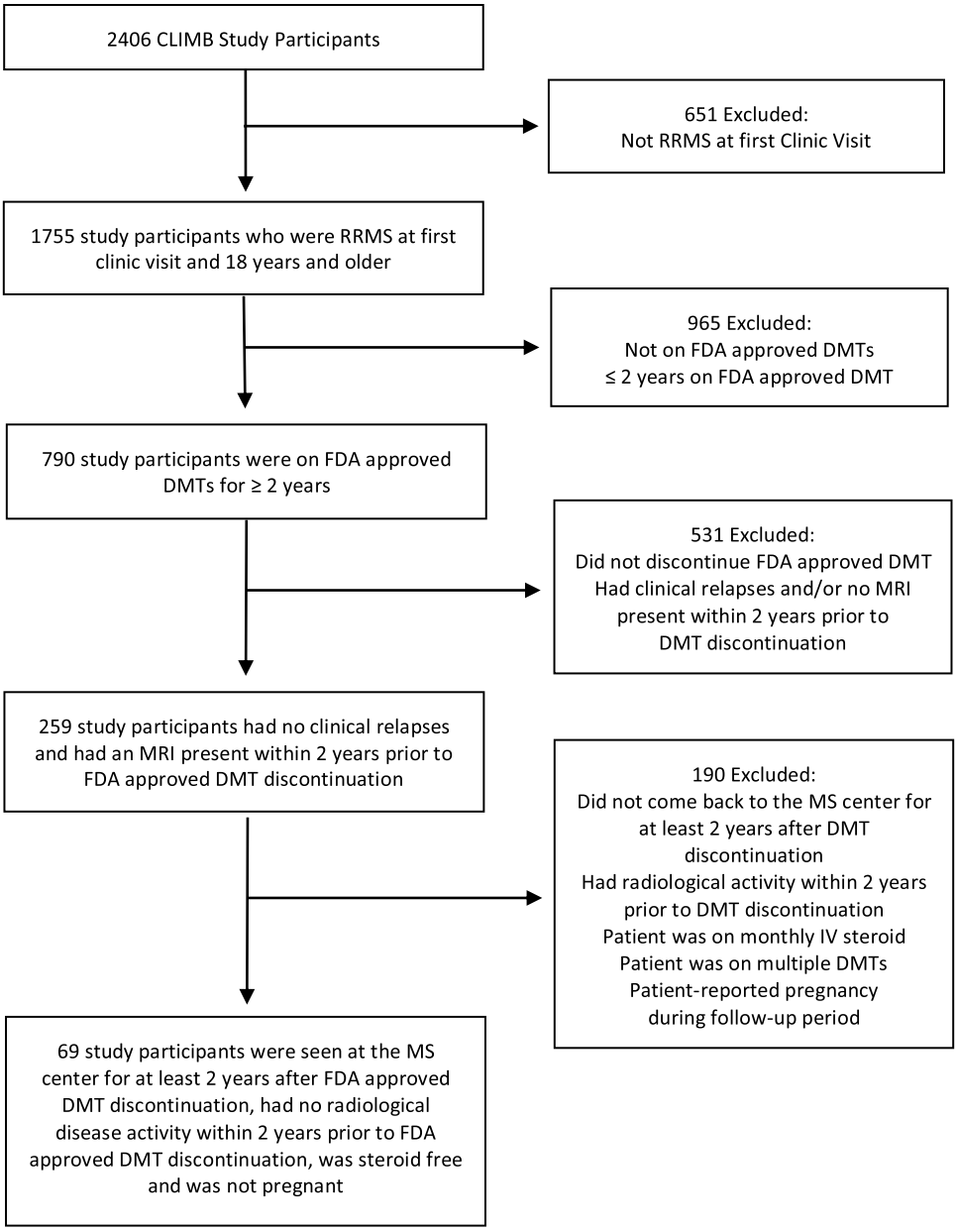


Fig. 1. Flow diagram of study participant.

time to restart: 19.7 months (6.1, 60.7)).

