RESEARCH ARTICLE

Disease Reactivation After Cessation of Disease-Modifying Therapy in Patients With Relapsing-Remitting Multiple Sclerosis

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Abstract

Background and Objectives

To evaluate the rate of return of disease activity after cessation of multiple sclerosis (MS) disease-modifying therapy.

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MSBase and OFSEP coinvestigators are listed in Appendix 2 at links.lww.com/WNL/C251.

Glossary

ARR = annualized rate of relapse; **DMT** = disease-modifying therapy; **EDMUS** = European Database for Multiple Sclerosis; **EDSS** = Expanded Disability Status Scale; **MS** = multiple sclerosis; **OFSEP** = Observatoire Français de la Sclérose en Plaques.

Methods

This was a retrospective cohort study from 2 large observational MS registries: MSBase and OFSEP. Patients with relapsing-remitting MS who had ceased a disease-modifying therapy and were followed up for the subsequent 12 months were included in the analysis. The primary study outcome was annualized relapse rate in the 12 months after disease-modifying therapy discontinuation stratified by patients who did, and did not, commence a subsequent therapy. The secondary endpoint was the predictors of first relapse and disability accumulation after treatment discontinuation.

Results

A total of 14,213 patients, with 18,029 eligible treatment discontinuation epochs, were identified for 7 therapies. Annualized rates of relapse (ARRs) started to increase 2 months after natalizumab cessation (month 2-4 ARR 0.47, 95% CI 0.43–0.51). Commencement of a subsequent therapy within 2-4 months reduced the magnitude of disease reactivation (mean ARR difference: 0.15, 0.08–0.22). After discontinuation of fingolimod, rates of relapse increased overall (month 1–2 ARR: 0.80, 0.70–0.89) and stabilized faster in patients who started a new therapy within 1-2 months (mean ARR difference: 0.14, −0.01 to 0.29). The magnitude of disease reactivation for other therapies was low but reduced further by commencement of another treatment 1–10 months after treatment discontinuation. Predictors of relapse were a higher relapse rate in the year before cessation, female sex, younger age, and higher EDSS score. Commencement of a subsequent therapy reduced both the risk of relapse (HR 0.76, 95% CI 0.72–0.81) and disability accumulation (0.73, 0.65–0.80).

Discussion

The rate of disease reactivation after treatment cessation differs among MS treatments, with the peaks of relapse activity ranging from 1 to 10 months in untreated cohorts that discontinued different therapies. These results suggest that untreated intervals should be minimized after stopping antitrafficking therapies (natalizumab and fingolimod).

Classification of Evidence

This study provides Class III that disease reactivation occurs within months of discontinuation of MS disease-modifying therapies. The risk of disease activity is reduced by commencement of a subsequent therapy.

Treatment interruptions are common in patients with multiple sclerosis (MS).[1,2] Disease-modifying therapies (DMTs) may be stopped or switched for reasons of efficacy, tolerability, safety, and preference. Treatments may also be discontinued as part of risk-mitigation strategies, i.e., limiting natalizumab treatment duration in patients who are JC virus seropositive to reduce the risk of progressive multifocal leukoencephalopathy or after a predetermined treatment course of mitoxantrone because of the cumulative risk of cardiotoxicity and leukemia.[3,4]

Treatment interruptions leave patients vulnerable to breakthrough disease activity.[5] The risks of disease reactivation after interrupting therapy cited in the literature vary widely. Clinical relapses have been reported in 9%-80% of patients who discontinued natalizumab,[6] and severe relapses have been reported in 10%–25% of patients who discontinued fingolimod.[7] Younger patients, females, and those with higher prediscontinuation relapse rates are at a higher risk of disease reactivation.[8-10] Cases of rebound activity, defined as disease severity that exceeds the patient's pretreatment baseline, have been reported after discontinuation of natalizumab and fingolimod.[7,11-15] Growing concern for disease reactivation after fingolimod cessation resulted in an FDA alert in November 2018.[16]

An immediate transition between sequential therapies is however not always possible because the diverse mechanisms of DMTs often require a period of immune reconstitution before commencement of a subsequent therapy.[17] Clinicians are therefore faced with a difficult balancing act in the period between treatment stop and starting the next switch therapy. Thus far, very little data exist on defining optimal wash-out times between ceasing a DMT and starting a new DMT.

In this study, we evaluated the return of disease activity after discontinuing DMTs, focusing on the association of disease activity with the duration of the untreated period. We aim to better understand safe untreated intervals for commonly used treatments in relapsing-remitting MS.

Methods

Patients

Longitudinal data were extracted from 2 nonoverlapping observational registries: MSBase (139 centers; 33 countries) and Observatoire Français de la Sclérose en Plaques (OFSEP) (39 French centers) in September and June 2020, respectively. Patients with MS, who attended a participating center and provided informed consent, were eligible for enrollment in each respective registry. Patients with relapsing-remitting MS[18,19] who stopped a DMT after ≥1-year treatment exposure were included in the analysis. Patients previously included in a randomized controlled trial or treated with autologous hematopoietic stem cell therapy were excluded. All eligible patients who discontinued a sufficiently represented therapy (defined below) were included in the analysis. Baseline was defined as treatment cessation (date of the last treatment dose), as entered by the treating clinician. Included patients required 1-year postbaseline follow-up and presence of the minimum dataset. The minimum dataset consisted of baseline: age, sex (categorized as male and female), MS duration, documentation of relapses in the prior 12 months, treatment start and stop date, and disability information as quantified by the Expanded Disability Status Scale (EDSS) score at baseline and 2 subsequent visits ≥6 months apart. The baseline visit occurred within an interval of 180 days before or 30 days after treatment stop. Subsequent visits were not required to occur before commencement of the subsequent therapy.

Procedures

All DMTs with >200 recorded treatment discontinuation epochs were included. Treatment with interferon-beta-1a SC, interferon-beta-1a IM, and interferon-beta-1b was merged into an interferon group. Consecutive treatment entries were merged into a continuous entry, given there was no intervening therapy, and the gap between the entries did not exceed 4 years for alemtuzumab, 2 years for cladribine, 365 days for rituximab or ocrelizumab, 190 days for mitoxantrone, and 60 days for other DMTs. Where multiple DMTs were recorded simultaneously, the treatment end date of the previous therapy was imputed as the commencement date of the following therapy.[20-22]

In patients who discontinued more than 1 eligible therapy during their available follow-up, multiple treatment discontinuations per patient were studied. Each treatment discontinuation was termed a discontinuation epoch and was defined as time from the 12 months before treatment discontinuation (baseline) until the last available EDSS score. When evaluating trends in annualized rates of relapse (ARRs) after treatment cessation, only the first 12 months after treatment discontinuation were considered.

Treatment discontinuation reason was described as documented by the treating clinician. A scheduled stop in treatment indicates that the patient has completed a treatment course of predetermined duration (i.e., mitoxantrone treatment course or JC virus–seropositive patients on natalizumab), or treatment stop was scheduled because of circumstances unrelated to inefficacy, intolerance, convenience, or pregnancy. The intention to remain untreated or start a subsequent therapy was not explicitly recorded at the time of treatment discontinuation.

Patient data were prospectively collected during routine clinical care. Data were recorded into the MSBase data entry system or European Database for Multiple Sclerosis (EDMUS) (OFSEP).[23,24] Data quality assurance procedures were applied (eTable 1, links.lww.com/WNL/C251).[25]

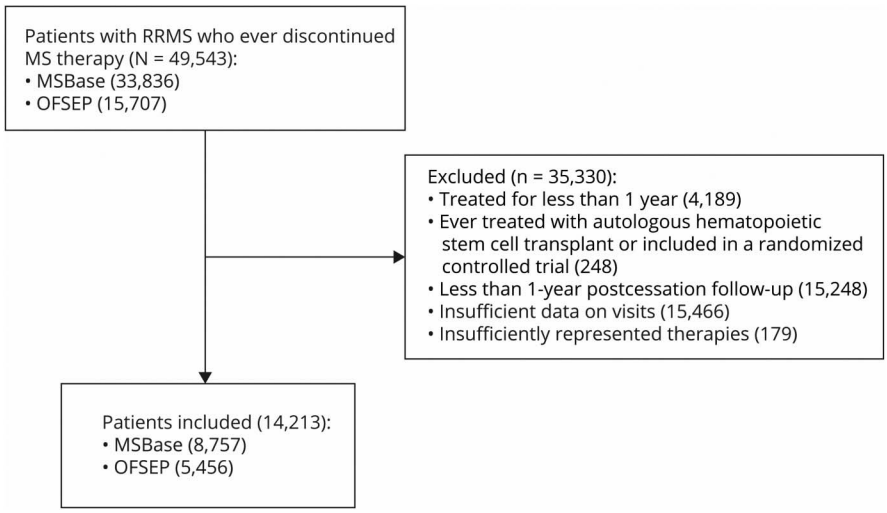
Study Outcomes

Relapses were defined as new symptoms, or exacerbation of existing symptoms, for at least 24 hours in the absence of a concurrent illness or fever and occurring ≥30 days after a previous relapse.[26] Confirmed disability accumulation was defined as an increase in the EDSS by 1.5 step if the EDSS score was 0 or 1 step if the EDSS score was 1-5.5 or an increase by 0.5 step if the baseline EDSS score was >5.5, confirmed over at least 6 months (in the absence of a relapse in the 30 days before confirmation) and sustained for the remainder of the discontinuation epoch.[27] Disability progression independent of relapse activity was defined as confirmed disability accumulation (see above), where the increase in disability could not be attributed to a preceding relapse (ensured by the absence of a recorded relapse between the EDSS score leading to the disability accumulation event and the most recent preceding EDSS score).[28] Relapse-associated worsening was defined as 6-month confirmed disability accumulation, where the increase in disability was attributed to a preceding relapse. Neurostatus EDSS certification was required at all participating centers.

ARRs were calculated in 2-month periods in the 12 months before, and 12 months after, treatment cessation (1-month period during months 0-1 and 1-2 after baseline) as the total number of relapses divided by the number of patient-years. Postbaseline ARRs in each 2-month period were stratified by patients who remained untreated and those who had commenced a subsequent therapy. Patients moved from the "untreated" to the "started on new treatment" group on the date they started a treatment after baseline. Within each 1-2 month period, patients could therefore contribute some time to both the "untreated" and "started on a new treatment" groups. Patients remained in the "started on new treatment" group, irrespective of further changes in treatment status. As relapse activity often increases in the 12 months before treatment cessation, we calculated the ARR during months -24 to -12 as a visual reference of relapse activity while stable on index DMT (only treated time was included). Finally, pretreatment ARR was calculated using up to 1 year of untreated time immediately before commencement of the index therapy (where this information was available).

The primary endpoint was the ARR in the 12 months after DMT discontinuation stratified by commencement of a subsequent therapy. The secondary endpoints were cumulative hazards of first relapse and disability accumulation after

Figure 1 Consort Diagram of Patient Disposition



Patients excluded due to insufficient visit data did not have a baseline visit (with the EDSS score recorded) within an interval of 180 days before or 30 days after cessation of therapy or had fewer than 2 postbaseline visits >6 months apart. Insufficiently represented therapies are those with fewer than 200 recorded treatment discontinuation events (alemtuzumab: 101; cladribine: 36; daclizumab: 13; ocrelizumab: 3; and rituximab: 26). EDSS = Expanded Disability Status Scale; RRMS = relapsing-remitting multiple sclerosis.

treatment discontinuation. An additional analysis explored the time to recurrence of the prebaseline level of relapse activity after treatment discontinuation.

Standard Protocol Approvals, Registrations, and Patient Consents

The MSBase registry[29] (ID ACTRN12605000455662) was approved by the Melbourne Health Human Research Ethics Committee and local ethics committees in all centers. The OFSEP cohort[23] (ID NCT02889965) was collected with approval from French *Commission Nationale Informatique et Libertés* and French law relative to observational research. Informed consent was obtained from all patients enrolled in MSBase and OFSEP.

Statistical Analysis

Bootstrapped 95% CIs were calculated for all ARRs and the differences in the mean ARR between the untreated groups and the groups who started new treatment.

In an additional analysis, the postbaseline ARR was weighted for factors that may influence the decision to start a subsequent therapy. The individual probability of starting a subsequent therapy after baseline was calculated with a survival model, including covariates as listed below. ARRs, weighted by the inverse probability of commencing a subsequent therapy, were calculated in patients who remained untreated after baseline.[30,31]

Cox proportional hazards models with treatment status (treated/untreated) as a time-varying covariate were computed to investigate the time to first relapse or disability accumulation event. The time-varying covariate accounted for change in null hazard function and allowed patients to switch once from untreated to treated. Patients were censored at the last follow-up. A frailty term was included for patient identity, and disability accumulation analyses were adjusted for visit density. The following baseline predictors were included in the model: DMT, age, sex, MS duration, EDSS score, number of relapses in the prior 12 months, year, and country. Schoenfeld residuals were used to evaluate the proportionality assumption.