3.2. Comparison of time to event

The estimated time to each event was similar for each of the outcomes between the those that discontinued DMT compared to those who continued their DMT (Fig. 2). When the two groups were compared, the estimated HRs ranged from 0.87 to 1.24 showing a similar hazard of the events in the two groups, and the difference between the groups was not statistically significant for any of the outcomes (Table 2). After adjusting for age and treatment duration, the results were similar. Among patients who received GA and IFNs, the estimated time to each event between the two groups were similar for each of the outcomes (Appendix A and Appendix B). When the two groups were compared, the estimated HRs favored the subjects who continued treatment in the GA group, especially for the time to disease progression (Appendix C). Conversely, the estimated HRs in the IFN group showed that the subjects who discontinued treatment generally had the lower hazard of an event (Appendix D).

Since immunosenescence and a decreased propensity towards relapses occurs with increasing age (Benson et al., 2014), we evaluated whether our results remained significant when accounting for older age. Prior studies have shown that age older than 45 is a predictor for disability progression (Bsteh et al., 2017; Tomassini et al., 2018). Therefore, as a subgroup analysis, we compared the impact of DMT discontinuation between older group (age $>$ 45) and younger group (age $\leq$ 45) of patient. Results summarized in Table 3 show a statistically significant difference (p-value for interaction) in effect of

Table 1
Baseline demographic characteristics of subjects.

Variables	Discontinuation group	Comparison group	Paired *p*-value
N	69	69	
Age (mean (SD))	44.6 (10.1)	45.3 (9.9)	0.024
Female (*N* (%))	60 (87.0)	60 (87.0)	<NA>
Disease duration (mean (SD))	12.6 (7.5)	12.5 (7.5)	0.713
Treatment duration (mean (SD))	6.0 (3.0)	5.5 (3.2)	0.013
EDSS (median (range))	1.5 (0, 7)	1.5 (0, 4)	0.467
DMT types (*N* (%))			
Glatiramer acetate	31 (44.9)		
IFN-β1a	29 (42.0)		
Natalizumab	6 (8.7)		
IFN-β1b	2 (2.9)		
Fingolimod	1 (1.4)		
Reason for discontinuation (N (%))			
Adverse events	35 (50.7%)		
Patients decisions	28 (40.6%)		
Planed discontinuation	6 (8.7%)		

EDSS = expanded disability status scale, DMT = disease modifying therapy.

discontinuation on time to MRI event ($p = 0.012$) and time to disease activity ($p = 0.0005$), and discontinuation was associated with a better disease course in the older subjects.

3.3. Identification of predictors of time to next event in discontinuation group

The associations between baseline demographic and clinical features and time to each outcome are provided in Table 4. A younger age at discontinuation was found to be associated with a shorter of time to MRI event (HR = 0.92) and time to disease activity (HR = 0.93). A shorter disease duration was also found to be associated with the time to MRI event (HR = 0.92). The reason for discontinuation was also statistically significantly associated with the time to MRI event, and the subjects who discontinued due to patient preference had the lowest hazard of an event.

4. Discussion

This study estimates the impact of DMT discontinuation on the clinical and radiological course of RRMS patients. Even though our study is a relatively small, single-center study, a key strength of our analysis was the assessment of MRI stability in our inclusion criteria to ensure that all subjects were completely disease activity free at the time of treatment discontinuation. We also use MRI events because MRI activity such as new or enlarging T2 hyperintense lesions or T1 Gd+ lesions are more sensitive than clinical disease activity as a measure of MS disease activity (Wattjes et al., 2015). Our analysis revealed that RRMS patients who were relapse and MRI activity free for more than 2 years had similar clinical course after DMT discontinuation compared to subjects who remained on DMT in terms of time to clinical relapse,