The time in which the same proportion of patients experienced relapses as during the 2 years before treatment discontinuation was estimated with Cox proportional hazards models (patients were censored at the earlier of commencement of new therapy or last recorded follow-up).

Sensitivity analyses were performed: (1) using a more stringent definition of relapses: only including events treated with corticosteroids or documented by the treating clinician to be severe (influencing activities of daily living or requiring hospitalization); (2) excluding patients who stopped therapy because of pregnancy or pregnancy planning; and (3) stratification by the presence or absence of relapses in the year before baseline. An additional visualization explored relapse trends in patients who did, and did not, commence another treatment within the first year after treatment discontinuation.

Data Availability

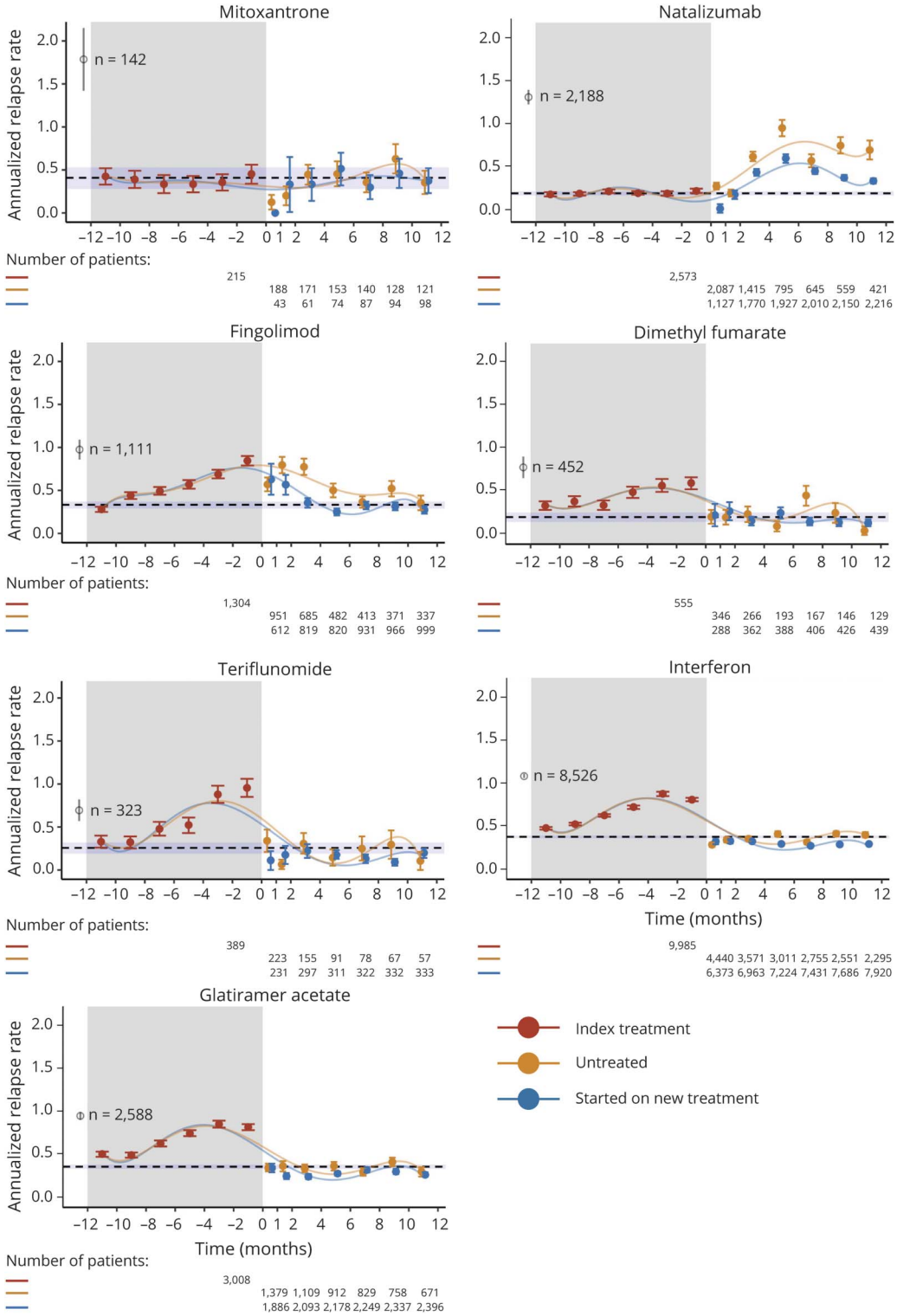
The MSBase and OFSEP registries are data processors and warehouse data from individual principal investigators who agree to share their datasets on a project-by-project basis. Data access to external parties can be granted on reasonable request at the sole discretion of the principal investigators, who will need to be approached individually for permission.

Results

Patients and Follow-up

A total of 135,868 patients with MS (68,709 MSBase and 67,159 OFSEP) were assessed for study inclusion. Of 49,543

Figure 2 Annualized Relapse Rate in the 12 Months Before Baseline (During Index Treatment) and After Treatment Cessation



Baseline (treatment cessation) is indicated by time point 0 and represents the last recorded date of medication administration. The period after treatment cessation is stratified by patients who remained untreated or have started a new treatment (for each 1- or 2-month period). The on-treatment period is indicated by the gray shaded area. Point and whiskers show the relapse rates in each epoch. Number of patients: patients who contribute some time to each period. Annualized relapse rates were calculated as the total number of relapses divided by the number of patient-years in each time period. The pre-treatment relapse rate and 95% CI is indicated by the open circle and line. The relapse rate was calculated using up to 1 year of untreated time immediately before treatment start (number of patients with data available as indicated). The dashed black line is a visual reference of the mean relapse rate during the second year before treatment cessation, with the shaded area indicating 95% CIs. Only treated time was included. Number of contributing patients: mitoxantrone 211, natalizumab 2,558, fingolimod 1,229, dimethyl fumarate 552, teriflunomide 388, interferon 9,931, and glatiramer acetate 2,999.

Table 1 Characteristics of the Study Population at Cessation of Index Therapy

Source	Mitoxantrone	Natalizumab	Fingolimod	Dimethyl fumarate	Teriflunomide	Interferon	Glatiramer acetate
Patients (% female)	214 (74)	2,453 (75)	1,279 (80)	553 (74)	389 (73)	8,933 (75)	2,891 (78)
Discontinuation epochs, n	215	2,573	1,304	555	389	9,985	3,008
Registry							
OFSEP	64 (30)	1,163 (45)	376 (29)	264 (48)	170 (44)	3,640 (37)	1,172 (39)
MSBase	151 (70)	1,410 (55)	928 (71)	291 (52)	219 (56)	6,345 (63)	1,836 (61)
Age, y	38.7 (10.2)	39.8 (10.0)	39.0 (9.9)	40.5 (11.0)	43.4 (11.1)	39.3 (10.5)	40.8 (10.2)
Disease duration, y	8.7 [5.8–13.7]	10.7 [6.5–15.9]	9.7 [6.1–14.8]	8.3 [4.9–14.7]	10.9 [5.9–17.4]	8.7 [5.0–14.1]	9.6 [5.7–15.0]
Disability, EDSS step	4.0 [3.0–6.0]	3.0 [1.5–4.0]	2.5 [1.5–4.0]	2.0 [1.0–3.0]	2.0 [1.5–3.5]	2.0 [1.0–3.0]	2.0 [1.5–4.0]
Relapse rate in 12 mo before cessation	0.38 (0.79)	0.23 (0.56)	0.54 (0.77)	0.44 (0.70)	0.57 (0.68)	0.67 (0.88)	0.67 (0.86)
Duration of discontinued therapy, y	1.7 [1.3–2.0]	2.5 [1.8–3.9]	2.3 [1.5–3.4]	1.8 [1.3–2.5]	1.7 [1.3–2.4]	3.3 [1.9–6.0]	2.9 [1.7–5.2]
Reason for treatment discontinuation (%)							
Reason specified	113 (63)	1,998 (78)	1,115 (86)	476 (86)	345 (89)	7,078 (71)	2,239 (74)
Convenience	3 (2.7)[a]	180 (9.0)[a]	56 (5.0)[a]	24 (5.1)[a]	17 (4.9)[a]	814 (11.5)[a]	282 (12.6)[a]
Lack of efficacy	8 (7.1)[a]	172 (8.6)[a]	523 (46.9)[a]	159 (33.5)[a]	203 (58.8)[a]	2,970 (42.0)[a]	997 (44.5)[a]
Lack of tolerance	4 (3.5)[a]	187 (9.3)[a]	217 (19.5)[a]	196 (41.3)[a]	78 (22.6)[a]	1,767 (25.0)[a]	512 (22.9)[a]
Scheduled stop	97 (85.8)[a]	1,056 (52.7)[a]	79 (7.1)[a]	28 (5.9)[a]	26 (7.5)[a]	798 (11.3)[a]	213 (9.5)[a]
Pregnancy (including planned)	0 (0.0)[a]	256 (12.8)[a]	214 (19.2)[a]	58 (12.2)[a]	16 (4.6)[a]	631 (8.9)[a]	195 (8.7)[a]
Others	1 (0.9)[a]	154 (7.7)[a]	26 (2.3)[a]	10 (2.1)[a]	5 (1.4)[a]	98 (1.4)[a]	40 (1.8)[a]
MRI: new or contrast-enhancing lesions (%)							
Baseline imaging available	41 (19)	1,172 (46)	565 (43)	241 (43)	211 (54)	2,866 (29)	965 (32)
Absent	29 (71)[b]	1,093 (93)[b]	280 (50)[b]	143 (59)[b]	76 (36)[b]	1,669 (58)[b]	495 (32)[b]
Present	12 (29)[b]	80 (7)[b]	285 (50)[b]	98 (41)[b]	135 (64)[b]	1,197 (42)[b]	470 (68)[b]
Time to next treatment, d	244 [61–1,057]	64 [34–137]	52 [25–133]	39 [6–133]	33 [10–83]	14 [1–107]	16 [1–100]
Next treatment category (%)							
High efficacy	38 (17.7)	674 (26.2)	637 (48.8)	148 (26.7)	98 (25.2)	1,716 (17.2)	584 (19.4)
Medium efficacy	20 (9.3)	1,407 (54.7)	335 (25.7)	196 (35.3)	185 (47.6)	2,642 (26.5)	1,079 (35.9)
Low efficacy	116 (54.0)	349 (13.6)	152 (11.7)	147 (26.5)	68 (17.5)	4,816 (48.2)	1,077 (35.8)
None	41 (19.1)	143 (5.6)	180 (13.8)	64 (11.5)	38 (9.8)	811 (8.1)	268 (8.9)
Prebaseline follow-up, y	4.0 [2.1–6.6]	5.5 [3.1–9.2]	5.4 [3.1–9.0]	4.6 [2.6–8.3]	5.2 [2.6–10.5]	4.6 [2.5–8.0]	5.0 [2.7–8.4]
Total time treated prebaseline	3.6 [2.1–6.3]	5.4 [3.1–9.1]	5.3 [3.1–8.8]	4.3 [2.5–7.6]	4.5 [2.3–8.7]	4.3 [2.4–7.5]	4.4 [2.5–7.4]
No. of previous DMTs	1 [0–2]	1 [1–2]	1 [1–2]	1 [1–2]	1 [0–2]	0 [0–1]	0 [0–1]
Top previous DMT category (%)							
High efficacy	13 (6.0)	378 (14.7)	333 (25.5)	54 (9.7)	20 (5.1)	291 (2.9)	219 (7.3)
Medium efficacy	2 (0.9)	192 (7.5)	75 (5.8)	52 (9.4)	39 (10.0)	40 (0.4)	31 (1.0)
Low efficacy	142 (66.0)	1,647 (64.0)	683 (52.4)	315 (56.8)	219 (56.3)	2,531 (25.3)	1,165 (38.7)

Continued

Table 1 Characteristics of the Study Population at Cessation of Index Therapy *(continued)*