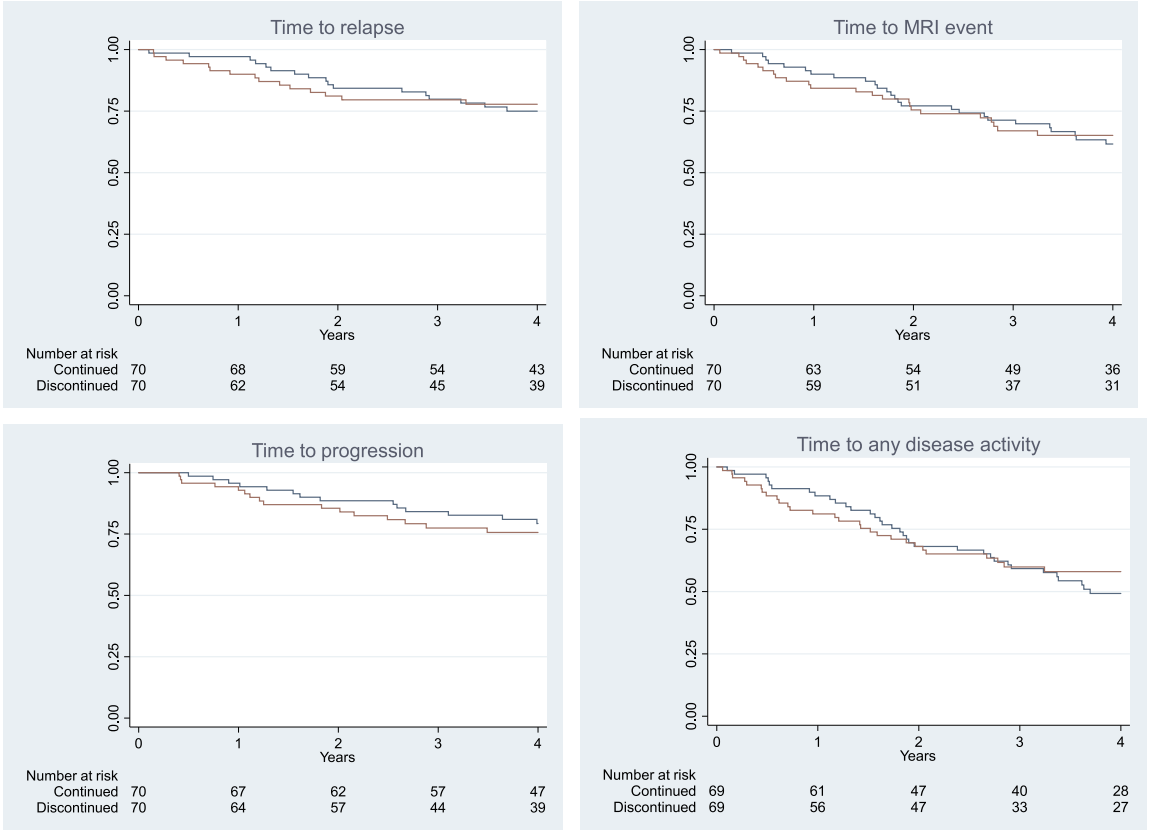


Fig. 2. Survival time to clinical relapse, MRI event, disability progression and any disease activity comparing subjects who discontinued and those who continued among all subjects. Red curve—discontinued group; blue curve—continued group.
The estimated time to each event was similar for each of the outcomes between the those who discontinued DMT (discontinued group) compared to those who continued their DMT (continued group).

Table 2
Estimated difference between subjects who discontinued and those who continued among all subjects ($N = 138$).

Time to	Unadjusted hazard ratio (95% CI); p value	Adjusted[a] hazard ratio (95% CI); p value
Clinical relapse	0.87 (0.44, 1.72); $p = 0.69$	0.84 (0.43, 1.66); $p = 0.62$
MRI event	0.95 (0.57, 1.59); $p = 0.84$	0.99 (0.58, 1.7); $p = 0.97$
Disability progression	1.24 (0.61, 2.53); $p = 0.55$	1.31 (0.64, 2.69); $p = 0.46$
Disease activity	0.89 (0.56, 1.42); $p = 0.62$	0.94 (0.57, 1.53); $p = 0.79$

[a] Adjusted for age and treatment duration.

Table 3
Results of subgroup analysis.

	Time to clinical relapse	Time to MRI event	Time to disability progression	Time to disease activity
Older group (age > 45)	0.44 (0.16, 1.19); $p = 0.11$	0.28 (0.08, 0.997); $p = 0.049$	1.58 (0.62, 3.98); $p = 0.34$	0.33 (0.15, 0.74); $p = 0.007$
Younger group (age ≤ 45)	1.74 (0.66, 4.59); $p = 0.26$	1.64 (0.94, 2.87); $p = 0.079$	0.87 (0.27, 2.76); $p = 0.81$	1.84 (1.06, 3.19); $p = 0.03$
Interaction	$p = 0.052$	$p = 0.012$	$p = 0.43$	$p = 0.0005$

Findings were reported as hazard ratio (95% CI); p value.

MRI event, disability progression, and disease activity. However, this result was mitigated by age at treatment cessation. Older subjects (age > 45) had a better disease course after discontinuation in terms of risk of MRI event and disease activity, while younger subjects (age ≤ 45) were more likely to experience disease activity after treatment cessation.

Our findings align with results of previous studies that focused on patients who discontinued DMTs after a longer period of stable state as measured by relapses only. Kister et al. has reported that MS patients who discontinued first-line DMT after ≥5 years without a relapse had a similar relapse rate as patients who stayed on DMT but time to disability progression was shorter among patients who discontinued DMT compare to patients who continued DMT (Kister et al., 2016). One explanation for the discrepancy in disability progression is the lower number of patients with high disability at baseline in our study population. A prior study has documented that mild (2–3.5) to moderate (4–5.5) baseline EDSS had a higher risk of disability progression than limited disability group (EDSS 0–1.5) (Kister et al., 2018). Our study population had median EDSS of 1.5 for patients who discontinued DMT and 1.5 for patients who continued DMT. Our result suggests that RRMS patients with limited disability who are clinically and radiologically stable could have similar prognosis in terms of disease activity or progression outcomes after DMT discontinuation as patients who remain on DMT even after shorter period of stable state.

In addition to this, our subgroup analysis provides helpful insights to apply our results in the clinical practice. Age has been shown to be one of the strongest prognostic factors, and younger MS patients have a higher risk for relapse compare to older patients (Bsteh et al., 2017; Kister et al., 2018; Tortorella et al., 2005; Tremlett et al., 2008). However, previous studies have not investigated whether age acts as an effect modifier in DMT discontinuation. We found a statistically significant difference in the effect of discontinuation on time to MRI event ($p = 0.012$), and time to disease activity ($p = 0.0005$) between older patients (age > 45) and younger patients (age ≤ 45), and DMT discontinuation was associated with a better disease course in the older subjects. We also performed the comparison of these groups for a set of cut-offs and found that there was a statistically significant interaction between age group and discontinuation for age cut-offs between 40 and 46, but not above age 46 (data not shown).

Our study also evaluated prognostic predictors among patients who discontinued DMT. We found that older age at discontinuation is a prognostic factor of new relapses, new MRI events and disease activity. Longer disease duration was also a prognostic factor for time to MRI event and disease activity. These findings were compatible with previous literatures and natural history studies that have reported the inverse correlation between age and risk of relapse (Tortorella et al., 2005; Tremlett et al., 2008). In addition, the reason for discontinuation was also statistically significantly associated with the time to MRI

Table 4
Predictors of time to event in subjects who discontinued treatment.