Source	Mitoxantrone	Natalizumab	Fingolimod	Dimethyl fumarate	Teriflunomide	Interferon	Glatiramer acetate
None	58 (27.0)	356 (13.8)	213 (16.3)	134 (24.1)	111 (28.5)	7,123 (71.3)	1,593 (53.0)
Postbaseline follow-up, y	9.3 [6.7–12.1]	4.1 [2.5–5.9]	2.8 [1.9–4.1]	2.3 [1.6–3.1]	2.1 [1.5–3.0]	5.3 [3.2–8.7]	4.8 [3.0–7.4]
Year of treatment cessation	2007 (4.5)	2014 (2.5)	2016 (1.7)	2016 (1.3)	2016 (1.5)	2011 (4.6)	2012 (3.7)

Abbreviations: DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; OFSEP = Observatoire Français de la Sclérose en Plaques.
Values are presented as mean (SD) or median [quartiles], unless otherwise stated.
Baseline refers to the date of treatment cessation. In patients in whom multiple eligible baselines were identified, multiple discontinuation epochs were included.
MRI performed within 3 mo preceding treatment cessation.
High-efficacy therapies: natalizumab, rituximab, ocrelizumab, and mitoxantrone.
Medium-efficacy therapies: cladribine, fingolimod, and dimethyl fumarate.
Low-efficacy therapies: Interferons, glatiramer acetate, and teriflunomide.
[a] Proportion with reason for treatment cessation available.
[b] Proportion with MRI available.

patients with relapsing-remitting MS who ever discontinued a DMT, 14,213 were included in the analysis (10.5% of the assessed population; Figure 1). Characteristics of the included patients are shown in Table 1. eTable 2, links.lww.com/WNL/C251, details the patient disposition per center and country. Patient characteristics were comparable between registries (eTable 3, links.lww.com/WNL/C251). Clinicodemographic details of the included population were similar to patients with MS who discontinued a MS therapy but were excluded from the study (eTable 4, links.lww.com/WNL/C251).

Mitoxantrone and Natalizumab

Most patients treated with mitoxantrone and natalizumab discontinued treatment because of a scheduled stop (85.8% and 52.7%, respectively), rather than lack of efficacy (7.1% and 8.6%, respectively). This is corroborated by stability in the ARR over the 12 months before treatment discontinuation and significant improvement in rates of relapse compared with the pretreatment period (Figure 2).

Patients who discontinued mitoxantrone started a subsequent therapy after a median time of 8 months (Table 1). After cessation, relapse rates remained stable over the subsequent year, with no difference in the ARR between patients who remained untreated and those who started a subsequent therapy (Table 2).

Patients who discontinued natalizumab started a subsequent therapy after a median of 2 months. Fingolimod was the subsequent treatment in 51%. From month 2-4 onward, rates of relapse increased above levels observed during natalizumab treatment in both untreated patients and those who commenced a subsequent therapy. ARRs were lower in those who started a subsequent therapy from month 2-4 (Table 2). Although ARRs peaked 4–6 months after treatment cessation at approximately 1 relapse per patient-year (0.98, CI 0.89–1.08), the pre-natalizumab ARR (1.36, CI 1.28–1.44) was not exceeded.

Fingolimod and Dimethyl Fumarate

33.5% of patients treated with dimethyl fumarate and 46.9% of patients treated with fingolimod discontinued treatment because of a lack of efficacy. This is corroborated by a steady increase in the ARR over the 12 months before baseline for both therapies (Figure 2). After cessation of fingolimod, the median time to commencement of a subsequent therapy was 1.7 months; 49% of patients subsequently commenced a high-efficacy therapy (Table 1). Patients who started a subsequent DMT early after fingolimod cessation experienced stabilization in ARRs by month 2-4 (Figure 2). Patients who remained untreated had higher ARRs than was observed in the second year before fingolimod cessation. Compared with patients who were untreated, ARRs were significantly lower in those who commenced a new therapy from month 1 to 2 onward (Table 2).

Among patients who did not commence another DMT 6-8 months after cessation of dimethyl fumarate, ARRs transiently increased above rates observed more than 1 year before baseline (Figure 2). Rates of relapse remained stable over the first year after dimethyl fumarate cessation in patients who started a subsequent therapy.

Teriflunomide, Interferon, and Glatiramer Acetate

Patients treated with teriflunomide, interferon, or glatiramer acetate most often discontinued therapy because of a lack of efficacy. This is supported by the steady rise in the ARR over the year before treatment cessation. After treatment cessation, relapse rates returned to the baseline rate on treatment.

Although the minority did not commence a subsequent therapy (8.1%–9.8%), 44%–72% started a higher efficacy therapy after a median of 2-4 weeks. ARRs in treated patients were lower than those previously observed while stable on low-efficacy therapy, most likely because of treatment escalation. Patients who started a subsequent therapy had marginally lower ARRs than those who remained untreated 8-10 months after teriflunomide

Table 2 Mean Difference in the Annualized Relapse Rate in Patients Who Are Untreated and Those Who Commence a Subsequent Therapy After Baseline

Months	Mitoxantrone	Natalizumab	Fingolimod	Dimethyl fumarate	Teriflunomide	Interferon	Glatiramer acetate
Mean [CI]							
0–1	0.12 [0.04 to 0.21][a]	0.26 [0.2 to 0.32][a]	−0.06 [−0.25 to 0.14]	−0.02 [−0.17 to 0.13]	0.23 [0.06 to 0.39][a]	−0.04 [−0.08 to 0.01]	0.0 [−0.07 to 0.08]
1–2	−0.13 [−0.48 to 0.22]	0.01 [−0.05 to 0.07]	**0.14 [0.01 to 0.29]**	−0.07 [−0.22 to 0.07]	−0.11 [−0.23 to 0.01]	−0.02 [−0.06 to 0.02]	**0.11 [0.03 to 0.18]**
2–4	0.11 [−0.11 to 0.34]	**0.15 [0.08 to 0.22]**	**0.47 [0.37 to 0.57]**	0.08 [−0.01 to 0.18]	0.09 [−0.06 to 0.23]	**0.04 [0.01 to 0.07]**	**0.09 [0.04 to 0.14]**
4–6	0.06 [−0.12 to 0.24]	**0.38 [0.28 to 0.47]**	**0.26 [0.18 to 0.35]**	−0.15 [−0.23 to 0.08]	−0.03 [−0.14 to 0.07][a]	**0.11 [0.08 to 0.15]**	**0.09 [0.03 to 0.14]**
6–8	−0.06 [−0.31 to 0.18]	**0.13 [0.04 to 0.22]**	0.05 [−0.03 to 0.12]	**0.27 [0.14 to 0.4]**	0.12 [−0.03 to 0.26][a]	**0.05 [0.02 to 0.08]**	−0.02 [−0.07 to 0.04]
8–10	0.17 [−0.07 to 0.41]	**0.36 [0.26 to 0.46]**	**0.21 [0.12 to 0.3]**	**0.14 [0.03 to 0.27]**	**0.2 [0.03 to 0.38][a]**	**0.13 [0.1 to 0.16]**	**0.12 [0.05 to 0.19]**
10–12	−0.02 [−0.21 to 0.17]	**0.39 [0.28 to 0.5]**	0.08 [−0.02 to 0.18]	−0.09 [−0.16 to 0.02]	−0.09 [−0.21 to 0.02][a]	**0.10 [0.06 to 0.13]**	0.03 [−0.03 to 0.08]