	Time to clinical relapse	Time to MRI event	Time to disability progression	Time to disease activity
Age at disease onset	0.99 (0.93, 1.05); $p = 0.71$	0.95 (0.9, 1); $p = 0.06$	1.02 (0.96, 1.07); $p = 0.6$	0.97 (0.92, 1.01); $p = 0.14$
Age at discontinuation	0.96 (0.91, 1.01); $p = 0.12$	0.92 (0.87, 0.96); $p = 0$	1.03 (0.98, 1.08); $p = 0.18$	0.93 (0.89, 0.97); $p = 0$
Sex				
Female	Reference	Reference	Reference	Reference
Male	1.09 (0.24, 4.89); $p = 0.91$	1.15 (0.34, 3.9); $p = 0.82$	1.04 (0.24, 4.57); $p = 0.96$	1.32 (0.46, 3.81); $p = 0.61$
EDSS at discontinuation	1.2 (0.88, 1.63); $p = 0.26$	1.02 (0.77, 1.37); $p = 0.88$	0.99 (0.7, 1.41); $p = 0.97$	0.98 (0.75, 1.28); $p = 0.9$
Disease duration	0.94 (0.86, 1.02); $p = 0.13$	0.92 (0.86, 0.99); $p = 0.02$	1.04 (0.98, 1.1); $p = 0.24$	0.92 (0.87, 0.98); $p = 0.01$
Treatment duration	1.02 (0.87, 1.21); $p = 0.79$	0.98 (0.85, 1.12); $p = 0.73$	1.03 (0.88, 1.2); $p = 0.71$	1.02 (0.91, 1.15); $p = 0.69$
Reason for discontinuation				
Patient's preference	Reference	Reference	Reference	Reference
Side effect	1.24 (0.44, 3.65); $p = 0.66$	2.31 (0.91, 5.87); $p = 0.08$	0.82 (0.28, 2.39); $p = 0.71$	1.89 (0.85, 4.22); $p = 0.12$
Planned discontinuation	NA*	5.06 (1.51 17.0); $p = 0.009$	0.59 (0.08, 4.62); $p = 0.62$	3.02 (0.97, 9.40); $p = 0.06$

For each predictor, the hazard ratio, 95% confidence interval, and p-value are reported for a one unit increase in the predictor. For the categorical predictors, the reference category is provided.

* Since no subjects who discontinued due to planned discontinuation had an event, we could not estimate this hazard ratio.

event, and the subjects who discontinued due to patient preference had the lowest hazard of an event. We compared the age in the patients who discontinued for each reason and found that mean age of patients who discontinued DMT due to AEs: $n = 24$; 41.0 (9.9), Pt preference: $n = 39$; 45.8 (9.6) and planned discontinuation: $n = 6$; 51.0 (10.9). The better prognosis of discontinuation compare to Pt preference can be partially explained by their characteristics of age at the time of DC. On the other hand, planned discontinuation has the highest mean age even though they showed the highest HR. However, we are aware that the number of subjects is limited in group 3 ($N = 6$) and we need a larger sample size to figure out this point.

According to the analysis among only patients who were on IFN and GA, we found a discrepancy between two treatment groups. The GA group showed favorable estimated HRs in the subjects who continued treatment (Appendix C), but the IFN group in subjects who discontinued treatment generally had the lower hazard of an event (Appendix D). Even though no research directly compares each DMTs regarding prognosis after discontinuation, one study regarding DMT discontinuation has reported that GA has non-statistically significant but slightly higher HR in clinical relapse and disability progression compared to Avonex (IFN-β1a) (Kister et al., 2016). Our IFNs group was mostly consisted of IFN-β1a (29 out of 31 patients) and may have shown similar results. One possible explanation of this result is that GA group had more patients who had been a “true responder” and their stability before DMT discontinuation were due to treatment effect, while patients in IFNs group were with “truly inactive” disease course regardless of treatment effect.

Another possible reason for this discrepancy is the demographic difference between two treatment groups. As shown in Appendix E, there is a statistical difference between two treatment groups in treatment duration, but our study has found that treatment duration is not a prognostic factor. On the other hand, IFN group has higher female ratio, older subjects, longer disease duration and treatment duration compared to the GA group. These demographics have been reported as a prognostic predictor for DMT discontinuation; older age at discontinuation was related to lower risk of relapse (Bsteh et al., 2017; Kister et al., 2018). On the other hand, female sex was related with higher risk of relapse and disability progression (Kister et al., 2018) and older age at discontinuation was related to higher risk of disability progression (Kister et al., 2016). Therefore, demographic characteristics may explain some part of discrepancy between two treatment groups but we need to take into consideration that our sample size is small (31 subjects on each group) and carefully interpret these results. We would conclude that treating DMT and demographic differences between two groups may have contributed to this discrepancy, but we need further investigation with larger cohort to confirm these findings.