[a] Interpret with caution: small number of patients in either or both groups.
Statistically significant findings indicated in bold.

discontinuation, 2-4 months after stopping interferons, and 1–2 months after stopping glatiramer acetate (Table 2).

Weighted ARRs, adjusted for the determinants of the start of subsequent therapy, were estimated for patients who had not yet commenced a subsequent therapy after baseline (eFigure 1, links.lww.com/WNL/C251). There were no significant differences between the weighted and unweighted ARRs, and the trends in rates of relapse remained consistent.

Predictors of Disease Reactivation After DMT Cessation

Younger age, female sex, higher EDSS score, and higher ARR in the prior 12 months were associated with a higher risk of a postbaseline relapse (Table 3). Older age, male sex, longer MS duration, and lower EDSS score were associated with a higher risk of a first accumulation of disability event. A higher number of relapses in the prior 12 months were associated with a reduced risk of disability accumulation independent of disease activity (0.92 [0.87–0.98]) but an increased risk of relapse-associated worsening (1.1 [1.02–1.19]) (eTable 5, links.lww.com/WNL/C251). The EDSS score was not a predictor of disability accumulation independent of disease activity (1.02 [0.99–1.05]).

Compared with interferon, cessation of natalizumab and fingolimod was associated with a 1.7-1.9 higher risk of a postbaseline relapse and twice the risk of disability accumulation. Commencement of a subsequent therapy reduced the risk of a postbaseline relapse (0.76 [0.72–0.81]) and disability accumulation (0.73 [0.65–0.80]).

Estimates of the survival time from the cessation of index therapy to the point when the same proportion of patients experienced relapse as during the second year before baseline are shown in eTable 6, links.lww.com/WNL/C251. These estimates represent a proxy for the time to disease reactivation after stopping therapy, accounting for the prebaseline on-treatment level of relapse activity. During the time of stable therapy, such an estimate would be expected to be approximately 12 months. Twenty-six percent of patients experienced a relapse in year 2 before stopping mitoxantrone; the same proportion of patients had a first relapse 10 months (95% CI 8–16) after mitoxantrone cessation. By contrast, 23% of patients experienced a first relapse 4.8 months (95% CI 3.9–6.9) after fingolimod cessation, and 17% experienced a first relapse 4.8 months (95% CI 4.5–5.5) after natalizumab cessation.

Sensitivity analyses, using (1) a more stringent definition of relapses (eFigure 2A, links.lww.com/WNL/C251), (2) excluding patients who discontinued therapy because of pregnancy (eFigure 2B, links.lww.com/WNL/C251), and (3) stratified by prebaseline relapses (eFigures 2C and 2D, links.lww.com/WNL/C251), showed consistent trends in ARRs after treatment discontinuation. Although relapse rates were higher in patients with relapses in the year before treatment cessation (eFigure 3, links.lww.com/WNL/C251), ARRs also increased in patients who stopped different therapies in the absence of prediscontinuation relapses (Figure 3). Commencement of a subsequent therapy helped mitigate the increase in rates of relapse. Visualized trends in relapse rates in patients who did, and did not, commence another treatment within the first year after

Table 3 Predictors of Relapse and Disability Accumulation After Cessation of Therapy

Term	First relapse	First disability accumulation event
	HR (95% CI, *p* value)	
Therapy		
Interferon	Reference	
Mitoxantrone	0.91 (0.74–1.13, $p = 0.401$)	1.12 (0.81–1.55, $p = 0.500$)
Natalizumab	**1.87 (1.73–2.03, $p < 0.001$)**	**2.06 (1.81–2.34, $p < 0.001$)**
Fingolimod	**1.67 (1.49–1.87, $p < 0.001$)**	**2.01 (1.67–2.43, $p < 0.001$)**
Dimethyl fumarate	1.08 (0.91–1.30, $p = 0.373$)	1.33 (0.97–1.81, $p = 0.079$)
Teriflunomide	0.89 (0.70–1.11, $p = 0.301$)	1.08 (0.74–1.57, $p = 0.699$)
Glatiramer acetate	1.01 (0.94–1.08, $p = 0.860$)	**1.17 (1.04–1.32, $p = 0.007$)**
Age at cessation	**0.97 (0.97–0.98, $p < 0.001$)**	**1.03 (1.02–1.03, $p < 0.001$)**
Sex (male)	**0.81 (0.76–0.87, $p < 0.001$)**	**1.32 (1.18–1.47, $p < 0.001$)**
MS duration at cessation	1.00 (0.99–1.00, $p = 0.105$)	**1.01 (1.00–1.02, $p = 0.004$)**
EDSS score at cessation	**1.05 (1.03–1.07, $p < 0.001$)**	**0.95 (0.93–0.98, $p = 0.001$)**
No. of relapses in the prior 12 mo	**1.27 (1.24–1.31, $p < 0.001$)**	0.98 (0.93–1.03, $p = 0.346$)
Commencement of subsequent therapy	**0.76 (0.72–0.81, $p < 0.001$)**	**0.73 (0.65–0.80, $p < 0.001$)**
Year at cessation	**0.93 (0.92–0.93, $p < 0.001$)**	**0.98 (0.97–0.99, $p = 0.001$)**

Abbreviations: EDSS = Expanded Disability Status Scale; HR = hazard ratio; MS = multiple sclerosis. Analysis adjusted for country.
Statistically significant findings indicated in bold.

treatment discontinuation were consistent with the primary analysis (eFigure 4, links.lww.com/WNL/C251).