Limitations in our study relate to the biases inherent in our observational study design including unmeasured confounding. Also, most of our patients were on first-line DMTs such as GA and IFNs. GA and IFNs were the first-approved DMTs for MS, and these are the most common agents as an initial therapy (La Mantia et al., 2014). Patients who had poor treatment response to first-line therapy tend to be non-responders in their later stage of disease course and switch to more effective, usually more aggressive treatment (Bermel et al., 2013; Coyle, 2013). Greatest among these biases is the nature of the population studied. Our patients had continued to use the often-discontinued injectable DMTs for a median of 5+ years. This, and the modest median EDSS scores of 1.5 more than a decade (mean disease duration of each group were 12.6 years and 12.5 years respectively) into their disease course reflects the relatively benign disease course in this population. Another limitation is that we do not have data regarding if patients who stopped DMT felt overall better or worse, which may be evaluated in part by patient reported outcome measures. Besides financial benefit, we need to evaluate how DMT discontinuation impacts patients’ quality of life. A further limitation is that our inclusion criteria required that patients were off treatment for six months to be included in the DMT discontinuation group. Although this decision was made to ensure we found patients who were truly stopping treatment rather than switching, patients who were stopping DMT and had a clinical event that required restarting treatment within six months would not be included in our study. A final limitation of our study was that patients in the DMT discontinuation group could restart treatment during follow-up because our goal was to compare the choice of stopping treatment. To ensure that our results were not due to patients restarting DMT, we censored subjects at the time of treatment restart and the results were generally similar to those reported.

5. Conclusion

This study showed being clinically and radiologically stable for more than 2 years can be a potential milestone to regard the discontinuation of first generation DMTs (GA and IFNs) as a reasonable option in a subset of patients, especially patients who are non-disabled, but the impact of discontinuing DMT may differ based on the age at the discontinuation. Stopping DMT for younger patients may lead to a higher risk on disease activities compare to older patients.

Role of funding source

The funding sources had no role in the conduct or analysis of this study.

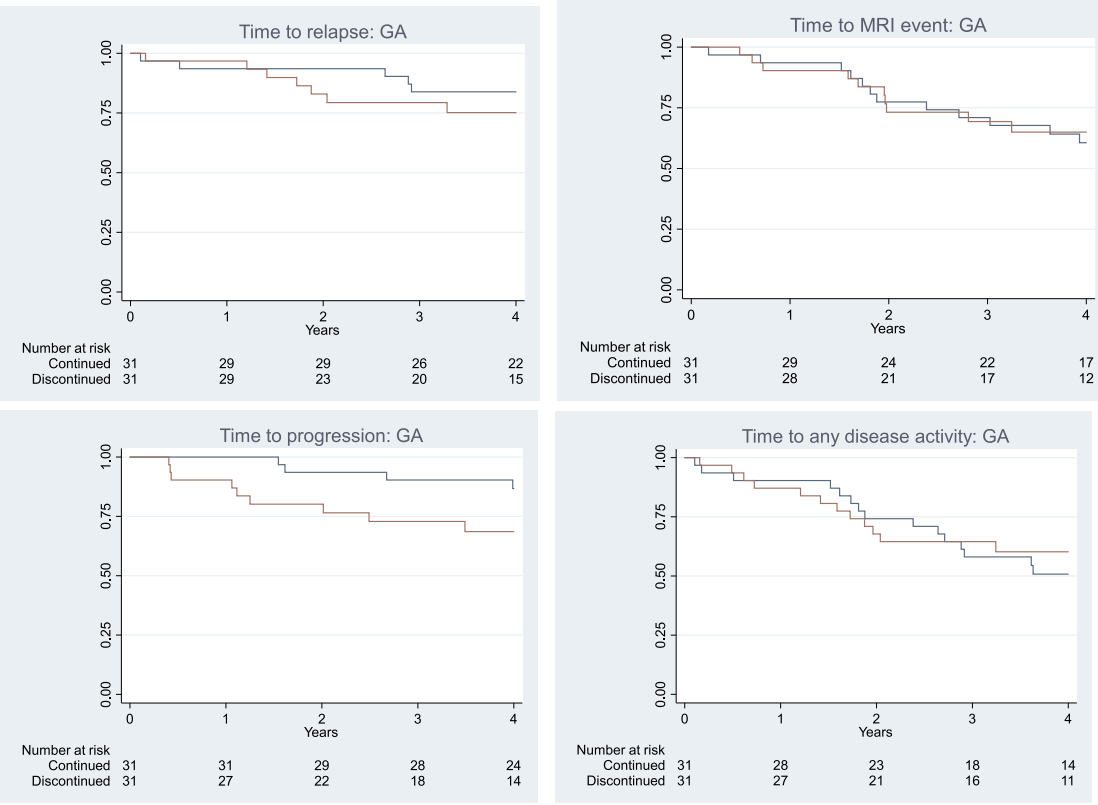
CRediT authorship contribution statement

Hajime Yano: Data curation, Formal analysis, Investigation, Writing - original draft. **Cindy Gonzalez:** Formal analysis, Writing - original draft. **Brian C. Healy:** . **Bonnie I. Glanz:** Data curation. **Howard L. Weiner:** Data curation. **Tanuja Chitnis:** Data curation, Investigation, Supervision, Funding acquisition.

Declaration of Competing Interest

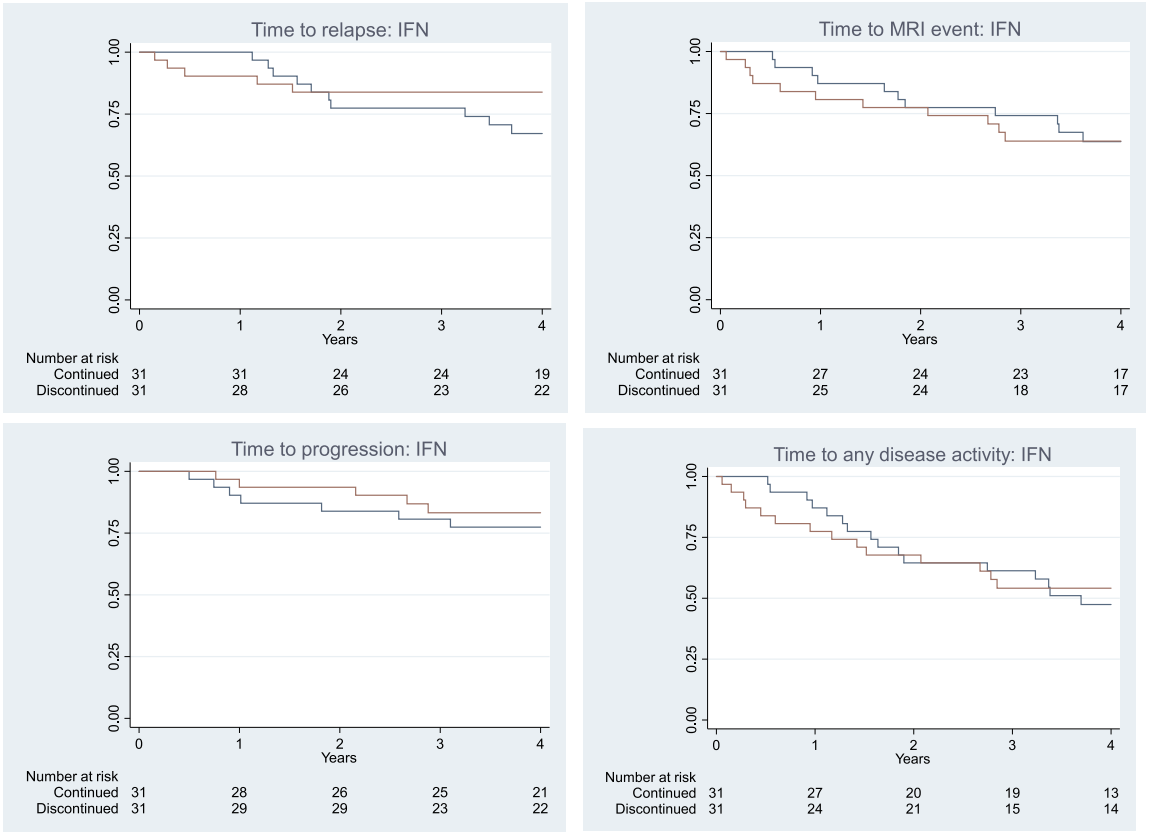
Dr. Yano has received the research grant from Yoshida scholarship foundation, Japan. Dr. Healy has received research support from Merck-Serono and Verily. Dr. Gonzalez has received research support from Merck-Serono and Verily. Dr. Weiner has served as a consultant for Biogen-Idec, Nasvax, Novartis, Merck-Serono, and Teva Neurosciences. He has received grant support from EMD Serono, NIH and National MS Society. Dr. Chitnis has served as an advisor for Biogen-Idec, Novartis, and Alexion and serves on clinical trials advisory boards for Novartis and Sanofi Aventis. She has received research support from the Department of Defense, NIH, National MS Society, Guthy Jackson Charitable Foundation, Verily, EMD-Serono and Novartis.