Discussion

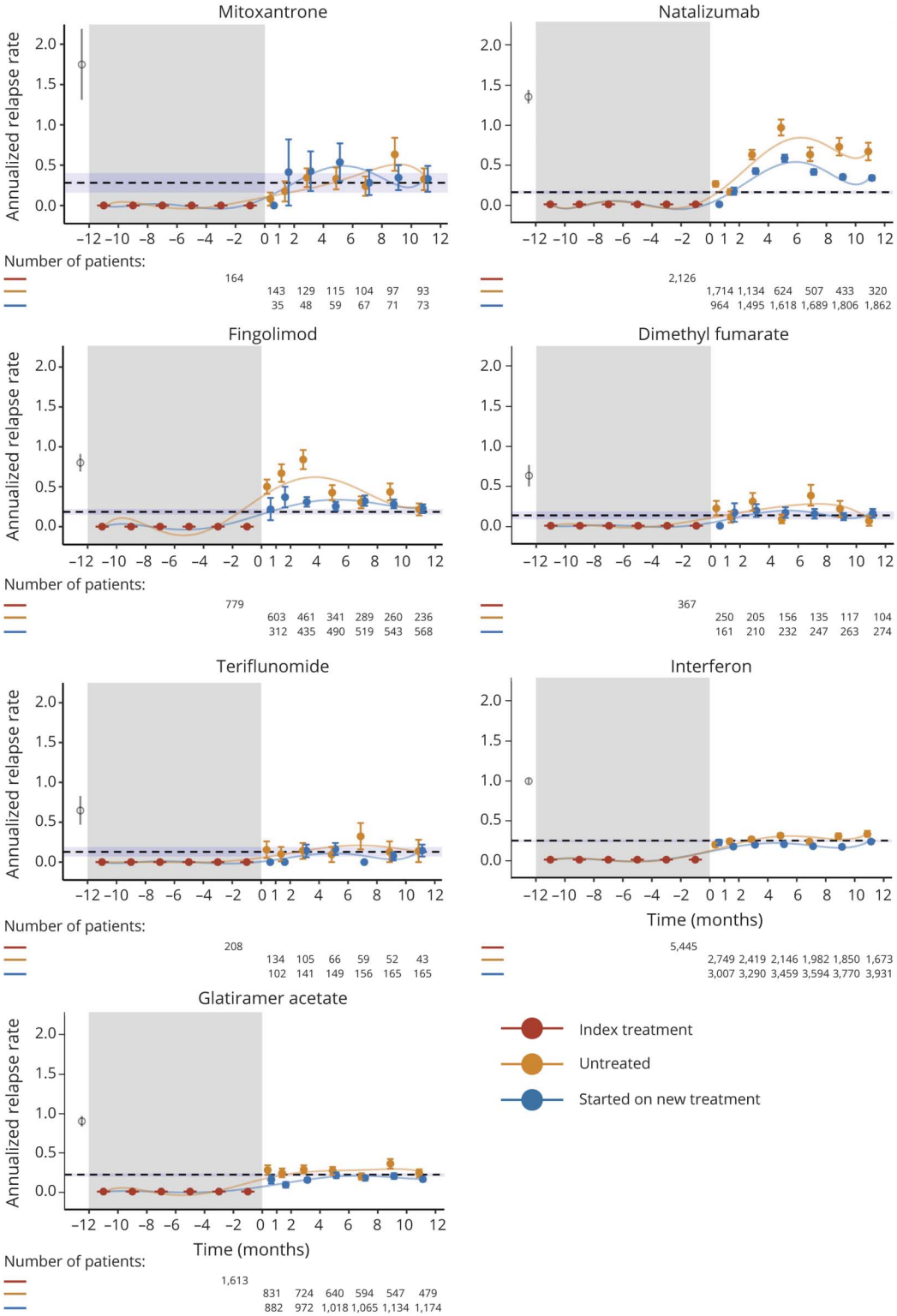
In this observational study from 2 large registries, we explored the return of disease activity after treatment cessation in MS. The rate of disease reactivation differs among DMTs, with the peaks of relapse activity ranging from 1 to 10 months in untreated cohorts that discontinued different therapies. For all studied therapies apart from mitoxantrone, disease reactivation is reduced by the commencement of a subsequent DMT within the first 10 months. Patients treated with natalizumab and fingolimod are at a highest risk of clinical disease activity after treatment cessation and benefit from the earliest introduction of a subsequent therapy (within 1 month for fingolimod and within 2 months for natalizumab). A higher relapse rate in the year before treatment cessation is associated with a higher risk of posttreatment relapse. Although being male, older, or having a lower EDSS score is associated with a lower risk of relapse, these characteristics are associated with a higher risk of posttreatment disability accumulation.

Consistent with the timing of pharmacodynamic natalizumab reversal,[32] relapse rates increased if a subsequent DMT was started >8 weeks after cessation of natalizumab. This is supported by findings from the RESTORE interruption of the natalizumab study, where 92% of relapses occurred 8-24 weeks after natalizumab discontinuation.[33,34] In accordance with a post hoc analysis of the AFFIRM, SENTINEL, and GLANCE studies, we observed an increase in ARR after natalizumab discontinuation irrespective of the commencement of a new DMT[11]; patients starting a new therapy did however have lower ARRs than those who remained untreated after 2 months from stopping natalizumab. Fingolimod was the most common post-natalizumab therapy. A lack of rebound activity is in keeping with an earlier MSBase study evaluating relapse rates in patients who discontinued natalizumab and started fingolimod.[9]

After fingolimod cessation, ARRs remained elevated when commencement of a subsequent therapy was delayed by >1–2 months. This adds to previous evidence that relapse activity increases within the first months after stopping fingolimod.[13,14,35,36] This timeframe of clinical disease reactivation aligns with the temporal profile of lymphocyte count reconstitution because absolute lymphocyte counts reach the lower limit of normal 6–8 weeks after fingolimod discontinuation.[37]

Mitoxantrone exerts a prolonged effect on suppressing relapse activity after discontinuation, with no difference in ARR in those who remained untreated vs those who commenced

Figure 3 Annualized Relapse Rate in the 12 Months Before Baseline (During Index Treatment) and After Treatment Cessation in Patients Without Relapses in the Year Before Baseline



Baseline (treatment cessation) is indicated by time point 0 and represents the last recorded date of medication administration. The period after treatment cessation is stratified by patients who remained untreated or have started a new treatment (for each 1- or 2-month period). The on-treatment period is indicated by the gray shaded area. Point and whiskers show the relapse rates in each epoch. Number of patients: patients who contribute some time to each period. The pretreatment relapse rate and 95% CI is indicated by the open circle and line. The relapse rate was calculated using up to 1 year of untreated time immediately before treatment start. The dashed black line is a visual reference of the mean relapse rate during the second year before treatment cessation, with the shaded area indicating 95% CIs. Only treated time was included.

subsequent DMT in the first year after cessation. This supports mitoxantrone as an induction therapy, with a long-term treatment effect.[38]

Relapse rates before treatment discontinuation reflect the nature of the treated cohorts and the reasons for discontinuation of different DMTs. Therapies that are more often discontinued due to inefficacy showed a gradual increase in relapse activity before treatment cessation. By aligning baseline at treatment cessation, an artificial peak in the ARRs was created for these DMTs. Once the reason for treatment discontinuation passes, patients return to baseline levels of disease activity. As all relapses within 30 days constitute a single event, this refractory period and regression to the mean contribute to the decline in relapses after baseline, especially in lower-efficacy therapies. Because the visualization of relapse rates is uncorrected for differences in the cohorts, direct comparisons between therapies are inappropriate. For instance, patients who relapse while treated with fingolimod have a differential propensity for neuroinflammatory activity than patients who relapse on lower-efficacy DMTs.[39]

By contrast, natalizumab and mitoxantrone discontinuation was frequently a scheduled stop. Because of an unfavorable cumulative adverse event profile, mitoxantrone is administered as a fixed treatment course, and natalizumab treatment duration is limited in JC virus–seropositive patients.[4] Correspondingly, ARRs remained stable in the period before mitoxantrone and natalizumab cessation.

Identified predictors of the first relapse and disability accumulation are consistent with several previous studies: higher risk of relapse in females, younger patients, and those with a higher ARR before treatment discontinuation.[8,35,40] Determinants of the risk of disability worsening after treatment cessation are in keeping with known risk factors of disability accumulation from natural history studies.[41-43] The small effect sizes for the risk of age, MS duration, and EDSS score in a cohort of our size should, however, be noted.

Although the size of our cohort is a strength, the observational nature of the data is its main limitation.[44] To minimize reporting bias and error in the data, we applied a rigorous validated quality control process.[25] The requirement for 1-year treatment persistence before discontinuation precludes generalizability of our findings to patients with early treatment discontinuation. The requirement for 1-year postdiscontinuation follow-up may have resulted in an underrepresentation of patients with stable disease after baseline. This study was not designed to compare postdiscontinuation disease activity between therapies. Outcomes between treatments should thus not be compared. Therapies with longer durations of action (anti-CD20 therapies, alemtuzumab, or cladribine) were not sufficiently represented for study inclusion. Because of the paucity of available MRI data, we only considered clinical markers of disease activity. Radiologic activity after discontinuation may provide more granular information about disease reactivation. A prospective trial with frequent neuroimaging would be required to study this further. Similarly, prospective acquisition of a broad panel of biological markers would be required to evaluate biological disease reactivation. Lack of biological data further precluded the evaluation of prolonged post-fingolimod or dimethyl fumarate lymphopenia[45,46] on the timing of subsequent treatment commencement. Because the reason for treatment discontinuation was only recorded for 63%–89% of discontinued therapies, analyses were not stratified by this variable to minimize the risk of informative missingness. Finally, relapses were analyzed as recorded by treating neurologists without a requirement for a validation with the EDSS score. Our findings, however, were confirmed in sensitivity analysis using a more stringent definition of relapses based on their severity.

With an increasing number of therapies available for the treatment of MS, decisions about treatment sequencing have become more complex. Accurate estimates of safe untreated intervals for different therapies are important to determine the optimal timing of the start of the next treatment. The risk of disease reactivation is strongly influenced by systematic differences between the cohorts treated with different DMTs and pharmacodynamics and pharmacokinetics of DMTs. Although the risk of disease reactivation was reduced by starting a new treatment across most studied therapies, patients treated with lower-efficacy DMTs were at the lowest and patients treated with antitrafficking agents (natalizumab and fingolimod) at the highest risk of disease reactivation after stopping a treatment. To minimize the risk of disease reactivation, we therefore suggest that untreated intervals be minimized, while taking into account potential safety consideration during treatment sequencing, which were not considered in this study. It is important that treatment decisions after discontinuation of DMTs should be individualized to the clinical profile, including prior on-treatment relapse activity, age, sex, and disability.

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Laplaud served on scientific advisory boards for Roche, Sanofi, Novartis, MedDay, Merck, and Biogen; received conference travel support and/or speaker honoraria from Novartis, Biogen, Roche, Sanofi, Celgene, and Merck; and received research support from Fondation ARSEP and Agence Nationale de la Recherche. E. Berger received honoraria and consulting fees from Novartis, Sanofi-Aventis, Biogen, Genzyme, Roche, and Teva Pharma. F. Grand'Maison received honoraria or research funding from Biogen, Genzyme, Novartis, Teva Neurosciences, Mitsubishi, and ONO Pharmaceuticals. C. Lebrun-Frénay received fees for consulting or lectures from Novartis, Genzyme, and Roche. C. Boz received conference travel support from Biogen, Novartis, Bayer-Schering, Merck, and Teva; has participated in clinical trials by Sanofi-Aventis, Roche, and Novartis. J. Lechner-Scott received travel compensation from Novartis, Biogen, Roche, and Merck. 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Kalincik served on scientific advisory boards for Roche, Sanofi Genzyme, Novartis, Merck, and Biogen; steering committee for Brain Atrophy Initiative by Sanofi Genzyme; received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Sanofi Genzyme, Teva, bioCSL, and Merck; and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene, and Merck. The other authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

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Appendix 1 *(continued)*

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Appendix 1 *(continued)*

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Continued

Appendix 1 *(continued)*

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Appendix 1 *(continued)*

Name	Location	Contribution
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Appendix 1 *(continued)*

Name	Location	Contribution
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Appendix 1 *(continued)*

Name	Location	Contribution
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Michael H Barnett, PhD	Brain and Mind Centre, Sydney, Australia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Celine Labeyrie, MD	CHU Bicêtre, Department of Neurology, Le Kremlin Bicêtre, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
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Appendix 1 *(continued)*

Name	Location	Contribution
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Appendix 1 *(continued)*

Name	Location	Contribution
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Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/C251.

References

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