Appendix A. Survival time to clinical relapse, MRI event, disability progression and disease activity comparing subjects who discontinued and those who continued among those treated with GA only



GA; glatiramer acetate. Red curve-discontinued group; blue curve-continued group. Among patients who received GA, the estimated time to each event was similar for each of the outcomes between the those that discontinued DMT (discontinued group) compared to those who continued their DMT (continued group).

Appendix B. Survival time to clinical relapse, MRI event, disability progression and disease activity among treatment groups in IFNs



IFNs; interferons (IFN-β1a 29 patients and IFN-β1b 2 patients). Red curve-discontinued group; blue curve-continued group. Among patients who received IFNs, the estimated time to each event was similar for each of the outcomes between the those that discontinued DMT (discontinued group) compared to those who continued their DMT (continued group).

Appendix C. Estimated difference between subjects who discontinued and those who continued among those treated with GA only (*N* = 62)

Time to	Unadjusted hazard ratio (95% CI); *p* value	Adjusted[a] hazard ratio (95% CI); *p* value
Clinical relapse	1.55 (0.51, 4.67); $p = 0.44$	1.56 (0.52, 4.71); $p = 0.43$
MRI event	0.9 (0.41, 1.94); $p = 0.78$	1.02 (0.43, 2.44); $p = 0.96$
Disability progression	2.77 (0.9, 8.56); $p = 0.08$	3.18 (1.11, 9.1); $p = 0.03$
Disease activity	0.88 (0.42, 1.83); $p = 0.73$	0.95 (0.42, 2.13); $p = 0.9$

[a] Adjusted for age and treatment duration.

Appendix D. Estimated difference between subjects who discontinued and those who continued among those treated with IFNs only (*N* = 62)

Time to	Unadjusted hazard ratio (95% CI); *p* value	Adjusted[a] hazard ratio (95% CI); *p* value
Clinical relapse	0.51 (0.18, 1.48); $p = 0.22$	0.47 (0.16, 1.36); $p = 0.17$
MRI event	1.09 (0.52, 2.32); $p = 0.81$	1.10 (0.5, 2.43); $p = 0.81$
Disability progression	0.69 (0.22, 2.17); $p = 0.53$	0.67 (0.22, 2.07); $p = 0.48$
Disease activity	0.95 (0.51, 1.78); $p = 0.88$	0.99 (0.52, 1.87); $p = 0.98$

[a] Adjusted for age and treatment duration.

Appendix E. Difference of baseline demographic characteristics between GA group and IFN group

	GA group	IFN group	*p*-value
N	31	31	<NA>
Age (Mean (SD))	43.8 (10.5)	46.8 (9.2)	0.241
Female (*N* (%))	24 (77.4)	29 (93.5)	0.149
Disease duration (mean (SD))	12 (8.6)	13.7 (6.5)	0.379
Treatment duration (mean (SD))	5.2 (2.5)	7.2 (3.3)	0.01
EDSS (mean (SD))	1.6 (1.4)	1.5 (1.3)	0.746

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